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NATURE OF CONVEYANCE:	SECURITY INTEREST

CONVEYING PARTY DATA

Name	Execution Date
BIOSUCCESS BIOTECH CO., LTD.	12/31/2018

RECEIVING PARTY DATA

Name:	SUGHRUE MION, PLLC
Street Address:	2100 PENNSYLVANIA AVENUE, N.W.
City:	WASHINGTON
State/Country:	D.C.
Postal Code:	20037

PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	13745740

CORRESPONDENCE DATA

Fax Number: (202)293-7860

Correspondence will be sent to the e-mail address first; if that is unsuccessful, it will be sent using a fax number, if provided; if that is unsuccessful, it will be sent via US Mail.

Phone: 202-293-7060
Email: SUGHRUE@SUGHRUE.COM, nmckoy@sughrue.com
Correspondent Name: SUGHRUE MION, PLLC
Address Line 1: 2100 PENNSYLVANIA AVENUE, N.W.
Address Line 2: SUITE 800
Address Line 4: WASHINGTON, D.C. 20037-3213

ATTORNEY DOCKET NUMBER:	A207145
NAME OF SUBMITTER:	NONA MCKOY, SECRETARY
SIGNATURE:	/Nona McKoy/
DATE SIGNED:	12/31/2018

Total Attachments: 97
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INTELLECTUAL PROPERTY SECURITY AGREEMENT

This Intellectual Property Security Agreement ("Agreement"), dated as of the date signed by both parties, is made by Biosuccess Biotech Co., Ltd. (the "Debtor"), with its chief executive office and mailing address at c/o Biosuccess Biotech Co. Ltd., Suite 200, 2570 North First Street, San Jose, CA 95121, USA in favor of Sughrue Mion, PLLC, 2100 Pennsylvania Ave., NW, Washington DC 20037 in its capacity as "Secured Party" under the Agreement referenced herein below.

WITNESSETH:

WHEREAS, Secured Party has done substantial legal work on Debtor's intellectual property portfolio, including patents and patent applications, for which Secured Party has not been paid;

WHEREAS, Debtor agrees that the amounts indicated on Secured Party's monthly statements of account, and related correspondence, are overdue and owed ("the Obligations");

WHEREAS, pursuant to the Agreement herein, Debtor has granted to Secured Party, for its benefit, security interests in and to and Liens on certain of Debtor's Intellectual Property and specifically including all of Debtor's registered United States patents and all of Debtor's filed United States applications, all whether now owned or hereafter created, arising and/or acquired (collectively, the "US Registered Intellectual Property"); and

WHEREAS, Debtor has agreed to execute and deliver this Agreement and to have a copy of this Agreement filed with the United States Patent and Trademark Office and any appropriate state or local government offices, in order to perfect and/or protect all of Secured Party's Liens in the US Registered Intellectual Property.

NOW THEREFORE, in consideration of the premises and mutual covenants and agreements set forth herein, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged by each party hereto, and with the intention of being legally bound hereby, the Debtor and the Secured Party agree as follows:

SECTION 1. Grant of Security Interest. The Debtor hereby grants to the Secured Party a lien on and continuing security interest in all of such Debtor's right, title, and interest in and to the following:

(a) all granted patents and pending patent applications in the United States (and all patents that issue therefrom), including all industrial designs, industrial models, utility models, certificates of invention and other indices of invention ownership, and all reissues, reexaminations, extensions, renewals, substitutes, divisions and continuations (including continuations-in-part and continuing prosecution applications) thereof, all rights to make applications for issuance and recordations, for the full term thereof, now existing or hereafter applied for, issued, or acquired ("Patents"), and

(b) any agreement, whether written or oral, providing for the grant of any right under any of the foregoing Patents ("IP Licenses"), including, without limitation, those items listed on Schedule A hereto (the foregoing collectively, the "IP Collateral"), as collateral security for the prompt and complete payment and performance when due (whether at the stated maturity, by acceleration or otherwise) of the Debtor's Obligations ("Obligations"), provided that the security interest created hereby does not constitute an assignment, shall not include any license or agreement to the extent that, and only during the period in which, a grant of security therein would violate or create a right of termination in favor of any other party thereto (other than any Debtor) to the extent such is not rendered unenforceable pursuant to applicable provisions of the UCC or other applicable law, and shall not include any of the foregoing to the extent that, and only during the period in which, a grant of security interest therein would void, invalidate, cancel, or impair the enforceability of such intellectual property rights.

SECTION 2. Security for Obligations. The grant of a security interest in the Patents and IP Collateral herein secures the payment of all of the Obligations.

SECTION 3. Recordation. The Debtor authorizes and requests that the United States Patent and Trademark Office, or other governmental agency record this Agreement.

SECTION 4. Debtor Remains Liable. Debtor hereby agrees that, anything herein to the contrary notwithstanding, Debtor shall retain full and complete responsibility for the prosecution, defense, enforcement or any other necessary or desirable actions in connection with their Intellectual Property, subject to this security interest hereunder. Secured Party is not required to continue prosecution of any patent applications in the U.S. or abroad, nor to maintain any granted patents through annuities or the like in the U.S. or abroad.

Section 5. Agreement to Deliver Supplements. Debtor hereby covenants and agrees that promptly upon the acquisition by Debtor of any new US Registered Intellectual Property Collateral (including any registration or issuance of any United States patent arising out of any filed United States patent application listed on Schedule A hereto or the Schedule to any other Supplement delivered to Secured Party in accordance with this paragraph), Debtor shall, deliver to Secured Party a duly executed Supplement to this Agreement listing all such newly acquired US Registered Intellectual Property, pursuant to which Debtor shall reconfirm the grant of a security interest in such newly acquired US Registered Intellectual Property Collateral to Secured Party, for its benefit and for the ratable benefit of Secured Party, to secure the Obligations. Each such Supplement is intended by the parties to be filed, and Debtor hereby authorizes Secured Party to file and record a copy of each such Supplement, with the United States Patent and Trademark Office and/or other local or state government offices, as applicable. Regardless of whether any Supplement is delivered by Debtor, and without limiting the generality of the provisions of Section 1 hereof above, Debtor hereby confirms and agrees that any and all such after-acquired US Registered Intellectual Property Collateral, and all IP Collateral relating thereto, shall immediately and automatically upon Debtor's acquisition of any right, title and interest therein become part of the IP Collateral hereunder. In the event that Debtor acquires any such new US Registered Intellectual Property but Debtor fails for whatever reason to promptly deliver a Supplement pursuant to this Section 5, Debtor hereby authorizes Secured Party, acting under its Power of Attorney

granted pursuant to Section 6 below, at any time thereafter and until the Termination, to execute in the name of Debtor an applicable Supplement with respect to such newly acquired US Registered Intellectual Property, arising and/or acquired and to file the same with the United States Patent and Trademark Office and any other applicable state or local government office.

Section 6. Power of Attorney. Without limiting the generality of any power of attorney granted to Secured Party under any Other Document, Debtor hereby authorizes Secured Party, its successors and assigns, and any officer, employee, attorney or agent thereof, as Debtor's true and lawful attorney-in-fact, with the power to execute and endorse on behalf of and in the name of Debtor any Supplement to this Agreement or other security agreement or similar document or instrument which Secured Party may deem necessary or desirable in order to create, protect, perfect or enforce the security interest in the Patents and/or IP Collateral provided for herein and in each case to file or record any such Supplement or other security agreement or similar document or instrument with the United States Patent and Trademark Office and any other applicable state or local government office, in the name of and on behalf of Debtor, and after the occurrence and during the continuance of an event of default, to execute and endorse on behalf of and in the name of Debtor any assignment, bill of sale or similar document or instrument which Secured Party may deem necessary or desirable in order for Secured Party to assign, pledge, convey or otherwise sell, transfer title in or dispose of the IP Collateral, and in each case to file or record with the United States Patent and Trademark Office and/or state or local government office, as applicable, in the name of and on behalf of Grantor any such assignment or bill of sale or other document executed by Secured Party, its successors and assigns, and any officer, employee, attorney or Secured Party thereof under this power of attorney. Debtor hereby unconditionally ratifies all that any person authorized under this power of attorney shall lawfully do or cause to be done by virtue hereof and in accordance with the terms hereof. This power of attorney is coupled with an interest and cannot be revoked until the Termination.

SECTION 7. Counterparts. This Agreement may be executed in counterparts, each of which will be deemed an original, but all of which together constitute one and the same original.

SECTION 8. Governing Law. This IP Security Agreement shall be governed by, and construed in accordance with, the laws of the District of Columbia. If any part of this Agreement is contrary to, prohibited by, or deemed invalid under Applicable Laws or regulations, such provision shall be inapplicable and deemed omitted to the extent so contrary, prohibited or invalid, but the remainder hereof shall not be invalidated thereby and shall be given effect so far as possible. This Agreement shall be binding upon and inure to the benefit of Debtor and Secured Party, and their respective successors and assigns, except that Debtor may not assign or transfer any of its rights or obligations under this Agreement without the prior written consent of Secured Party.

[SIGNATURE PAGES FOLLOW]

IN WITNESS WHEREOF, the parties hereto have caused this Intellectual Property Security Agreement to be duly executed and delivered by their respective officers thereunto duly authorized as of the Effective Date of December 31, 2018.

DEBTOR:

BIOSUCCESS BIOTECH CO., LTD.

By: _____
Name: Fred Wu
Title: CEO

SECURED PARTY:

SUGHRUE MION, PLLC

By: _____
Name: John F. Rabena
Title: Managing Partner

Schedule A
To Intellectual Property Security Agreement

Debtor's U.S. Issued Patents

Title	Patent No.	Application No.	Issued (MM/DD/YYYY)
COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS	9,132,113	13/794,467	09/15/2015
COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS	9,603,825	14/824,688	03/28/2017
COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS	9,907,775	15/429,311	03/06/2018
COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS IN THE TREATMENT OF NEOPLASMS	9,974,764	14/026,473	05/22/2018
COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS FOR THE TREATMENT OF STROKE	9,533,938	14/026,534	01-03-2017
COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS FOR THE TREATMENT OF STROKE	10,010,519	15/358,388	07-03-2018
COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS FOR THE TREATMENT OF STROKE	9,550,722	14/025,176	01-24-2017
COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS	9,636,317	14/027,320	05-02-2017
COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS	9,750,713	15/154,100	09-05-2017

Debtor's U.S. Pending Patent Applications

Title	Appl. No.	Publication No.	Filing Date
COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS IN THE TREATMENT OF NEOPLASMS	15/938,182	2018-0214409	03-28-2018
COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS IN THE TREATMENT OF NEOPLASMS	14/025,206	2016-0332955 and 2015-0072960	09-12-2013
COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS IN THE TREATMENT OF NEOPLASMS	16/127,315		09-11-2018
COMPOSITIONS AND METHODS OF	13/745,742	2014-0140979	01-18-2013

USE OF PHORBOL ESTERS FOR THE TREATMENT OF STROKE			
COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS FOR THE TREATMENT OF STROKE	15/991,596		05-29-2018
COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS	13/745,740	2016-0106698 and 2014-0206762	01-18-2013
COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS	15/658,730	2017-0319533	07-25-2017
COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS FOR THE TREATMENT OF STROKE	15/371,787	2017-0087112	12-07-2016
COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS	14/025,163	2018-0256529 and 2015-0071874	09-12-2013
PHORBOL ESTER COMPOSITIONS AND METHODS OF USE FOR TREATING OR REDUCING THE DURATION OF CYTOPENIA	14/930,849	2016-0120836	11-03-2015
PHORBOL ESTER COMPOSITIONS AND METHODS OF USE FOR TREATING OR REDUCING THE DURATION OF CYTOPENIA	15/495,163	2017-0224648	04-24-2017

US 20140206762A1

(19) **United States**

(12) **Patent Application Publication**

Han et al.

(10) **Pub. No.: US 2014/0206762 A1**

(43) **Pub. Date: Jul. 24, 2014**

(54) **COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS**

(71) Applicants: **Zheng Tao Han**, Zhengzhou (CN); **Hung-Fong Chen**, Taipei (TW)

(72) Inventors: **Zheng Tao Han**, Zhengzhou (CN); **Hung-Fong Chen**, Taipei (TW)

(21) Appl. No.: **13/745,740**

(22) Filed: **Jan. 18, 2013**

Publication Classification

(51) **Int. Cl.**

A61K 31/215 (2006.01)

A61K 45/06 (2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/215*** (2013.01); ***A61K 45/06*** (2013.01)

USPC **514/510**; 560/194

(57) **ABSTRACT**

Methods and compositions containing a phorbol ester or a derivative of a phorbol ester are provided for the treatment of chronic and acute conditions. Such conditions may be caused by disease, be symptoms or sequelae of disease. Chronic and acute conditions may be due to viral infections such as HIV and AIDS, neoplastic diseases stroke, kidney disease, urinary incontinence, autoimmune disorders, Parkinson's disease, prostate hypertrophy, aging, or the treatment of such diseases. Additional compositions and methods are provided which employ a phorbol ester or derivative compound in combination with at least one additional agent to yield more effective treatment tools against acute and chronic conditions in mammalian subjects.

COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS

RELATED APPLICATIONS

[0001] This application is a United States Continuation-In-Part of U.S. patent application Ser. No. 12/023,753, filed Jan. 31, 2008, which claims priority benefit of U.S. Provisional Patent Application Ser. No. 60/898,810, filed Jan. 31, 2007, U.S. Provisional Patent Application Ser. No. 61/588,162, filed Jan. 18, 2012, U.S. Provisional Patent Application Ser. No. 61/588,165, filed Jan. 18, 2013, and U.S. Provisional Patent Application Ser. No. 61/588,167, each of which is incorporated herein in its entirety by reference.

TECHNICAL FIELD

[0002] The present invention relates generally to the medicinal use of phorbol esters.

BACKGROUND

[0003] Plants have historically served many medicinal purposes. The World Health Organization (WHO) estimates that 4 billion people, 80% of the world population, presently use herbal medicine for some aspect of primary health care. (WHO Fact sheet Fact sheet No 134 December 2008) However, it can be difficult to isolate the specific compound that has the medicinal effect and to reproduce it on a commercial scale. Additionally, while active compounds may be isolated from a plant, the other parts of a plant such as the minerals, vitamins, volatile oils, glycosides, alkaloids, bioflavanoids, and other substances may also be involved in the functioning of the active ingredient, or the medicinal effect for which the plant is known making the use, purification and commercialization of plant based pharmaceutical agents a challenge.

[0004] Phorbol is a natural, plant-derived organic compound of the tigliane family of diterpenes. It was first isolated in 1934 as a hydrolysis product of croton oil derived from the seeds of *Croton tiglium*, a leafy shrub of the Euphorbiaceae family that is native to Southeastern Asia. Various esters of phorbol have important biological properties including the reported ability to mimic diacylglycerols and activate protein kinase C N, Rosenmund C., J Cell Sci; 115:4399-411 (2002)). Some phorbol esters also induce nuclear factor-kappa B (NF-κB). The most notable physiological property of phorbol esters is their reported capacity to act as tumor promoters. (Blumberg, 1988; Goel, G et al., Int, Journal of Toxicology 26, 279-288 (2007)).

[0005] 12-O-tetradecanoylphorbol-13-acetate (TPA), also called phorbol-12-myristate-13-acetate (PMA), is a phorbol ester used in models of carcinogenesis as an inducer for differentiation and/or apoptosis in multiple cell lines and primary cells. TPA has also been reported to cause an increase in circulating white blood cells and neutrophils in patients whose bone marrow function has been depressed by chemotherapy (Han Z. T. et al. Proc. Natl. Acad. Sci. 95, 5363-5365 (1998)) and inhibit the HIV-cytopathic effects on MT-4 cells. (Mekkawy S. et al., Phytochemistry 53, 47-464 (2000)). However, due to a variety of factors, including caustic reactions when contacted with the skin and concerns for its potential toxicity, TPA has not been shown to be an effective tool for treating, managing, or preventing HIV or AIDS or as an adjuvant to chemotherapy. Indeed, as phorbol esters play a key role in activation of protein kinase C (PKC), which triggers various cellular responses resulting in inflammatory responses and tumor development (Goel et al., Int, Journal of Toxicology 26, 279-288 (2007)), phorbol esters would generally be excluded from possible treatment candidates for cancer or inflammatory diseases such as rheumatoid arthritis or conditions that involve inflammatory reactions such as stroke, autoimmune disorders or prostate hypertrophy.

[0006] As modern medicine has developed, survival rates from both chronic and acute disease has increased, generating new challenges in managing both chronic conditions and the sequelae of acute disease and treatment side effects. There is a continuing need for the identification of pharmaceutical agents, including plant based pharmaceutical agents, which can be used to treat disease, prevent damage from acute episodes, manage the symptoms of disease conditions, and manage the side effects of disease treatments. While molecular targeting has produced a number of successful pharmaceutical agents, frequently multiple pathways of signaling are involved, and blocking one pathway can easily be compensated for elsewhere. There is clearly a need for new and more effective treatments and side effect management for individuals suffering from a variety of conditions, particularly chronic or potentially recurring conditions such as cancer, immune disorders, autoimmune disorders, stroke, rheumatoid arthritis, inflammation, uterine fibroids, prostate hypertrophy, urinary incontinence, Parkinson's disease and kidney disease.

SUMMARY

[0007] The present invention relates to compositions containing and methods of using phorbol esters. These compositions and methods are effective in treating chronic or potentially recurring conditions, or to repair the damage left by acute episodes of particular diseases.

[0008] In one embodiment, phorbol esters and derivatives of phorbol esters are used to treat diseases such as HIV and associated conditions such as AIDS. The compositions and methods of the present invention may accomplish the treatment of HIV and associated conditions such as AIDS by any means possible. In some embodiments, the compositions and methods may modify HIV receptor activity in mammalian subjects. In another embodiment, the compositions and methods as described herein may decrease the number of latent HIV reservoirs in an HIV-infected subject. In a further embodiment, the compositions and methods as described herein may enhance HIV activation in latent pro-viral cells. In additional embodiments, they may inhibit HIV-cytopathic effects.

[0009] In another embodiment, compositions containing phorbol esters and phorbol ester derivatives may be used for treating and managing symptoms of HIV and AIDS in mammalian subjects. Targeted symptoms for treatment and management employing the compositions and methods described herein include, but are not limited to, oral lesions, fatigue, skin thrush, fever, lack of appetite, diarrhea, apthous ulcers, malabsorbtion, thrombocytopenia, weight loss, anemia, lymph node enlargement, susceptibility to and severity of secondary conditions such as mycobacterium avium complex, salmonellosis, syphilis, neuroshyphilis, tuberculosis (TB), bacillary angiomatosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, pelvic inflammatory disease, Burkitt's lymphoma, cryptococcal meningitis, histoplasmosis, Kaposi's sarcoma, lymphoma, systemic non-Hodgkin's lymphoma (NHL), primary CNS lymphoma, cryptosporidiosis, isosporiasis, microsporidiosis, pneumocystis carinii pneumonia (PCP), toxoplasmosis, cytomegalovirus (CMV),

hepatitis, herpes simplex, herpes zoster, human papiloma virus (HPV, genital warts, cervical cancer), molluscum contagiosum, oral hairy leukoplakia (OHL), and progressive multifocal leukoencephalopathy (PML).

[0010] In a further embodiment, compounds containing phorbol esters and derivatives of phorbol esters may be used to treat neoplastic diseases. Such neoplasms may be malignant or benign. In some embodiments, neoplasms may be solid or non-solid cancers. In other embodiments, the neoplasms may be relapses. In another embodiment, the neoplasms may be refractory. Exemplary neoplasms include, but are not limited to, hematologic malignancies/bone marrow disorders, including, but not limited to, leukemia, including acute myeloid leukemia (AML), chronic myeloid leukemia (CML), chronic myeloid leukemia blast crisis, myelodysplasia, and myeloproliferative syndrome; lymphoma, including Hodgkin's and non-Hodgkin's lymphoma; subcutaneous adenocarcinoma; ovarian teratocarcinoma; liver cancer; breast cancer; bone cancer; lung cancer; pancreatic, non-small cell lung cancer and prostate cancer. Other neoplastic conditions amenable to treatment using the methods and compositions as described herein include other cancer disorders and conditions, including solid tumors of various types. Successful treatment and/or remission will be determined according to conventional methods, such as determining size reduction of solid tumors, and/or histopathological studies to assess growth, stage, metastatic state or potential, presence or expression levels of histological cancer markers, etc.

[0011] Compositions and methods herein may additionally be used treat symptoms of neoplastic disease including, but not limited to, anemia; chronic fatigue; excessive or easy bleeding, such as bleeding of the nose, gums, and under the skin; easy bruising, particularly bruising with no apparent cause; shortness of breath; petechiae; recurrent fever; swollen gums; slow healing of cuts; bone and joint discomfort; recurrent infections; weight loss; itching; night sweats; lymph node swelling; fever; abdominal pain and discomfort; disturbances in vision; coughing; loss of appetite; pain in the chest; difficulty swallowing; swelling of the face, neck and upper extremities; a need to urinate frequently, especially at night; difficulty starting urination or holding back urine; weak or interrupted flow of urine; painful or burning urination; difficulty in having an erection; painful ejaculation; blood in urine or semen; frequent pain or stiffness in the lower back, hips, or upper thighs; and weakness.

[0012] Compositions and methods herein may further be used to treat the side effects of chemotherapy and radiation therapy which are commonly used as treatments for neoplastic disease. Such side effects include, but not limited to, alopecia, nausea, vomiting, poor appetite, soreness, neutropenia, anemia, thrombocytopenia, dizziness, fatigue, constipation, oral ulcers, itchy skin, peeling, nerve and muscle damage, auditory changes, weight loss, diarrhea, immunosuppression, bruising, heart damage, bleeding, liver damage, kidney damage, edema, mouth and throat sores, infertility, fibrosis, epilation, moist desquamation, mucosal dryness, vertigo and encephalopathy.

[0013] In yet another embodiment, the phorbol esters and derivatives of phorbol esters as described herein may be used to modulate cell signaling pathways. Such modulation may have a variety of results, for example, in some embodiments, the use of compositions containing phorbol esters and derivatives of phorbol esters may increase white blood cell counts in mammalian subjects. In another embodiment, compositions containing phorbol esters and/or phorbol ester derivatives may alter the release of Th1 cytokines in mammalian subjects. In a further embodiment, compositions containing phorbol esters and/or phorbol ester derivatives may alter the release of interleukin 2 (IL-2) in mammalian subjects. In an additional embodiment, compositions containing phorbol esters and/or phorbol ester derivatives may alter the release of interferon in mammalian subjects. In yet another embodiment, compositions containing phorbol esters and/or phorbol ester derivatives may alter the rate of ERK phosphorylation.

[0014] In a further embodiment, the phorbol esters and derivatives of phorbol esters as described herein may be used in the prevention and treatment of stroke and damage due to stroke. Effects of stroke that may be prevented or treated by using the phorbol esters and derivatives of phorbol esters as described herein include, but are not limited to, paralysis, spatial impairment, impaired judgment, left-sided neglect, memory loss, aphasia, coordination and balance problems, nausea, vomiting, cognitive impairment, perception impairment, orientation impairment, homonymous hemianopsia and impulsivity.

[0015] In yet another embodiment, the phorbol esters and derivatives of phorbol esters as described herein may be used in the treatment of rheumatoid arthritis. Symptoms of rheumatoid arthritis that may be prevented or treated by the phorbol esters and derivatives of phorbol esters as described herein include, but are not limited to, sore joints, morning stiffness, firm bumps of tissue under the skin of the arms, fatigue, loss of energy, lack of appetite, low-grade fever or muscle and joint aches.

[0016] In additional embodiments, the phorbol esters and derivatives of phorbol esters as described herein may be used in the treatment of prostate hypertrophy. The compositions and methods as described herein may be used to prevent or treat symptoms of prostate hypertrophy including, but not limited to, dribbling at the end of urination, urinary retention, incomplete emptying of the bladder, incontinence, excessive urinary frequency, pain with urination, bloody urine, delayed urination, straining to urinate, weak urine stream or strong and sudden urge to urinate.

[0017] In a further embodiment, the phorbol esters and derivatives of phorbol esters as described herein may be used in the treatment of kidney disease.

[0018] In an additional embodiment, the phorbol esters and derivatives of phorbol esters as described herein may be used in the treatment of urinary incontinence.

[0019] In another embodiment, the phorbol esters and derivative of phorbol esters as described herein may be used in the treatment of uterine fibroids.

[0020] In another embodiment, the phorbol esters and derivative of phorbol esters as described herein may be used in the treatment of dementia.

[0021] In another embodiment, the phorbol esters and derivative of phorbol esters as described herein may be used in the treatment of diabetes.

[0022] In an embodiment, the phorbol esters and derivatives of phorbol esters as described herein may be used to decrease visible signs of aging in individuals.

[0023] In an additional embodiment, the phorbol esters and derivatives of phorbol esters as described herein may be used to decrease swelling around the eyes.

[0024] In a further embodiment, the phorbol esters and derivatives of phorbol esters as described herein may be used in the treatment of autoimmune disorders including, but not

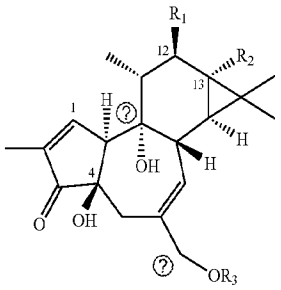
limited to, myasthenia gravis. Symptoms of myasthenia gravis that may be prevented or treated by use of the compositions and methods described herein include, but are not limited to, ptosis, diplopia, speech impairment, fatiguability, muscle weakness, dysphagia or dysarthria.

[0025] In an additional embodiment, the phorbol esters and derivatives of phorbol esters as described herein may be used in the treatment and prevention of central nervous system disorders such as Parkinson's disease. Symptoms of Parkinson's disease that may be treated or prevented by the use of the compositions and methods described herein include, but are not limited to, tremor at rest, stiffness, bradykinesia, rigidity, speech impairment, cognitive impairment, dementia, mood impairment, drowsiness, insomnia and postural instability.

[0026] In yet another embodiment, the phorbol esters and derivatives of phorbol esters as described herein may be used in the treatment and prevention of carpal tunnel syndrome.

[0027] The invention achieves the foregoing and satisfies additional objects and advantages by providing novel and surprisingly effective methods and compositions for modulating cell signaling pathways and/or treating diseases and symptoms of diseases or conditions using compositions containing a phorbol ester or derivative composition of the Formula I, below:

Formula I



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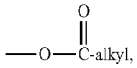
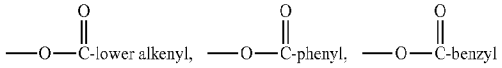
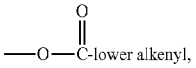
wherein R_1 and R_2 may be hydrogen;



wherein the alkyl group contains 1 to 15 carbon atoms;

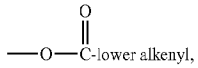


and substituted derivatives thereof and R_3 may be hydrogen or

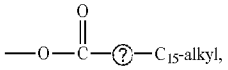


and substituted derivatives thereof.

[0028] In some embodiments, at least one of R_1 and R_2 are other than hydrogen and R_3 is hydrogen or



and substituted derivatives thereof. In another embodiment, either R_1 or R_2 is



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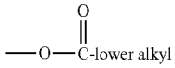
the remaining R_1 or R_2 is

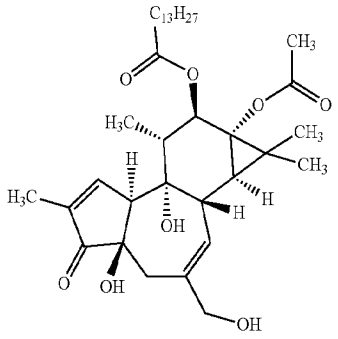


and R_3 is hydrogen.

[0029] The alkyl, alkenyl, phenyl and benzyl groups of the formulas herein may be unsubstituted or substituted with halogens, preferably, chlorine, fluorine or bromine; nitro; amino; and/or similar type radicals.

[0030] In a further embodiment, the invention achieves these objects and satisfies additional objects and advantages by providing novel and surprisingly effective methods and compositions for modulating cell signaling pathways and/or treating diseases or conditions associated with diseases using an exemplary phorbol ester composition such as 12-O-tetradecanoylphorbol-13-acetate (TPA) of Formula II, below:

Formula II



[0031] Useful phorbol esters and related compounds and derivatives within the formulations and methods of the invention include, but are not limited to, other pharmaceutically acceptable active salts of said compounds, as well as active isomers, enantiomers, polymorphs, glycosylated derivatives, solvates, hydrates, and/or prodrugs of said compounds. Exemplary forms of phorbol esters for use within the compositions and methods of the invention include, but are not limited to, phorbol 13-butyrate; phorbol 12-decanoate; phorbol 13-decanoate; phorbol 12,13-diacetate; phorbol 13,20-diacetate; phorbol 12,13-dibenzoate; phorbol 12,13-dibu-

tyrate; phorbol 12,13-didecanoate; phorbol 12,13-dihexanoate; phorbol 12,13-dipropionate; phorbol 12-myristate; phorbol 13-myristate; phorbol 12-myristate-13-acetate (also known as TPA or PMA); phorbol 12,13,20-triacetate; 12-deoxyphorbol 13-angelate; 12-deoxyphorbol 13-angelate 20-acetate; 12-deoxyphorbol 13-isobutyrate; 12-deoxyphorbol 13-isobutyrate-20-acetate; 12-deoxyphorbol 13-phenylacetate; 12-deoxyphorbol 13-phenylacetate 20-acetate; 12-deoxyphorbol 13-tetradecanoate; phorbol 12-tigliate 13-decanoate; 12-deoxyphorbol 13-acetate; phorbol 12-acetate; and phorbol 13-acetate.

[0032] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the invention include, but are not limited to, subjects with HIV and AIDS, as well as subjects with symptoms, or secondary or opportunistic diseases associated with HIV and AIDS, such as oral lesions, fatigue, skin thrush, fever, lack of appetite, diarrhea, apthous ulcers, malabsorption, thrombocytopenia, weight loss, anemia, lymph node enlargement, mycobacterium avium complex, salmonellosis, syphilis, neuroshyphilis, tuberculosis (TB), bacillary angiomatosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, pelvic inflammatory disease, Burkitt's lymphoma, cryptococcal meningitis, histoplasmosis, Kaposi's sarcoma, lymphoma, systemic non-Hodgkin's lymphoma (NHL), primary CNS lymphoma, cryptosporidiosis, isosporiasis, microsporidiosis, pneumocystis carinii pneumonia (PCP), toxoplasmosis, cytomegalovirus (CMV), hepatitis, herpes simplex, herpes zoster, human papiloma virus (HPV, genital warts, cervical cancer), molluscum contagiosum, oral hairy leukoplakia (OHL), and progressive multifocal leukoencephalopathy (PML).

[0033] Additional mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include, but are not limited to, subjects suffering from neoplastic diseases including malignant neoplastic diseases such as solid and non-solid cancers. Non-solid cancers may include, hematologic malignancies/bone marrow disorders, including, but not limited to, leukemia, including acute myeloid leukemia (AML), chronic myeloid leukemia (CML), chronic myeloid leukemia blast crisis, myelodysplasia, myeloproliferative syndrome. Solid cancers may include, but are not limited to, lymphoma, including Hodgkin's and non-Hodgkin's lymphoma, subcutaneous adenocarcinoma, ovarian teratocarcinoma, lung cancer; bone cancer; breast cancer; liver cancer; pancreatic cancer; oral cancer; non-small cell lung cancer and prostate cancer.

[0034] Subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, further include those suffering from symptoms of such neoplastic diseases such as, but not limited to, anemia; chronic fatigue; excessive or easy bleeding, such as bleeding of the nose, gums, and under the skin; easy bruising, particularly bruising with no apparent cause; shortness of breath; petechiae; recurrent fever; swollen gums; slow healing of cuts; bone and joint discomfort; recurrent infections; weight loss; itching; night sweats; lymph node swelling; fever; abdominal pain and discomfort; disturbances in vision; coughing; loss of appetite; pain in the chest; difficulty swallowing; swelling of the face, neck and upper extremities; a need to urinate frequently, especially at night; difficulty starting urination or holding back urine; weak or interrupted flow of urine; painful or burning urination; difficulty in having an erection; painful ejaculation; blood in urine or semen; frequent pain or stiffness in the lower back, hips, or upper thighs; and weakness. In some embodiments, such cancers may be relapses or refractory.

[0035] Further mammalian subjects that are amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include, but are not limited to, subjects suffering from side effects of chemotherapy or radiation therapy for the treatment of neoplastic diseases including malignant neoplastic diseases such as solid and non-solid cancers. Such side effects include, but are not limited to alopecia, nausea, vomiting, poor appetite, soreness, neutropenia, anemia, thrombocytopenia, dizziness, fatigue, constipation, oral ulcers, itchy skin, peeling, nerve and muscle damage, auditory changes, weight loss, diarrhea, immunosuppression, bruising, heart damage, bleeding, liver damage, kidney damage, edema, mouth and throat sores, infertility, fibrosis, epilation, and moist desquamation, mucosal dryness, vertigo and encephalopathy.

[0036] Additional mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods and compositions of the present invention include, but are not limited to individuals who have suffered a stroke. Subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, additionally include those suffering from the effects of a stroke including, but not limited to, paralysis, spatial impairment, impaired judgment, left-sided neglect, memory loss, aphasia, coordination and balance problems, nausea, vomiting, cognitive impairment, perception impairment, orientation impairment, homonymous hemianopsia and impulsivity.

[0037] Other mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention, include individuals suffering from rheumatoid arthritis. Symptoms of rheumatoid arthritis that may be prevented or treated by the phorbol esters of Formula I, particularly TPA, include, but are not limited to, sore joints, morning stiffness, firm bumps of tissue under the skin of the arms, fatigue, loss of energy, lack of appetite, low-grade fever or muscle and joint aches.

[0038] Additional mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention, include individuals suffering from prostate hypertrophy. The compositions and methods as described herein may be used to prevent or treat symptoms of prostate hypertrophy including, but not limited to, dribbling at the end of urination, urinary retention, incomplete emptying of the bladder, incontinence, excessive urinary frequency, pain with urination, bloody urine, delayed urination, straining to urinate, weak urine stream or strong and sudden urge to urinate.

[0039] Further mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include individuals suffering from kidney disease.

[0040] Further mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include individuals suffering from urinary incontinence.

[0041] Additional mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include individuals with visible signs of aging.

[0042] Other mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include individuals with swelling around the eyes.

[0043] Additional mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include individuals with uterine fibroids.

[0044] Additional mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include individuals with dementia.

[0045] Additional mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include individuals with diabetes.

[0046] Further mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include those suffering from autoimmune disorders including, but not limited to, myasthenia gravis. Symptoms of myasthenia gravis that may be prevented or treated by use of the compositions and methods described herein include, but are not limited to, ptosis, diplopia, speech impairment, fatiguability, muscle weakness, dysphagia or dysarthria.

[0047] Additional mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include individuals with Parkinson's disease. Symptoms of Parkinson's disease that may be treated or prevented by the use of the compositions and methods described herein include, but are not limited to, tremor at rest, stiffness, bradykinesia, rigidity, speech impairment, cognitive impairment, dementia, mood impairment, drowsiness, insomnia and postural instability.

[0048] In yet another embodiment, mammalian subjects with carpal tunnel syndrome may be treated with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention.

[0049] These and other subjects are effectively treated, prophylactically and/or therapeutically, by administering to the subject an effective amount of a phorbol ester of Formula I sufficient to prevent or reduce viral load, decrease latent reservoirs of HIV, increase immune responsiveness, increase the release of Th1 cytokines, prevent or reduce symptoms and conditions associated with HIV and AIDS, decrease and/or eliminate neoplastic cells, increase white blood cell counts, induce remission, maintain remission, prevent or reduce symptoms and conditions associated with malignancies, increase ERK phosphorylation, decrease or eliminate radiation damage, boost the immune system, decrease nausea, decrease or prevent hair loss, increase appetite, decrease soreness, increase energy levels, relieve gastrointestinal distress, decrease bruising, eliminate oral ulcers, decrease or eliminate skin damage due to radiation, increase or maintain neutrophil levels, increase or maintain platelet levels, decrease edema, decrease or eliminate moist desquamation, prevent or treat paralysis, increase spatial awareness, decrease memory loss, decrease aphasia, increase coordination and balance, improve cognition, decrease or eliminate tremors, decrease or eliminate stiffness and rigidity, improve sleep quality, increase stability, improve mobility, improve bladder control, improve appetite, ease muscle or joint aches, improve vision, and/or improve muscle control.

[0050] Therapeutically useful methods and formulations of the invention will effectively use a phorbol ester of Formula I in a variety of forms, as noted above, including any active, pharmaceutically acceptable salts of said compounds, as well as active isomers, enantiomers, polymorphs, solvates, hydrates, prodrugs, and/or combinations thereof. TPA of formula II is employed as an illustrative embodiment of the invention within the examples herein below.

[0051] Within additional aspects of the invention, combinatorial formulations and methods are provided which employ an effective amount of a phorbol ester of Formula I in combination with one or more secondary or adjunctive active agent(s) that is/are combinatorially formulated or coordinately administered with the phorbol ester compound of Formula I to yield an effective response in the subject.

[0052] Exemplary combinatorial formulations and coordinate treatment methods in the treatment of viral cytopathic diseases such as HIV and AIDS employ the phorbol ester compound of Formula I in combination with one or more additional, retroviral, HIV or AIDS treating or other indicated secondary or adjunctive therapeutic agents. Such combinatorial formulations and coordinate treatment methods may, for example, follow or be derived from various highly active antiretroviral therapy protocols (HAART protocols) and include regimens such as, but not limited to, two nucleoside analogue reverse transcriptase inhibitors plus one or more protease inhibitor or non-nucleoside analogue reverse transcriptase inhibitor among other combinations. Other combinatorial formulations and coordinate treatment methods may, for example, include treatments for opportunistic infections as well as the compounds for the HAART protocols. The secondary or adjunctive therapeutic agents used in combination with a phorbol ester, e.g., TPA, in these embodiments may possess direct or indirect antiviral effects, alone or in combination with, e.g. TPA; may exhibit other useful adjunctive therapeutic activity in combination with a phorbol ester, e.g. TPA (such as HIV preventing, HIV treating, HIV reservoir activating, Th1 cytokine increasing activity); or may exhibit adjunctive therapeutic activity useful for treating opportunistic infections associated with HIV alone or in combination with a phorbol ester, e.g. TPA.

[0053] Useful adjunctive therapeutic agents in these combinatorial formulations and coordinate treatment methods include, for example, protease inhibitors, including, but not limited to, saquinavir, indinavir, ritonavir, nelfinavir, atazanavir, darunavir, fosamprenavir, tipranavir and amprenavir; nucleoside reverse transcriptase inhibitors including but not limited to, zidovudine, didanosine, stavudine, lamivudine, zalcitabine, emtricitabine, tenofovir disoproxil fumarate, AVX754 and abacavir; non-nucleoside reverse transcriptase inhibitors including, but not limited to, nevaripine, delavirdine, calanolide A, TMC125 and efavirenz; combination drugs including, but not limited to, efavirenz/emtricitabine/tenofovir disoproxil fumarate, lamivudine/zidovudine, abacavir/lamivudine, abacavir/lamivudine/zidovudine, emtricitabine/tenofovir disoproxil fumarate, sulfamethoxazole/trimethoprim, and lopinavir/ritonavir; entry and fusion inhibitors, including, but not limited to, enfuvirtide, AMD070, BMS-488043, fozivudine tidoxil, GSK-873,140, PRO 140, PRO 542, Peptide T, SCH-D, TNX-355, and UK-427,857; treatments for opportunistic infections and other conditions associated with AIDS and HIV including, but not limited to, acyclovir, adefovir dipivoxil, aldesleukin, amphotericin b, azithromycin, calcium hydroxylapatite,

clarithromycin, doxorubicin, dronabinol, entecavir, epoetin alfa, etoposide, fluconazole, ganciclovir, immunoglobulins, interferon alfa-2, isoniazid, itraconazole, megestrol, paclitaxel, peginterferon alfa-2, pentamidine, poly-1-lactic acid, ribavirin, rifabutin, rifampin, somatropin, testosterone, trimetrexate, and valganciclovir; integrase inhibitors including, but not limited to, GS 9137, MK-0518; microbicides, including, but not limited to, BMS-378806, C31G, carbopol 974P, carrageenan, cellulose sulfate, cyanovirin-N, dextran sulfate, hydroxyethyl cellulose, PRO 2000, SPL7013, tenofovir, UC-781 and IL-2.

[0054] Exemplary combinatorial formulations and coordinate treatment methods in the treatment of neoplastic disease employ a phorbol ester compound of Formula I in combination with one or more additional, neoplastic disease treating or other indicated, secondary or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with a phorbol ester, e.g., TPA, in these embodiments may possess direct or indirect chemotherapeutic effects, alone or in combination with, e.g. TPA; may exhibit other useful adjunctive therapeutic activity in combination with a phorbol ester, e.g. TPA (such as cytotoxic, anti-inflammatory, NF-κB inhibiting, apoptosis inducing, Th1 cytokine increasing activity); or may exhibit adjunctive therapeutic activity useful for treating neoplasms or associated symptoms alone or in combination with, e.g. TPA.

[0055] Useful adjunctive or secondary therapeutic agents in these combinatorial formulations and coordinate treatment methods for the treatment of neoplastic diseases include doxorubicin, vitamin D3, cytarabine, cytosine arabinoside, daunorubicin, cyclophosphamide, gemtuzumab ozogamicin, idarubicin, mercaptopurine, mitoxantrone, thioguanine, aldesleukin, asparaginase, carboplatin, etoposide phosphate, fludarabine, methotrexate, etoposide, dexamethasone, and choline magnesium trisalicylate. In addition, adjunctive or secondary therapies may be used such as, but not limited to, radiation treatment, hormone therapy and surgery.

[0056] Exemplary combinatorial formulations and coordinate treatment methods in the prevention or treatment of side effects from chemotherapy employ a phorbol ester compound of Formula I in combination with one or more additional, chemoprotective or other indicated, secondary or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with the phorbol ester, e.g., TPA, in these embodiments may possess direct or indirect chemoprotective effects, alone or in combination with the phorbol ester, e.g. TPA; may exhibit other useful adjunctive therapeutic activity in combination with a phorbol ester, e.g. TPA (such as anti-inflammatory, neutrophil stimulating, erythropoiesis stimulating, bone resorption inhibiting, bone strengthening, antiemetic, pain relieving); or may exhibit adjunctive therapeutic activity useful for treating or preventing side effects of chemotherapy or associated symptoms alone or in combination with a phorbol ester, e.g. TPA.

[0057] Useful adjunctive or secondary therapeutic agents in these combinatorial formulations and coordinate treatment methods for the prevention or treatment of side effects of chemotherapy in a mammalian subject include, but are not limited to, pegfilgrastim, epoeitn alfa, darbepoetin alfa, alendronate sodium, risedronate, ibandronate, G-CSF, 5-HT_3 receptor antagonists, NK_1 antagonists, olanzapine, corticosteroids, dopamine antagonists, serotonin antagonists, benzodiazepines, aprepitant, and cannabinoids.

[0058] Exemplary combinatorial formulations and coordinate treatment methods in the prevention or treatment of side effects from radiation therapy as contemplated herein employ a phorbol ester compound of Formula I in combination with one or more additional, radiation protective or other indicated, secondary or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with a phorbol ester e.g., TPA, in these embodiments may possess direct or indirect protection from radiation damage, alone or in combination with a phorbol ester, e.g. TPA; may exhibit other useful adjunctive therapeutic activity in combination with the phorbol ester, e.g. TPA (such as anti-swelling, cytoprotective, anti-mucositis, epithelial stimulating, anti-fibrotic, platelet stimulating); or may exhibit adjunctive therapeutic activity useful for treating or preventing side effects of radiation therapy or associated symptoms alone or in combination with, e.g. TPA.

[0059] Useful adjunctive or secondary therapeutic agents in these combinatorial formulations and coordinate treatment methods for the prevention or treatment of side effects of radiation therapy in a mammalian subject include, but are not limited to, steroids, amifostine, chlorhexidine, benzydamine, sucralfate, keratinocyte growth factor (KGF), palifermin, Cu/Zn superoxide dismutase, Interleukin 11, or prostaglandins.

[0060] Exemplary combinatorial formulations and coordinate treatment methods in the treatment of stroke employ a phorbol ester compound of Formula I in combination with one or more additional, stroke preventing, treating or other indicated, secondary or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with a phorbol ester, e.g., TPA, in these embodiments may possess direct or indirect effects on prevention or recovery from stroke, alone or in combination with the phorbol ester, e.g. TPA; may exhibit other useful adjunctive therapeutic activity in combination with, e.g. TPA (such as anti-clotting, anticholesterolemic, vasodilating, antihypertensive); or may exhibit adjunctive therapeutic activity useful for treating or preventing stroke or associated symptoms alone or in combination with, e.g. TPA.

[0061] Useful adjunctive or secondary therapeutic agents in these combinatorial formulations and coordinate treatment methods for the prevention or treatment of stroke in a mammalian subject include, but are not limited to, tissue plasminogen activator, anticoagulant, statin, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitor, beta-blocker, calcium channel blocker, or diuretic. In addition, adjunctive or secondary therapies may be used such as, but not limited to, carotid endarterectomy, angioplasty, stent placement, craniotomy, endovascular coil emobilization, or patent foramen ovale closure.

[0062] Exemplary combinatorial formulations and coordinate treatment methods in the treatment of Parkinson's disease employ the phorbol ester compound of Formula I in combination with one or more additional, Parkinson's disease treating or other indicated, secondary, or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with a phorbol ester, e.g., TPA, in these embodiments may possess direct or indirect anti-Parkinsonian effects, alone or in combination with, e.g. TPA; may exhibit other useful adjunctive therapeutic activity in combination with, e.g. TPA (dopamine increasing, catechol-O-methyl transferase inhibiting, aromatic L-amino acid decarboxylase inhibiting, dopamine agonist, neuroprotective,

anticholinergic); or may exhibit adjunctive therapeutic activity useful for treating or preventing side effects of chemotherapy or associated symptoms alone or in combination with, e.g. TPA.

[0063] Useful adjunctive or secondary therapeutic agents in these combinatorial formulations and coordinate treatment methods for the prevention or treatment of symptoms of Parkinson's disease in a mammalian subject include, but are not limited to, levodopa, tolcapone, carbidopa, dopamine agonist, MAO-B inhibitors, pyridoxine, amantidine, pyridoxine, seleyiline, rasagiline, or anticholinergics. In addition, adjunctive or secondary therapies may be used such as, but not limited to, deep brain stimulation or lesion formation.

[0064] Exemplary combinatorial formulations and coordinate treatment methods in the treatment of prostate hypertrophy employ a phorbol ester compound of Formula I in combination with one or more additional, prostate hypertrophy treating or other indicated, secondary or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with a phorbol ester, e.g., TPA, in these embodiments may possess direct or indirect effects, alone or in combination; may exhibit other useful adjunctive therapeutic activity in combination with, e.g. TPA (type II 5-alpha reductase inhibitor, muscle relaxant); or may exhibit adjunctive therapeutic activity useful for treating or preventing prostate hypertrophy or associated symptoms alone or in combination with, e.g. TPA.

[0065] Useful adjunctive or secondary therapeutic agents in these combinatorial formulations and coordinate treatment methods for the prevention or treatment of prostate hypertrophy in a mammalian subject include, but are not limited to, finasteride, dutasteride, terazosin, doxazosin, tamsulosin, or an alpha blocker. In addition, adjunctive or secondary therapies may be used such as, but not limited to, transurethral resection of the prostate, transurethral incision of the prostate, laser surgery, or prostatectomy.

[0066] Exemplary combinatorial formulations and coordinate treatment methods in the treatment of rheumatoid arthritis employ a phorbol ester compound of Formula I in combination with one or more additional, rheumatoid arthritis treating or other indicated, secondary or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with a phorbol ester, e.g., TPA, in these embodiments may possess direct or indirect effects, alone or in combination with a phorbol ester, e.g. TPA; may exhibit other useful adjunctive therapeutic activity in combination with a phorbol ester, e.g. TPA (such as anti-inflammatory, immunosuppressing, TNF inhibiting, antibiotic, calcineurin inhibitor, pyrimidine synthesis inhibitor, 5-LO inhibitor, antifolate, IL-1 receptor antagonist, T cell costimulation inhibitor); or may exhibit adjunctive therapeutic activity useful for treating or preventing rheumatoid arthritis or associated symptoms alone or in combination with, e.g. TPA.

[0067] Useful adjunctive or secondary therapeutic agents in these combinatorial formulations and coordinate treatment methods for the prevention or treatment of rheumatoid arthritis in a mammalian subject include, but are not limited to, non-steroidal anti-inflammatory agent, steroid, disease-modifying anti-rheumatic drug, an immunosuppressant, TNF-α inhibitor, anakinra, abatacept, adalimumab, azathioprine, chloroquine, hydroxychloroquine, ciclosporin, D-penicillamine, etanercept, golimumab, gold salts, infliximab, leflunomide, methotrexate, minocycline, sulfasalazine, rituximab, or tocilizumab.

[0068] Exemplary combinatorial formulations and coordinate treatment methods in the treatment of autoimmune disorders employ a phorbol ester compound of Formula I in combination with one or more additional, autoimmune disease treating or other indicated, secondary or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with a phorbol ester, e.g., TPA, in these embodiments may possess direct or indirect effects, alone or in combination with the phorbol ester, e.g. TPA; may exhibit other useful adjunctive therapeutic activity in combination with the phorbol ester, e.g. TPA (such as immunosuppressive, antibody suppressing, anticholinesterase); or may exhibit adjunctive therapeutic activity useful for treating or preventing autoimmune disorders including myasthemia gravis or associated symptoms alone or in combination with the phorbol ester, e.g. TPA.

[0069] Useful adjunctive or secondary therapeutic agents in these combinatorial formulations and coordinate treatment methods for the prevention or treatment of autoimmune disorders in a mammalian subject include, but are not limited to, anticholinesterase, corticosteroid, or immunosuppressive agent.

[0070] Exemplary combinatorial formulations and coordinate treatment methods in the treatment of kidney disease employ the phorbol ester compound of Formula I in combination with one or more additional, kidney disease treating or other indicated, secondary or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with, e.g., TPA, in these embodiments may possess direct or indirect effects, alone or in combination with, e.g. TPA, may exhibit other useful adjunctive therapeutic activity in combination with, e.g. TPA (such as anticholinergic, antidepressant); or may exhibit adjunctive therapeutic activity useful for treating or preventing kidney disease or associated symptoms alone or in combination with, e.g. TPA.

[0071] Useful adjunctive or secondary therapeutic agents in these combinatorial formulations and coordinate treatment methods for the prevention or treatment of kidney disease in a mammalian subject include, but are not limited to, anticholinergic, topical estrogen, imipramine or duloxetine.

[0072] Exemplary combinatorial formulations and coordinate treatment methods in the treatment of urinary incontinence employ the phorbol ester compound of Formula I in combination with one or more additional, urinary incontinence treating or other indicated, secondary or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with, e.g., TPA, in these embodiments may possess direct or indirect effects, alone or in combination with, e.g. TPA, may exhibit other useful adjunctive therapeutic activity in combination with, e.g. TPA (such as anticholinergic, antidepressant); or may exhibit adjunctive therapeutic activity useful for treating or preventing urinary incontinence or associated symptoms alone or in combination with, e.g. TPA.

[0073] Useful adjunctive or secondary therapeutic agents in these combinatorial formulations and coordinate treatment methods for the prevention or treatment of urinary incontinence in a mammalian subject include, but are not limited to, anticholinergic, topical estrogen, imipramine or duloxetine.

[0074] The forgoing and additional objects, features, aspects and advantages of the present invention will become apparent from the following detailed description.

DETAILED DESCRIPTION

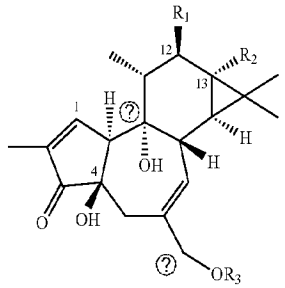
[0075] Novel methods and compositions have been identified for use in treating chronic or recurring conditions, or to repair the damage left by episodes of illness or treatment of illness in mammalian subjects, including humans.

[0076] In various embodiments, the methods and compositions are effective to prevent or treat HIV and AIDS and related conditions, diseases caused by HIV and AIDS, symptoms of HIV and AIDS, and/or diseases acquired because of HIV or AIDS infection. In other embodiments, the methods and compositions are effective to prevent or treat neoplastic diseases and symptoms of such diseases. Such neoplastic diseases may or may not be malignant. In some embodiments, the neoplastic diseases may be solid or non-solid cancers. In other embodiments, the cancers may be refractory or relapses. In additional embodiments, the methods and compositions are effective in preventing or ameliorating damage or side effects from chemotherapeutic agents. In further embodiments, the methods and compositions as described herein are effective in preventing or ameliorating damage or side effects from radiation therapy. In other embodiments, the methods and compositions as described herein are effective in preventing or treating damage from stroke. In additional embodiments, the methods and compositions as described herein are effective in treating rheumatoid arthritis. In other embodiments, the methods and compositions as described herein are effective in decreasing the signs of aging. In another embodiment, the methods and compositions as described herein are effective in treating prostate hypertrophy. In additional embodiments, the methods and compositions as described herein are effective in treating autoimmune disorders. In further embodiments, the methods and compositions a described herein are effective in treating urinary incontinence. In other embodiments, the methods and compositions as described herein are effective in treating kidney disease. In additional embodiments, the methods and compositions as described herein are effective in treating Parkinson's disease.

[0077] The composition and methods as described herein may prevent or reduce viral load, decrease latent reservoirs of HIV, increase immune responsiveness, increase the release of Th1 cytokines, prevent or reduce symptoms and conditions associated with HIV and AIDS, decrease and/or eliminate neoplastic cells, increase white blood cell counts, induce remission, maintain remission, prevent or reduce symptoms and conditions associated with malignancies, increase ERK phosphorylation, decrease or eliminate radiation damage, boost the immune system, decrease nausea, decrease or prevent hair loss, increase appetite, decrease soreness, increase energy levels, relieve gastrointestinal distress, decrease bruising, eliminate oral ulcers, decrease or eliminate skin damage due to radiation, increase or maintain neutrophil levels, increase or maintain platelet levels, decrease edema, decrease or eliminate moist desquamation, prevent or treat paralysis, increase spatial awareness, decrease memory loss, decrease aphasia, increase coordination and balance, improve cognition, decrease or eliminate tremors, decrease or eliminate stiffness and rigidity, improve sleep quality, increase stability, improve mobility, improve bladder control, increase continence, improve appetite, ease muscle or joint aches, improve vision, and/or improve muscle control, and strengthening in the immune system.

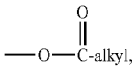
[0078] Formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I as more fully described in U.S. patent application Ser. No. 12/023,753, filed Jan. 31, 2008, which claims priority benefit of U.S. Provisional patent application Ser. No. 60/898,810, filed Jan. 31, 2007, each of which is incorporated herein in its entirety by reference,

Formula I

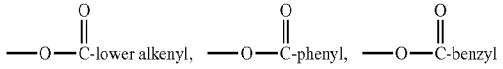


? indicates text missing or illegible when filed

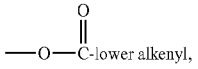
wherein R_1 and R_2 may be hydrogen;



wherein the alkyl group contains 1 to 15 carbon atoms;



and substituted derivatives thereof and R_3 may be hydrogen or



including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as novel HIV and AIDS treating compounds.

[0079] Viral load decreasing formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as novel viral load decreasing agents.

[0080] Immune responsiveness increasing formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as immune stimulatory compounds.

[0081] Th1 cytokine increasing formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as novel Th1 cytokine increasing agents.

[0082] Formulations and methods provided herein additionally employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof in the treatment of neoplastic diseases.

[0083] Apoptosis inducing formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as chemotherapeutic agents that induce apoptosis in neoplasms.

[0084] Remission inducing formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as anti-neoplasm agents.

[0085] Formulations and methods provided herein further employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof in the prevention or treatment of side effects from chemotherapy.

[0086] Formulations and methods provided herein additionally employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof in the prevention or treatment of side effects from radiation therapy.

[0087] Stroke treating formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as anti-stroke agents.

[0088] Rheumatoid arthritis treating formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as anti-rheumatoid agents.

[0089] Anti-Parkinsonian formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as anti-Parkinsonian agents.

[0090] Formulations and methods provided herein also employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof in the treatment of prostate hypertrophy.

[0091] Formulations and methods provided herein additionally employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof in the treatment of autoimmune disorders.

[0092] Formulations and methods provided herein further employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof in the treatment of carpal tunnel syndrome.

[0093] Formulations and methods provided herein additionally employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof in the treatment of kidney disease.

[0094] Continence inducing formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as continence increasing agents.

[0095] A broad range of mammalian subjects, including human subjects, are amenable to treatment using the formulations and methods of the invention. These subjects include, but are not limited to, individuals suffering from diseases or conditions including neoplastic diseases and viral diseases such as HIV and AIDS, as well as individuals suffering from Parkinson's disease, stroke, rheumatoid arthritis, side effects from chemotherapy, side effects from radiation therapy, prostate hypertrophy, urinary incontinence, Myasthemia gravis, and kidney disease.

[0096] Subjects amenable to treatment include HIV+ human and other mammalian subjects presenting with oral lesions, fatigue, skin thrush, fever, lack of appetite, diarrhea, apthous ulcers, malabsorption, thrombocytopenia, weight loss, anemia, lymph node enlargement, susceptibility to and severity of secondary conditions such as mycobacterium avium complex, salmonellosis, syphilis, neuroshyphilis, tuberculosis (TB), bacillary angiomatosis, aspergillosis, can-

didiasis, coccidioidomycosis, listeriosis, pelvic inflammatory disease, Burkitt's lymphoma, cryptococcal meningitis, histoplasmosis, Kaposi's sarcoma, lymphoma, systemic non-Hodgkin's lymphoma (NHL), primary CNS lymphoma, cryptosporidiosis, isosporiasis, microsporidiosis, pneumocystis carinii pneumonia (PCP), toxoplasmosis, cytomegalovirus (CMV), hepatitis, herpes simplex, herpes zoster, human papiloma virus (HPV, genital warts, cervical cancer), molluscum contagiosum, oral hairy leukoplakia (OHL), and progressive multifocal leukoencephalopathy (PML).

[0097] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for treating HIV/AIDS and/or related disorders. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent (s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the treatment of HIV/AIDS and related conditions.

[0098] Acquired immune deficiency syndrome or acquired immunodeficiency syndrome (AIDS or Aids) is a collection of symptoms and infections resulting from damage to the immune system caused by infection with the human immunodeficiency virus (HIV). The damage to the immune system leaves individuals prone to opportunistic infections and tumors. Although treatments for AIDS and HIV exist to slow the virus's progression and the severity of the symptoms, there is no known cure.

[0099] HIV is a retrovirus that primarily infects components of the human immure system such as CD4+ T cells, macrophages and dendritic cells. When CD4+ T cells are destroyed and their total count decreases to below 200 CD4+ T cells/μL of blood or the percentage of CD4+ T-cell as a fraction of the total lymphocytes falls to less than 14%, cellular immunity is lost, leading to AIDS.

[0100] It is currently believed that a change in the T_h1 and T_h2 cytokine balance can contribute to immune dysregulation associated with HIV infection. T_h1 cells produce cytokines that stimulate proliferation of cytotoxic T cells. T_h2 cells produce cytokines that are responsible for activation of the humoral immune responses in healthy people. Progression from HIV infection to AIDS is characterized by a decrease in levels of T_h1 cytokines IL-2, IL-12 and IFN-γ with a concomitant increase in levels of T_h2 cytokines IL-4, IL-5 and IL-10. (Clerci, Immunology Today, v. 14, No. 3, p. 107-110, 1993; Becker, Virus Genes 28:1, 5-18 (2004)). Resistance to HIV infection and/or resistance to progression to AIDS may therefore be dependent on a $T_h1>T_h2$ dominance.

[0101] A fraction of CD4+ memory T cells contain integrated transcriptionally inactive proviruses for HIV. These latent reservoirs may be activated to produce active infectious virus following activation by specific antigens or cytokines. The half life of these CD4 memory T cells is at least 44 months making it extremely difficult to eliminate HIV and requiring extended continuation of antiretroviral therapy even when HIV levels in the peripheral blood are undetectable.

[0102] Prostratin, 12-deoxyphorbol 13-acetate, a non-tumor promoting phorbol ester, has reportedly shown some effectiveness for inhibiting HIV induced cell killing and viral replication. Prostratin reportedly activated viral expression in latently-infected cell lines, but had little or no effect on chronically-infected cell lines. (Gulakowski, et al., Antiviral Research v. 33, 87-97 (1997); Williams, et al., JBC v. 279, No. 40, P. 42008-42017 (2004)). Prostratin represents a distinct subclass of protein kinase C activators which has unique biological activities that differ from tumor-promoting phorbol esters such as TPA.

[0103] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention additionally include, but are not limited to, mammalian subjects with neoplastic diseases including solid and non-solid cancers, including hematologic malignancies/bone marrow disorders, such as leukemia, including acute myeloid leukemia (AML), chronic myeloid leukemia (CML), chronic myeloid leukemia blast crisis, myelodysplasia, myeloproliferative syndrome; lymphoma, including Hodgkin's and non-Hodgkin's lymphoma; subcutaneous adenocarcinoma; ovarian teratocarcinoma; and prostate cancer. In some embodiments, such cancers may be relapses or refractory.

[0104] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for treating neoplastic diseases. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the treatment of neoplastic diseases and symptoms of such diseases.

[0105] Neoplastic disease is any growth or tumor caused by abnormal and uncontrolled cell division; it may spread to other parts of the body through the lymphatic system or the blood stream. Such growths may be malignant or benign, solid or non-solid.

[0106] In some embodiments, the neoplastic diseases may be a hematological neoplasm/bone marrow disorder such as acute myeloid leukemia (AML). AML (also called acute myelogenous leukemia, acute myeloblastic leukemia, acute granulocytic leukemia, and acute nonlymphocytic leukemia) is the most common type of acute leukemia in adults. In AML, stem cells produced by the bone marrow usually develop into a type of immature white blood cell called myeloblasts (or myeloid blasts). In individuals suffering from AML, these myeloblasts do not mature into healthy white blood cells. Additionally, stem cells in individuals with AML may develop into abnormal red blood cells or platelets. The lack of normal blood cells increases incidences of infection, anemia, and easy bleeding. Additionally, the leukemia cells can spread outside the blood to other parts of the body, including the central nervous system (brain and spinal cord), skin, and gums.

[0107] The average age of a patient with AML is over 64 years of age. Patients over the age of 60 treated for AML with

standard chemotherapeutics have a remission rate of less than 20%. Additionally, patients who develop AML after an antecedent hematologic disorder or prior leukemogenic chemotherapy/radiation therapy have similarly poor outcomes.

[0108] Chemotherapy is the treatment of cancer with an anti-neoplastic drug or combination of such drugs. Chemotherapy works by impairing the reproduction of rapidly splitting cells, a property common in cancerous cells. However it does not actively distinguish between healthy cells that are also rapidly splitting and cancerous cells and it has a number of side effects such as, but not limited to, alopecia, nausea, vomiting, poor appetite, soreness, neutropenia, anemia, thrombocytopenia, dizziness, fatigue, constipation, oral ulcers, itchy skin, peeling, nerve and muscle leprosy, auditory changes, problems with blood, weight loss, diarrhea, immunosuppression, bruising, tendency to bleed easily, heart damage, liver damage, kidney damage, vertigo and encephalopathy.

[0109] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention additionally include, but are not limited to, mammalian subjects undergoing chemotherapy.

[0110] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for preventing or treating side effects due to chemotherapy. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of side effects due to chemotherapy.

[0111] Radiation therapy uses high-energy radiation to shrink tumors and kill cancer cells. It may be applied externally, internally, or systemically. It can cause acute or chronic side effects. Acute side effects occur during treatment, and chronic side effects occur months or even years after treatment ends. The side effects that develop depend on the area of the body being treated, the dose given per day, the total dose given, the patient's general medical condition, and other treatments given at the same time. (National Cancer Institute, 2011). Common side effects of radiation therapy are moist desquamation, soreness, diarrhea, nausea, vomiting, appetite loss, constipation, itchy skin, peeling, mouth and throat sores, edema, infertility, fibrosis, epilation, and mucosal dryness.

[0112] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention additionally include, but are not limited to, mammalian subjects undergoing radiation therapy.

[0113] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for preventing or treating side effects due to radiation therapy. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of side effects due to radiation therapy.

[0114] Rheumatoid arthritis affects about 1% of the U.S. population. While the cause is unknown, it is currently believed to be caused by a combination of genetic and environmental factors. It is a chronic form of arthritis that typically occurs in joints on both sides of the body and is also considered an autoimmune disease. In rheumatoid arthritis, the immune system attaches the synovium leading to fluid buildup in the joints, causing pain and frequently systemic inflammation. While symptoms present differently in different people, it generally causes joint pain, stiffness—particularly in the morning or after sitting for long periods of time, joint swelling, fever, muscle aches, inflammation of the joints, and rheumatoid nodules.

[0115] Mammalian subjects amenable to treatment with phorbol esters of Formula. I, particularly TPA, according to the methods of the present invention additionally include, but are not limited to, mammalian subjects with rheumatoid arthritis.

[0116] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for preventing or treating symptoms of rheumatoid arthritis. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of rheumatoid arthritis and symptoms thereof.

[0117] It is estimated that 4 to 6 million people worldwide suffer from Parkinson's disease, a chronic and progressive neurodegenerative brain disorder. It is believed to have both genetic and environmental triggers, but the exact cause is unknown. May symptoms of Parkinson's disease result from a lack of dopamine and low norepinephrine levels. It is also characterized by the presence of Lewy bodies though their exact function is unknown. Parkinson's disease is characterized by tremors, bradykinesia, rigidity, speech impairment, postural instability and dementia.

[0118] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include, but are not limited to, mammalian subjects with Parkinson's disease.

[0119] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for preventing or treating Parkinson's

disease. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of Parkinson's disease and symptoms thereof.

[0120] Worldwide, stroke is the second leading cause of death, responsible for 4.4 million (9 percent) of the total 50.5 million deaths each year. (http://www.theuniversityhospital.com/stroke/stats.htm_University Hospital, Newark N.J., 2011) Ninety percent of stroke survivors suffer some type of impairment and it is the leading cause of disability among adults in the U.S. A stroke occurs when a blood vessel in the brain is blocked or bursts. Without oxygen, brain cells begin to die causing sudden numbness, tingling, weakness or loss of movement in the face, am or leg. It can also cause sudden vision changes, trouble speaking, confusion, problems with walking or balance and a sudden, severe headache. After a stroke, an individual may suffer from paralysis, spatial impairment, impaired judgment, left-sided neglect, memory loss, aphasia, coordination and balance problems, nausea, vomiting, cognitive impairment, perception impairment, orientation impairment, homonymous hemianopsia and impulsivity.

[0121] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include, but are not limited to, mammalian subjects who have suffered or are at risk for a stroke.

[0122] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for preventing or treating the effects of a stroke. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of stroke and symptoms thereof.

[0123] Prostate hypertrophy causes symptoms in more than half of men in their sixties and as many as 90 percent in their seventies and eighties. As the prostate enlarges, the layer of tissue surrounding it stops it from expanding, causing the gland to press against the urethra. The bladder wall becomes thicker and irritable and begins to contract even when it contains small amounts of urine, causing more frequent urination. Eventually, the bladder weakens and loses the ability to empty itself. (NIH Publication No. 07-3012, 2006) The most common symptoms of prostate hypertrophy are a hesitant, interrupted, weak stream; urgency and leaking or dribbling; and more frequent urination, especially at night. Additional symptoms include dribbling at the end of urination, urinary retention, incomplete emptying of the bladder, incontinence, urinary frequency, pain with urination, bloody urine, slowed or delayed urination, or straining to urinate.

[0124] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include, but are not limited to, mammalian subjects who have suffered or are at risk for prostate hypertrophy.

[0125] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for preventing or treating prostate hypertrophy. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of prostate hypertrophy and symptoms thereof.

[0126] Autoimmune disorders are conditions that occur when the immune system mistakenly attacks and destroys healthy body tissue. In individuals with an autoimmune disorder, the immune system can't tell the difference between healthy body tissue and antigens. The result is an immune response that destroys normal body tissues. In Myasthemia Gravis, antibodies are directed against the body's own proteins. The autoantibodies most commonly act against the nicotinic acetylcholine receptor (nAChR), the receptor in the motor end plate for the neurotransmitter acetylcholine that stimulates muscular contraction. (Patrick J, Lindstrom J. Autoimmune response to acetylcholine receptor. Science (1973) 180:871-2.) Symptoms of myasthemia gravis include ptosis, diplopia, speech impairment, fatigability, muscle weakness, dysphagia, or dysarthria.

[0127] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include, but are not limited to, mammalian subjects who have or are at risk for autoimmune disorders.

[0128] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for preventing or treating autoimmune disorders including myasthemia gravis. In exemplary embodiments. TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of autoimmune disorders including myasthemia gravis and symptoms thereof.

[0129] Carpal tunnel syndrome occurs when the median nerve, which runs from the forearm into the palm of the hand, becomes pressed or squeezed at the wrist. Sometimes, thickening from irritated tendons or other swelling narrows the tunnel and causes the median nerve to be compressed. The result may be pain, weakness, or numbness in the hand and wrist, radiating up the arm. Although painful sensations may indicate other conditions, carpal tunnel syndrome is the most common and widely known of the entrapment neuropathies in which the body's peripheral nerves are compressed or traumatized. (NIH Publication No. 03-4898, 2002)

[0130] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include, but are not limited to, mammalian subjects who have or are at risk for carpal tunnel syndrome.

[0131] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for preventing or treating carpal tunnel syndrome. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent (s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of carpal tunnel syndrome.

[0132] Chronic kidney disease are conditions that damage the kidneys and decrease their ability to regulate the balance of water and electrolytes, discharge metabolic waste and secreting hormones essential to human body. Symptoms of kidney disease include urinary incontinence, increased excretion of urine, uremia, and oliguria.

[0133] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include, but are not limited to, mammalian subjects who have or are at risk for kidney disease.

[0134] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for preventing or treating kidney disease. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of kidney disease and symptoms thereof.

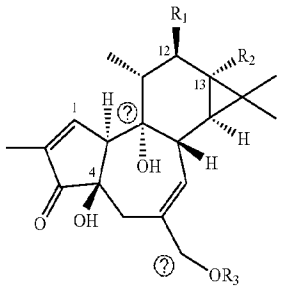
[0135] Urinary incontinence is a common and often embarrassing problem. The severity can range from occasionally leaking urine when coughing or sneezing, to losing complete control. Urinary incontinence may be caused by a variety of conditions including infection, pregnancy, aging, bladder stones, prostate cancer, bladder cancer, obstruction, prostatitis, hysterectomy, and medication. It may be transitory or permanent.

[0136] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include, but are not limited to, mammalian subjects who have or are at risk for urinary incontinence.

[0137] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for preventing or treating urinary incontinence. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of urinary incontinence and symptoms thereof.

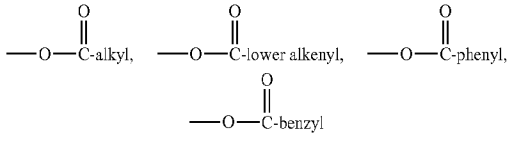
[0138] Phorbol is a natural, plant-derived polycyclic alcohol of the tigliane family of diterpenes. It was first isolated in 1934 as the hydrolysis product of croton oil derived from the seeds of *Croton tiglium*. It is well soluble in most polar organic solvents and in water. Esters of phorbol have the general structure of Formula I, below:

Formula I

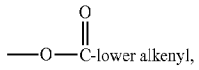


? indicates text missing or illegible when filed

wherein R_1 and R_2 are selected from the group consisting of hydrogen;



wherein the alkyl group contains 1 to 15 carbon atoms, and substituted derivatives thereof and R_3 may be hydrogen,



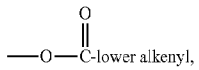
or substituted derivatives thereof.

[0139] The term "lower alkyl" or "lower alkenyl" as used herein means moieties containing 1-7 carbon atoms. In the compounds of the Formula I, the alkyl or alkenyl groups may be straight or branched chain. In some embodiments, either or both R_1 or R_2, are a long chain carbon moiety (i.e., Formula I is decanoate or myristate).

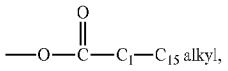
[0140] The alkyl, alkenyl, phenyl and benzyl groups of the formulas herein may be unsubstituted or substituted with halogens, preferably, chlorine, fluorine or bromine; nitro; amino and similar type radicals.

[0141] Organic and synthetic forms of phorbol esters, including any preparations or extracts from herbal sources such as *croton tiglium*, are contemplated as useful compositions comprising phorbol esters (or phorbol ester analogs, related compounds and/or derivatives) for use within the embodiments herein. Useful phorbol esters and/or related compounds for use within the embodiments herein will typically have a structure as illustrated in Formula I, although functionally equivalent analogs, complexes, conjugates, and derivatives of such compounds will also be appreciated by those skilled in the art as within the scope of the invention.

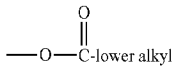
[0142] In more detailed embodiments, illustrative structural modifications according to Formula I above will be selected to provide useful candidate compounds for treating and/or preventing HIV and AIDS and/or neoplastic diseases, wherein: at least one of R_1 and R_2 are other than hydrogen and R_3 is selected from the group consisting of hydrogen



[0143] and substituted derivatives thereof. In another embodiment, either R_1 or R_2 is



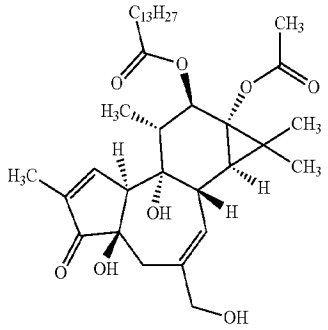
the remaining R_1 or R_2 is



and R_3 is hydrogen.

[0144] An exemplary embodiment of a phorbol ester compound of Formula I useful in the treatment of cytopathic diseases such as HIV and AIDS and/or neoplastic diseases, particularly AML, is found in phorbol 12-myristate-13-acetate (also known as PMA or 12-O-tetradecanoyl-phorbol-13-acetate (TPA)) shown in Formula II, below.

Formula II



[0145] Additional useful phorbol esters and related compounds and derivatives within the formulations and methods of the invention include, but are not limited to, other pharmaceutically acceptable active salts of said compounds, as well as active isomers, enantiomers, polymorphs, glycosylated derivatives, solvates, hydrates, and/or prodrugs of said compounds. Further exemplary forms of phorbol esters for use within the compositions and methods of the invention include, but are not limited to, phorbol 13-butyrate; phorbol 12-decanoate; phorbol 13-decanoate; phorbol 12,13-diacetate; phorbol 13,20-diacetate; phorbol 12,13-dibenzoate; phorbol 12,13-dibutyrate; phorbol 12,13-didecanoate; phorbol 12,13-dihexanoate; phorbol 12,13-dipropionate; phorbol 12-myristate; phorbol 13-myristate; phorbol 12,13,20-triacetate; 12-deoxyphorbol 13-angelate; 12-deoxyphorbol 13-angelate 20-acetate; 12-deoxyphorbol 13-isobutyrate; 12-deoxyphorbol 13-isobutyrate-20-acetate; 12-deoxyphorbol 13-phenylacetate; 12-deoxyphorbol 13-phenylacetate 20-acetate; 12-deoxyphorbol 13-tetradecanoate; phorbol 12-tigliate 13-decanoate; 12-deoxyphorbol 13-acetate; phorbol 12-acetate; and phorbol 13-acetate.

[0146] Phorbol ester compositions herein comprise HIV- and AIDS-treating compositions comprising an anti-AIDS effective amount of a phorbol ester compound of Formula I, which is effective for prophylaxis and/or treatment of HIV, AIDS, and/or HIV-related symptoms, including opportunistic infections, in a mammalian subject. An "anti-HIV", "anti-AIDS", or "AIDS treating" effective amount of the active compound is therapeutically effective, in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more symptoms of AIDS in a subject, and/or to alleviate one or more symptom(s) or condition(s) associated with HIV infection in the subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to alleviate symptoms of AIDS or other HIV-related conditions in human and other mammalian subjects vulnerable to HIV infection.

[0147] Phorbol ester compositions herein additionally may comprise chemotherapeutic compositions comprising an anti-neoplastic effective amount of a phorbol ester or derivative compound of Formula I, which is effective for maintenance and treatment of malignancies or symptoms caused by cancer in a mammalian subject. A "chemotherapeutic", "anti-tumor," "cancer treating", "apoptosis inducing", "remission inducing", "remission maintaining" effective amount of the active compound is therapeutically effective, in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more symptoms of malignancy in a subject, and/or to alleviate one

or more symptom(s) or condition(s) associated with malignancy in the subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to alleviate symptoms of neoplastic disease related conditions in human and other mammalian subjects vulnerable to malignancies.

[0148] Compositions as described herein comprise chemoprotective compositions comprising an effective amount of a phorbol ester compound of Formula I to prevent or alleviate the side effects of chemotherapy. A "chemoprotective," "anti-inflammatory," "neutrophil stimulating," "erythropoiesis stimulating," "bone resorbtion inhibiting," "bone strengthening," "antiemetic," "pain relieving" effective amount of the active compound is therapeutically effective, in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more of the side effects of chemotherapy in a subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to alleviate side effects of chemotherapy in human and other mammalian subjects undergoing chemotherapy.

[0149] Compositions as described herein comprise radiation therapy protective compositions comprising an effective amount of a phorbol ester compound of Formula I to prevent or alleviate the side effects of radiation therapy. A "radiation protective," "radioprotective," "anti-swelling," "cytoprotective," "anti-mucositis," "epithelial stimulating," "anti-fibrotic," "platelet stimulating" effective amount of the active compound is therapeutically effective, in single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more of the side effects of chemotherapy in a subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to alleviate side effects of radiation therapy in human and other mammalian subjects undergoing radiation therapy.

[0150] Compositions as described herein comprise stroke treating compositions comprising a stroke damage alleviating or preventing effective amount of a phorbol ester compound of Formula I, which is effective for prophylaxis and/or treatment of stroke or stroke related symptoms or sequelae in a mammalian subject. A "stroke treating," "anti-clotting," "anticholesterolemic," "vasodilating," "antihypertensive," or "neuroprotective" effective amount of the active compound is therapeutically effective, in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more symptoms or sequelae of stroke in the subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to prevent or alleviate symptoms of stroke or sequelae of stroke in human and other mammalian subjects vulnerable to or who have suffered a stroke.

[0151] Compositions as described herein further comprise Parkinson's disease treating compositions comprising an effective amount of a phorbol ester compound of Formula I which is effective for prophylaxis and/or treatment of Parkinson's disease or related symptoms in a mammalian subject. A "Parkinson's disease treating," "dopamine increasing," "catechol-O-methyl transferase inhibiting," "aromatic L-amino acid decarboxylase inhibiting," "dopamine agonist," "neuroprotective," or "anticholinergic" effective amount of the active compound is therapeutically effective in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate or prevent one or more of the symptoms of Parkinson's disease in the subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to prevent or alleviate symptoms of Parkinson's disease in human and other mammalian subjects suffering from or at risk for Parkinson's disease.

[0152] Compositions as described herein additionally comprise prostate hypertrophy treating compositions comprising an effective amount of a phorbol ester of a compound of Formula I, which is effective for prophylaxis and/or treatment of prostate hypertrophy or related symptoms or sequelae in a mammalian subject. A "prostate hypertrophy treating", "type II 5-alpha reductase inhibitor," or "muscle relaxant" effective amount of the active compound is therapeutically effective, in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more symptoms or sequelae of prostate hypertrophy in the subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to prevent or alleviate symptoms of prostate hypertrophy or sequelae in human and other mammalian subjects who have or are at risk for prostate hypertrophy.

[0153] Compositions as described herein further comprise rheumatoid arthritis treating compositions comprising anti-rheumatoid effective amounts of a phorbol ester of a compound of Formula I, which is effective for prophylaxis and/or treatment of rheumatoid arthritis or related symptoms in a mammalian subject. A "anti-rheumatoid," "anti-inflammatory," "immunosuppressing," "TNF inhibiting," "antibiotic," "calcineurin inhibitor," "pyrimidine synthesis inhibitor," "5-LO inhibitor," "antifolate," "IL-1 receptor antagonist," or "T cell costimulation inhibitor" effective amount of the active compound is therapeutically effective, in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more symptoms of rheumatoid arthritis in the subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to prevent or alleviate symptoms of rheumatoid arthritis in human and other mammalian subjects who have or are at risk for rheumatoid arthritis.

[0154] Compositions as described herein additionally comprise autoimmune disease treating compositions comprising an autoimmune disease treating effective amount of a phorbol ester of a compound of Formula I, which is effective for prophylaxis and/or treatment of an autoimmune disease such as myasthemia gravis or related symptoms or sequelae in a mammalian subject. An "autoimmune disorder treating," "myasthemia gravis treating," "immunosuppressive," "antibody suppressing," or "anticholinesterase" effective amount of the active compound is therapeutically effective, in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more symptoms or sequelae of autoimmune disease, specifically myasthemia gravis in the subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to prevent or alleviate symptoms of myasthemia gravis in human and other mammalian subjects who have or are at risk for myasthemia gravis.

[0155] Compositions as described herein additionally comprise kidney disease treating compositions comprising an effective amount of a phorbol ester of a compound of Formula I, which is effective for prophylaxis and/or treatment of kidney disease or related symptoms or sequelae in a mammalian subject. A "kidney disease treating," "anticholinergic," or

"antidepressant" effective amount of the active compound is therapeutically effective, in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more symptoms or sequelae of kidney disease, including incontinence in the subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to prevent or alleviate symptoms of kidney disease in human and other mammalian subjects who have or are at risk for kidney disease.

[0156] Compositions as described herein additionally comprise urinary incontinence treating compositions comprising an effective amount of a phorbol ester of a compound of Formula I, which is effective for prophylaxis and/or treatment of urinary incontinence in a mammalian subject. A "continence increasing," "anticholinergic," "antibiotic," or "antidepressant" effective amount of the active compound is therapeutically effective, in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more symptoms of urinary incontinence in the subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to prevent or alleviate symptoms of urinary incontinence in human and other mammalian subjects who have or are at risk for kidney disease.

[0157] Phorbol ester treating, including chemotherapeutic, chemoprotectant, radioprotectant, stroke mitigating, Parkinson's disease treating, prostate hypertrophy treating, rheumatoid arthritis treating, anti-aging, kidney disease treating, continence increasing, autoimmune disease treating, and HIV treating, compositions of the invention typically comprise an effective amount or unit dosage of a phorbol ester compound of Formula I, which may be formulated with one or more pharmaceutically acceptable carriers, excipients, vehicles, emulsifiers, stabilizers, preservatives, buffers, and/or other additives that may enhance stability, delivery, absorption, half-life, efficacy, pharmacokinetics, and/or pharmacodynamics, reduce adverse side effects, or provide other advantages for pharmaceutical use. Effective amounts of a phorbol ester compound or related or derivative compound of Formula I (e.g., a unit close comprising an effective concentration/amount of TPA, or of a selected pharmaceutically acceptable salt, isomer, enantiomer, solvate, polymorph and/or prodrug of TPA) will be readily determined by those of ordinary skill in the art, depending on clinical and patient-specific factors. Suitable effective unit dosage amounts of the active compounds for administration to mammalian subjects, including humans, may range from about 10 to about 1500 μg, about 20 to about 1000 μg, about 25 to about 750 μg, about 50 to about 500 μg, about 150 to about 500 μg, about 125 μg to about 500 μg, about 180 to about 500 μg, about 190 to about 500 μg, about 220 to about 500 μg, about 240 to about 500 μg, about 260 to about 500 μg, about 290 to about 500 μg. In certain embodiments, the disease treating effective dosage of a phorbol ester compound or related or derivative compound of Formula I may be selected within narrower ranges of, for example, 10 to 25 μg, 30-50 μg, 75 to 100 μg, 100 to 300 μg, or 150 to 500 μg. These and other effective unit dosage amounts may be administered in a single dose, or in the form of multiple daily, weekly or monthly doses, for example in a dosing regimen comprising from 1 to 5, or 2 to 3, doses administered per day, per week, or per month. In one exemplary embodiment, dosages of 10 to 30 μg, 30 to 50 μg, 50 to 100 μg, 100 to 300 μg, or 300 to 500 μg, are administered one, two, three, four, or five times per day. In more detailed embodiments, dosages of 50-100 μg, 100-300 μg, 300-400 μg, or 400-600 μg are administered once or twice daily. In a further embodiment, dosages of 50-100 μg, 100-300 μg, 300-400 μg, or 400-600 μg are administered every other day. In alternate embodiments, dosages are calculated based on body weight, and may be administered, for example, in amounts from about 0.5 $\mu g/m^2$ to about 300 $\mu g/m^2$ per day, about 1 $\mu g/m^2$ to about 200 $\mu g/m^2$, about 1 $\mu g/m^2$ to about 187.5 $\mu g/m^2$ per day, about 1 $\mu g/m^2$ per day to about 175 $\mu g/m^2$ per day, about 1 $\mu g/m^2$ per day to about 157 $\mu g/m^2$ per day about 1 $\mu g/m^2$ to about 125 $\mu g/m^2$ per day, about 1 $\mu g/m^2$ to about 75 $\mu g/m^2$ per day, 1 $\mu g/m^2$ to about 50 $\mu g/m^2$ per clay, 2 $\mu g/m^2$ to about 50 $\mu g/m^2$ per day, 2 $\mu g/m^2$ to about 30 $\mu g/m^2$ per day or 3 $\mu g/m^2$ to about 30 $\mu g/m^2$ per day.

[0158] In other embodiments, dosages may be administered less frequently, for example, 0.5 $\mu g/m^2$ to about 300 $\mu g/m^2$ every other day, about 1 $\mu g/m^2$ to about 200 $\mu g/m^2$, about 1 $\mu g/m^2$ to about 187.5 $\mu g/m^2$ every other day, about 1 $\mu g/m^2$ to about 175 $\mu g/m^2$ every other day, about 1 $\mu g/m^2$ per day to about 157 $\mu g/m^2$ every other day about 1 $\mu g/m^2$ to about 125 $\mu g/m^2$ every other day, about 1 $\mu g/m^2$ to about 75 $\mu g/m^2$ every other day, 1 $\mu g/m^2$ to about 50 $\mu g/m^2$ every other day, 2 $\mu g/m^2$ to about 50 $\mu g/m^2$ every other day, 2 $\mu g/m^2$ to about 30 $\mu g/m^2$ per day or 3 $\mu g/m^2$ to about 30 $\mu g/m^2$ per day. In additional embodiments, dosages may be administered 3 times/week, 4 times/week, 5 times/week, only on weekdays, only in concert with other treatment regimens, on consecutive days, or in any appropriate dosage regimen depending on clinical and patient-specific factors

[0159] The amount, timing and mode of delivery of compositions of the invention comprising a cytopathic disease treating effective amount of a phorbol ester compound of Formula I (AIDS treating, HIV preventing, HIV treating, HIV reservoir activating, Th1 cytokine increasing, ERK phosphorylation inducing, chemotherapeutic, anti-tumor, cancer treating, remission inducing, remission maintaining, apoptosis inducing effective amount) will be routinely adjusted on an individual basis, depending on such factors as weight, age, gender, and condition of the individual, the acuteness of the cytopathic disease and/or related symptoms, whether the administration is prophylactic or therapeutic, and on the basis of other factors known to effect drug delivery, absorption, pharmacokinetics, including half-life, and efficacy.

[0160] An effective dose or multi-dose treatment regimen for the instant disease treating (alternatively, "AIDS treating", "HIV treating", "HIV preventing", "HIV reservoir activating", or "Th1 cytokine increasing", "ERK phosphorylation inducing", "chemotherapeutic", "anti-tumor", "cancer treating", "apoptosis inducing", "remission inducing", "remission maintaining", "chemoprotective," "anti-inflammatory," "neutrophil stimulating," "erythropoiesis stimulating," "bone resorbtion inhibiting," "bone strengthening," "antiemetic," "pain relieving," "radiation protective," "anti-swelling," "cytoprotective," "anti-mucositis," "epithelial stimulating," "anti-fibrotic," "platelet stimulating," "stroke treating," "anti-clotting," "anticholesterolemic," "vasodilating," "antihypertensive," "Parkinson's disease treating," "dopamine increasing," "catechol-O-methyl transferase inhibiting," "aromatic L-amino acid decarboxylase inhibiting," "dopamine agonist," "neuroprotective," "anticholinergic," "prostate hypertrophy treating", "type II 5-alpha reductase inhibitor," "muscle relaxant," "anti-rheumatoid," "anti-inflammatory," "immunosuppressing," "TNF inhibiting," "antibiotic," "calcineurin inhibitor," "pyrimidine synthesis inhibitor," "5-LO inhibitor,"

"antifolate," "IL-1 receptor antagonist," "T cell costimulation inhibitor," "autoimmune disorder treating," "myasthemia gravis treating," "immunosuppressive," "antibody suppressing," "anticholinesterase" "kidney disease treating," "continence increasing," "antidepressant") formulations of the invention will ordinarily be selected to approximate a minimal dosing regimen that is necessary and sufficient to substantially prevent or alleviate the symptoms of the disease including AIDS or neoplastic diseases such as cancer and related opportunistic diseases, stroke, autoimmune disease, kidney disease, urinary incontinence, Parkinson's disease, carpal tunnel syndrome, or prostate hypertrophy, in the subject, and/or to substantially prevent or alleviate one or more symptoms associated with AIDS, neoplastic diseases such as cancer, stroke, autoimmune disease, aging, urinary incontinence, kidney disease, Parkinson's disease, carpal tunnel syndrome, prostate hypertrophy, chemotherapy treatment, or radiation treatment in the subject. A dosage and administration protocol will often include repeated dosing therapy over a course of several days or even one or more weeks or years. An effective treatment regime may also involve prophylactic dosage administered on a day or multi-dose per day basis lasting over the course of days, weeks, months or even years.

[0161] Various assays and model systems can be readily employed to determine the therapeutic effectiveness of the treatment of cytopathic diseases. For example in the treatment of HIV or AIDS effectiveness may be demonstrated by a decrease in viral load, an increase in CD4 counts, an increase in CD3 counts, an increase in IL-2 and IFN production, a decrease in IL-4 and IL-10 production, and a decrease or elimination of the symptoms of AIDS among other methods of determining effectiveness known to those of skill in the art.

[0162] Effectiveness of the compositions and methods of the invention may be demonstrated, for example, through blood tests for HIV antibodies, viral load, CD4 levels, CD8 counts, and CD3 counts. Normal levels of CD4 are usually between 600 and 1200 per microliter, or 32-68% of lymphocytes. Individuals with a CD4 count of less than 350 have a weakened immune system. Those with a CD4 count of less than 200 are considered to have AIDS. CD8 levels in a healthy individual are generally between 150-1000 per microliter. CD3 levels in a healthy individual are generally between about 885-2270 per microliter. Levels of CD3, CD4 and CD8 cells may be measured, for example, using flow cytometry. Effective amounts of the compositions of the invention will increase levels of CD3, CD4 and CD8 positive cells by at least 10%, 20%, 30%, 50% or greater reduction, up to a 75-90%, or 95% or greater. Effective amounts will also move the CD3, CD4 and CD8 profile of an individual towards the optimal category for each type of glycoprotein.

[0163] Individuals may also be evaluated using a $beta_2$-microglobulin ($beta_2$-M) test. $Beta_2$-microglobulin is a protein released into the blood when a cell dies. A rising $beta_2$-M blood level can be used to measure the progression of AIDS. Effective amounts of a composition of the present invention will lead to a decrease or cessation of increase in the amount of $beta_2$-M.

[0164] Effectiveness may further be demonstrated using a complete blood count (CBC). The measurements taken in a CBC include a white blood cell count (WBC), a red blood cell count (RBC), the red cell distribution width, the hematocrit, and the amount of hemoglobin. Specific AIDS-related signs in a CBC include a low hematocrit, a sharp decrease in the number of blood platelets, and a low level of neutrophils. An effective amount of a composition of the present invention will increase the levels measured in a complete blood count by 10%, 20%, 30%, 50% or greater increase, up to a 75-90%, or 95% or greater. Effective amounts will also move the blood protein of an individual towards the optimal category for each type of protein.

[0165] Effectiveness of the compositions and methods of the invention may also be demonstrated by a decrease in the symptoms of HIV or AIDS including, but not limited to, oral lesions, fatigue, skin thrush, fever, lack of appetite, diarrhea, apthous ulcers, malabsorption, thrombocytopenia, weight loss, anemia, and lymph node enlargement.

[0166] Effectiveness of the compositions and methods of the invention may also be demonstrated by a decrease in the susceptibility to and severity of secondary or opportunistic conditions such as mycobacterium avium complex, salmonellosis, syphilis, neuroshyphilis, tuberculosis (TB), bacillary angiomatosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, pelvic inflammatory disease, Burkitt's lymphoma, cryptococcal meningitis, histoplasmosis, Kaposi's sarcoma, lymphoma, systemic non-Hodgkin's lymphoma (NHL), primary CNS lymphoma, cryptosporidiosis, isosporiasis, microsporidiosis, pneumocystis carinii pneumonia (PCP), toxoplasmosis, cytomegalovirus (CMV), hepatitis, herpes simplex, herpes zoster, human papiloma virus (HPV, genital warts, cervical cancer), molluscum contagiosum, oral hairy leukoplakia (OHL), and progressive multifocal leukoencephalopathy (PML).

[0167] Effectiveness may further be demonstrated by reduction of detectable HIV in the HIV-infected subject; maintaining a normal T cell count; or maintaining normal p24 antigen levels.

[0168] Effectiveness in the treatment of neoplastic diseases may also be determined by a number of methods such as, but not limited to, ECOG Performance Scale, the Karnofsky Performance Scale, microscopic examination of blood cells, bone marrow aspiration and biopsy, cytogenetic analysis, biopsy, immunophenotyping, blood chemistry studies, a complete blood count, lymph node biopsy, peripheral blood smear, visual analysis of a tumor or lesion, or any other method of evaluating and/or diagnosing malignancies and tumor progression known to those of skill in the art.

[0169] For example, effectiveness of the compositions and methods herein in the treatment of hematologic malignancies/bone marrow disorders may be evaluated using, an absolute neutrophil count (ANC). A normal ANC is between 1,500 to 8,000/mm^3. Individuals suffering from hematologic malignancies/bone marrow disorders frequently have an ANC below 1500/mm^3, and may even reach levels below 500/mm^3. Effective amounts of the compositions and methods herein will increase an individual's ANC by 10%, 20%, 30%, 50% or greater increase, up to a 75-90%, or 95% or greater. Effective amounts may increase ANC levels above 1500/mm^3.

[0170] Effectiveness of the compositions and methods herein in the treatment of hematologic malignancies/bone marrow disorders may further be evaluated using, for example, a platelet count. A platelet count is normally between 150,000 to 450,000 platelets per microliter (×10−6/Liter). Individuals suffering from hematologic malignancies/bone marrow disorder may have platelet counts below 100,000 per microliter. Effective amounts of the compositions and methods herein will increase an individual's platelet count by

10%, 20%, 30%, 50% or greater increase, up to a 75-90%, or 95% or greater. Effective amounts may increase platelet levels above 100,000 per microliter.

[0171] Effectiveness of the compositions and methods herein in the treatment of hematologic malignancies/bone marrow disorders may additionally be evaluated, for example, by measuring the number of myeloblasts. Myeloblasts normally represent less than 5% of the cells in the bone marrow but should not be present in circulating blood. Effective amounts of the compositions and methods herein will decrease the number of myeloblasts by 10%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease. Effective amounts may decrease myeloblasts to below 5%.

[0172] Effectiveness of the compositions and methods herein in the treatment of hematologic malignancies/bone marrow disorders may further be evaluated by examining myeloblasts for the presence of Auer rods. Effective amounts of the compositions of the present invention will decrease the number of Auer rods visible by 10%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease up to the complete elimination of Auer rods.

[0173] Effectiveness of the compositions and methods of the invention may also be demonstrated by a decrease in the symptoms of subjects suffering from neoplastic disease including, but not limited to, anemia; chronic fatigue; excessive or easy bleeding, such as bleeding of the nose, gums, and under the skin; easy bruising, particularly bruising with no apparent cause; shortness of breath; petechiae; recurrent fever; swollen gums; slow healing of cuts; bone and joint discomfort; recurrent infections; weight loss; itching; night sweats; lymph node swelling; fever; abdominal pain and discomfort; disturbances in vision; coughing; loss of appetite; pair in the chest; difficulty swallowing; swelling of the face, neck and upper extremities; a need to urinate frequently, especially at night; difficulty starting urination or holding back urine; weak or interrupted flow of urine; painful or burning urination; difficulty in having an erection; painful ejaculation; blood in urine or semen; frequent pain or stiffness in the lower back, hips, or upper thighs; and weakness.

[0174] Effectiveness of the compositions and methods of the invention may also be demonstrated by a decrease in the symptoms of chemotherapeutic treatment including, but not limited to, alopecia, nausea, vomiting, poor appetite, soreness, neutropenia, anemia, thrombocytopenia, dizziness, fatigue, constipation, oral ulcers, itchy skin, peeling, nerve and muscle leprosy, auditory changes, problems with blood, weight loss, diarrhea, immunosuppression, bruising, tendency to bleed easily, heart damage, liver damage, kidney damage, vertigo and encephalopathy.

[0175] Effectiveness of the compositions and methods of the invention may also be demonstrated by a decrease in the symptoms that accompany radiation therapy including, but not limited to, moist desquamation, soreness, diarrhea, nausea, vomiting, appetite loss, constipation, itchy skin, peeling, mouth and throat sores, edema, infertility, fibrosis, epilation, and mucosal dryness in comparison to others who have received similar radiotherapy treatments.

[0176] Effectiveness in the treatment of rheumatoid arthritis may be demonstrated, for example, through the use of a variety of animal models including collagen-induced arthritis, as described below in Example 30, pristane induced arthritis, adjuvant induced arthritis, streptococcal cell wall induced arthritis, ovalbumin induced arthritis, antigen induced arthritis, or the air-pouch model.

[0177] Effectiveness of the compositions and methods of the invention in the treatment of rheumatoid arthritis may also be demonstrated by a decrease in the symptoms of rheumatoid arthritis including, but not limited to, joint pain, stiffness—particularly in the morning or after sitting for long periods of time, joint swelling, fever, muscle aches, inflammation of the joints, and rheumatoid nodules.

[0178] Effectiveness of the compositions and methods of the invention in the treatment of rheumatoid arthritis may also be demonstrated by a change in the erythrocyte sedimentation rate. Individuals with rheumatoid arthritis frequently have elevated levels of erythrocyte sedimentation. An effective amount of the compositions of the invention would decrease the levels of erythrocyte sedimentation by 10%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease over the initial diagnostic levels of erythrocyte sedimentation. Effectiveness may also be demonstrated by a change in the levels of rheumatoid factor and anti-cyclic citrullinated antibodies.

[0179] Effectiveness of the compositions and methods of the invention in the treatment of Parkinson's disease may be demonstrated by a decrease in the symptoms of Parkinson's including, but not limited to, tremors, bradykinesia, rigidity, speech impairment, postural instability and dementia. Effectiveness of the phorbol ester compounds of the present invention in the treatment of Parkinson's disease may further be demonstrated by an increase in dopamine and/or norepinephrine levels. Such levels may increase 10%, 20%, 30%, 50% or greater increase, up to a 75-90%, or 95% or greater of normal levels.

[0180] Effectiveness of the compositions and methods of the invention in the treatment of Parkinson's disease may further be demonstrated by a decrease in the presence of Lewy bodies. Effectiveness may also demonstrated through the use of animal models, such as MPTP induced Parkinson's, rotenone induced Parkinson's, surgically induced Parkinson's, paraquat induced Parkinson's, 6-OHDA induced Parkinson's, or α-synuclein overexpressing mice. The use of the compositions and methods of the invention will decrease the symptoms of Parkinson's disease expressed in these models by 0%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease over control animals.

[0181] Effectiveness of the compositions and methods of the invention in the treatment of stroke may be demonstrated using a variety of model systems including temporary middle cerebral artery occlusion as shown in Example 22, permanent middle cerebral artery occlusion as shown in Example 21, endovascular filament middle cerebral artery occlusion, embolic middle cerebral artery occlusion as shown in Example 20, endothelin-1-induced constriction of arteries and veins, or cerebrocortical photothrombosis. Use of the phorbol ester compositions of the present invention will decrease the symptoms exhibited by the model systems by 0%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease over control animals.

[0182] Effectiveness of the compositions and methods of the invention in the treatment of stroke may further be demonstrated by a decrease in the symptoms exhibited in individuals who have suffered a stroke. Such symptoms include, but are not limited to, paralysis, spatial impairment, impaired judgment, left-sided neglect, memory loss, aphasia, coordination and balance problems, nausea, vomiting, cognitive impairment, perception impairment, orientation impairment, homonymous hemianopsia and impulsivity. Use of the phor-

bol ester compositions of the present invention will decrease the symptoms exhibited by individuals by 0%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease over initial states.

[0183] Effectiveness of the compositions and methods of the invention in the treatment of prostate hypertrophy may be demonstrated by a decrease in the symptoms associated with prostate hypertrophy including, but not limited to, hesitant, interrupted, weak stream; urgency and leaking or dribbling; more frequent urination; dribbling at the end of urination; urinary retention; incomplete emptying of the bladder; incontinence; urinary frequency; pain with urination; bloody urine; slowed or delayed urination; or straining to urinate. Use of the phorbol ester compositions of the present invention will decrease the symptoms exhibited by individuals by 0%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease over initial states.

[0184] Effectiveness of the compositions and methods of the invention in the treatment of prostate hypertrophy may additionally be demonstrated through the use of various tests such as post-void residual urine test, pressure flow studies or a cytoscopy. Use of the phorbol ester compositions of the present invention will decrease the amount of residual urine, or increase the pressure flow by 0%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater over the results prior to treatment with a phorbol ester compound.

[0185] Effectiveness of the compositions and methods of the invention in the treatment of Myasthemia gravis may be demonstrated by a decrease in the symptoms associated with Myasthemia gravis including, but not limited to, ptosis, diplopia, speech impairment, fatigability, muscle weakness, dysphagia, or dysarthria. Use of the phorbol ester compositions of the present invention will decrease the symptoms exhibited by individuals by 0%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease over initial states.

[0186] Effectiveness of the compositions and methods of the invention in the treatment of Myasthemia gravis may also be determined using the Tensilon test or the ice test, nerve conduction studies, Single Fibre EMG, or detection of serum antibodies to the acetylcholine receptor. Effectiveness can additionally be determined using animal models of Myasthemia gravis such as by immunizing animals with torpedo californica acetylcholine receptors (AChR) in complete Freund's adjuvant. Use of the phorbol ester compositions of the present invention will decrease the symptoms exhibited by individuals by 0%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease over initial states and/or controls.

[0187] Effectiveness of the compositions and methods of the invention in the treatment of Carpal Tunnel syndrome maybe demonstrated by a decrease in symptoms associated with carpal tunnel syndrome including, but not limited to, pain, weakness, or numbness in the hand and wrist, radiating up the arm. Use of the phorbol ester compositions of the present invention will decrease the symptoms exhibited by individuals by 0%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease over initial states.

[0188] Effectiveness of the compositions and methods of the invention in the treatment of kidney disease may be demonstrated by a decrease in symptoms associated with kidney disease including, but not limited to, urinary incontinence, increased excretion of urine, uremia, or oliguria. Use of the phorbol ester compositions of the present invention will decrease the symptoms exhibited by individuals by 0%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease over initial states.

[0189] Effectiveness of the compositions and methods of the invention in the treatment of urinary incontinence may be demonstrated by a decrease in symptoms associated with urinary incontinence. Use of phorbol ester compositions of the present invention will decrease the symptoms exhibited by individuals by 0%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease over initial states.

[0190] For each of the indicated conditions described herein, test subjects will exhibit a 10%, 20%, 30%, 50% or greater reduction, up to a 75-90%, or 96% or greater, reduction, in one or more symptom(s) caused by, or associated with, die disease, or related diseases or conditions in the subject, compared to placebo-treated or other suitable control subjects.

[0191] Within additional aspects of the invention, combinatorial disease treating ("AIDS treating," "HIV preventing," "HIV treating," "HIV reservoir activating," "Th1 cytokine increasing," "ERK phosphorylation inducing," "apoptosis inducing," "chemotherapeutic," "anti-tumor," "cancer treating," "remission inducing," "remission maintaining," "chemoprotective," "anti-inflammatory," "neutrophil stimulating," "erythropoiesis stimulating," "bone resorbtion inhibiting," "bone strengthening," "antiemetic," "pain relieving," "radiation protective," "anti-swelling," "cytoprotective," "anti-mucositis," "epithelial stimulating," "anti-fibrotic," "platelet stimulating," "stroke treating," "anti-clotting," "anticholesterolemic," "vasodilating" "antihypertensive," "incontinence increasing," "Parkinson's disease treating," "dopamine increasing," "catechol-O-methyl transferase inhibiting," "aromatic L-amino acid decarboxylase inhibiting," "dopamine agonist," "neuroprotective," "anticholinergic," "prostate hypertrophy treating", "type II 5-alpha reductase inhibitor," "muscle relaxant," "anti-rheumatoid," "anti-inflammatory," "immunosuppressing," "TNF inhibiting," "antibiotic," "calcineurin inhibitor," "pyrimidine synthesis inhibitor," "5-LO) inhibitor," "antifolate," "IL-1 receptor antagonist," "T cell co stimulation inhibitor," "autoimmune disorder treating," "myasthemia gravis treating," "antibody suppressing," "anticholinesterase" "kidney disease treating," "antidepressant") formulations and coordinate administration methods are provided which employ an effective amount of a phorbol ester compound of Formula I and one or more secondary or adjunctive agent(s) that is/are combinatorially formulated or coordinately administered with the phorbol ester compound of Formula I to yield a combined, multi-active disease treating composition or coordinate treatment method.

[0192] Exemplary combinatorial formulations and coordinate treatment methods in this context employ the phorbol ester of Formula I in combination with the one or more secondary anti-AIDS agent(s), or with one or more adjunctive therapeutic agent(s) that is/are useful for treatment or prophylaxis of the targeted (or associated) disease, condition and/or symptom(s) in the selected combinatorial formulation or coordinate treatment regimen. For most combinatorial formulations and coordinate treatment methods of the invention, a phorbol ester compound of Formula I or related or derivative compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or

coordinately useful to treat HIV/AIDS and/or one or more symptom(s) of a opportunistic or secondary disease or condition in the subject. Exemplary combinatorial formulations and coordinate treatment methods in this context employ a phorbol ester compound of Formula I in combination with one or more secondary or adjunctive therapeutic agents selected from, e.g., protease inhibitors, including, but not limited to, saquinavir, indinavir, ritonavir, nelfinavir, atazanavir, darunavir, fosamprenavir, tipranavir and amprenavir; nucleoside reverse transcriptase inhibitors including but not limited to, zidovudine, didanosine, stavudine, lamivudine, zalcitabine, emtricitabine, tenofovir disoproxil fumarate, AVX754 and abacavir; non-nucleoside reverse transcriptase inhibitors including, but not limited to, nevaripine, delavirdine, calanolide A, TMC125 and efavirenz; combination drugs including, but not limited to, efavirenz/emtricitabine/tenofovir disoproxil fumarate, lamivudine/zidovudine, abacavir/lamivudine, abacavir/lamivudine/zidovudine, emtricitabine/tenofovir disoproxil fumarate, sulfamethoxazole/trimethoprim, and lopinavir/ritonavir; entry and fusion inhibitors, including, but not limited to, enfuvirtide, AMD070, BMS-488043, fozivudine tidoxil, GSK-873,140, PRO 140, PRO 542, Peptide T, SCH-D, TNX-355, and UK-427,857; treatments for opportunistic infections and other conditions associated with AIDS and HIV including, but not limited to, acyclovir, adefovir dipivoxil, aldesleukin, amphotericin b, azithromycin, calcium hydroxylapatite, clarithromycin, doxorubicin, dronabinol, entecavir, epoetin alfa, etoposide, fluconazole, ganciclovir, immunoglobulins, interferon alfa-2, isoniazid, itraconazole, megestrol, paclitaxel, peginterferon alfa-2, pentamidine, poly-1-lactic acid, ribavirin, rifabutin, rifampin, somatropin, testosterone, trimetrexate, and valganciclovir; integrase inhibitors including, but not limited to, GS 9137, MK-0518; microbicides, including, but not limited to, BMS-378806, C31G, carbopol 974P, carrageenan, cellulose sulfate, cyanovirin-N, dextran sulfate, hydroxyethyl cellulose, PRO 2000, SPL7013, tenofovir, UC-781, and IL-2.

[0193] Additional exemplary combinatorial formulations and coordinate treatment methods may additionally employ the phorbol ester of Formula I in combination with one or more secondary anti-tumor agent(s), or with one or more adjunctive therapeutic agent(s) that is/are useful for treatment or prophylaxis of the targeted (or associated) disease, condition and/or symptom(s) in the selected combinatorial formulation or coordinate treatment regimen. For most combinatorial formulations and coordinate treatment methods of the invention, a phorbol ester compound of Formula I or related or derivative compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or coordinately useful to treat neoplastic diseases and one or more symptom(s) of a secondary disease or condition in the subject. Exemplary combinatorial formulations and coordinate treatment methods in this context employ a phorbol ester compound of Formula I in combination with one or more secondary or adjunctive therapeutic agents selected from, e.g., chemotherapeutic agents, anti-inflammatory agents, doxorubicin, vitamin D3, cytarabine, cytosine arabinoside, daunorubicin, cyclophosphamide, gemtuzumab ozogamicin, idarubicin, mercaptopurine, mitoxantrone, thioguanine, aldesleukin, asparaginase, carboplatin, etoposide phosphate, fludarabine, methotrexate, etoposide, dexamethasone, and choline magnesium trisalicylate. In addition, adjunctive or secondary therapies may be used such as, but not limited to, radiation treatment, hormone therapy and surgery.

[0194] Exemplary combinatorial formulations and coordinate treatment methods in the prevention or treatment of side effects from chemotherapy employ the phorbol ester compound of Formula I in combination with one or more additional, chemoprotective or other indicated, secondary or adjunctive therapeutic agents that is/are useful for treatment or prophylaxis of the targeted disease, condition and/or symptom(s). For most combinatorial formulations and coordinate treatment methods of the invention, a phorbol ester compound of Formula I or related or derivative compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or coordinately useful to prevent or treat side effects of chemotherapy in the subject. Exemplary combinatorial formulations and coordinate treatment methods in this context employ a phorbol ester compound of Formula I in combination with one or more secondary or adjunctive therapeutic agents selected from, pegfilgrastim, epoeitn alfa, darbepoetin alfa, alendronate sodium, risedronate, ibandronate, G-CSF, 5-HT_3 receptor antagonists, NK_1 antagonists, olanzapine, corticosteroids, dopamine antagonists, serotonin antagonists, benzodiazepines, aprepitant, and cannabinoids.

[0195] Exemplary combinatorial formulations and coordinate treatment methods in the prevention or treatment of side effects from radiation therapy employ the phorbol ester compound of Formula I in combination with one or more additional, radioprotective or other indicated, secondary or adjunctive therapeutic agents that is/are useful for treatment or prophylaxis of the targeted condition and/or symptom(s). For most combinatorial formulations and coordinate treatment methods of the invention, a phorbol ester compound of Formula I or related or derivative compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or coordinately useful to prevent or treat side effects of radiation therapy in the subject. Exemplary combinatorial formulations and coordinate treatment methods in this context employ a phorbol ester compound of Formula I in combination with one or more secondary or adjunctive therapeutic agents selected from steroids, amifostine, chlorhexidine, benzydamine, sucralfate, keratinocyte growth factor (KGF), palifermin, Cu/Zn superoxide dismutase. Interleukin 11, or prostaglandins.

[0196] Exemplary combinatorial formulations and coordinate treatment methods in the prevention or treatment of stoke employ the phorbol ester compound of Formula I in combination with one or more additional, neuroprotective or other indicated, secondary or adjunctive therapeutic agents that is/are useful for treatment or prophylaxis of the targeted disease, condition and/or symptom(s). For most combinatorial formulations and coordinate treatment methods of the invention, a phorbol ester compound of Formula I or related or derivative compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or coordinately useful to prevent or treat stroke, or the effects

of stroke. Exemplary combinatorial formulations and coordinate treatment methods in this context employ a phorbol ester compound of Formula I in combination with one or more secondary or adjunctive therapeutic agents selected from tissue plasminogen activator, an anticoagulant, a statin, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitor, beta-blocker, calcium channel blocker, or diuretic.

[0197] Exemplary combinatorial formulations and coordinate treatment methods in the prevention or treatment of Parkinson's disease employ the phorbol ester compound of Formula I in combination with one or more additional, neuroprotective or other indicated, secondary or adjunctive therapeutic agents that is/are useful for treatment or prophylaxis of the targeted disease, condition and/or symptom(s). For most combinatorial formulations and coordinate treatment methods of the invention, a phorbol ester compound of Formula I or related or derivative compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or coordinately useful to prevent or treat Parkinson's disease. Exemplary combinatorial formulations and coordinate treatment methods in this context employ a phorbol ester compound of Formula I in combination with one or more secondary or adjunctive therapeutic agents selected from MAO-B inhibitors, pyridoxine, amantidine, pyridoxine, seleyiline, rasagiline, or anticholinergics.

[0198] Exemplary combinatorial formulations and coordinate treatment methods in the prevention or treatment of prostate hypertrophy employ the phorbol ester compound of Formula I in combination with one or more indicated, secondary or adjunctive therapeutic agents that is/are useful for treatment or prophylaxis of the targeted disease, condition and/or symptom(s). For most combinatorial formulations and coordinate treatment methods of the invention, a phorbol ester compound of Formula I or related or derivative compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or coordinately useful to prevent or treat prostate hypertrophy. Exemplary combinatorial formulations and coordinate treatment methods in this context employ a phorbol ester compound of Formula I in combination with one or more secondary or adjunctive therapeutic agents selected from finasteride, dutasteride, terazosin, doxazosin, tamsulosin, or an alpha blocker.

[0199] Exemplary combinatorial formulations and coordinate treatment methods in the prevention or treatment of rheumatoid arthritis employ the phorbol ester compound of Formula I in combination with one or more additional, antirheumatoid or other indicated, secondary or adjunctive therapeutic agents that is/are useful for treatment or prophylaxis of the targeted disease, condition and/or symptom(s). For most combinatorial formulations and coordinate treatment methods of the invention, a phorbol ester compound of Formula I or related or derivative compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or coordinately useful to prevent or treat rheumatoid arthritis. Exemplary combinatorial formulations and coordinate treatment methods in this context employ a phorbol ester compound of Formula I in combination with one or more secondary or adjunctive therapeutic agents selected from non-steroidal anti-inflammatory agent, steroid, disease-modifying anti-rheumatic drug, an immunosuppressant, TNF-α inhibitor, anakinra, abatacept, adalimumab, azathioprine, chloroquine, hydroxychloroquine, ciclosporin, D-penicillamine, etanercept, golimumab, gold salts, infliximab, leflunomide, methotrexate, minocycline, sulfasalazine, rituximab, or tocilizumab.

[0200] Exemplary combinatorial formulations and coordinate treatment methods in the prevention or treatment of myasthemia gravis employ the phorbol ester compound of Formula I in combination with one or more indicated, secondary or adjunctive therapeutic agents that is/are useful for treatment or prophylaxis of the targeted disease, condition and/or symptom(s). For most combinatorial formulations and coordinate treatment methods of the invention, a phorbol ester compound of Formula I or related or derivative compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or coordinately useful to prevent or treat myasthemia gravis. Exemplary combinatorial formulations and coordinate treatment methods in this context employ a phorbol ester compound of Formula I in combination with one or more secondary or adjunctive therapeutic agents selected from anticholinesterase, corticosteroid, or immunosuppressive agent.

[0201] Exemplary combinatorial formulations and coordinate treatment methods in the prevention or treatment of kidney disease employ the phorbol ester compound of Formula I in combination with one or more anti-incontinent or other indicated, secondary or adjunctive therapeutic agents that is/are useful for treatment or prophylaxis of the targeted disease, condition and/or symptom(s). For most combinatorial formulations and coordinate treatment methods of the invention, a phorbol ester compound of Formula I or related or derivative compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or coordinately useful to prevent or treat kidney disease. Exemplary combinatorial formulations and coordinate treatment methods in this context employ anticholinergic, topical estrogen, imipramine or duloxetine.

[0202] In certain embodiments the invention provides combinatorial disease treating ("AIDS treating," "HIV preventing," "HIV treating," "HIV reservoir activating," "Th1 cytokine increasing," "ERK phosphorylation inducing," "apoptosis inducing," "chemotherapeutic," "anti-tumor," "cancer treating," "remission inducing," "remission maintaining," "chemoprotective," "anti-inflammatory," "neutrophil stimulating," "erythropoiesis stimulating," "bone resorbtion inhibiting," "bone strengthening," "antiemetic," "pain relieving," "radiation protective," "anti-swelling," "cytoprotective," "anti-mucositis," "epithelial stimulating," "anti-fibrotic," "platelet stimulating," "stroke treating," "anti-clotting," "anticholesterolemic," "vasodilating," "antihypertensive," "Parkinson's disease treating," "dopamine increasing," "catechol-O-methyl transferase inhibiting," "aromatic L-amino acid decarboxylase inhibiting," "dopamine agonist," "neuroprotective," "anticholinergic," "prostate hypertrophy treating", "type II 5-alpha reductase inhibitor," "muscle relaxant," "anti-rheumatoid," "anti-inflammatory," "immunosuppressing," "TNF inhibiting," "antibiotic," "calcineurin inhibitor,"

"pyrimidine synthesis inhibitor," "5-LO inhibitor," "antifolate," "IL-1 receptor antagonist," "T cell costimulation inhibitor," "autoimmune disorder treating," "myasthemia gravis treating," "immunosuppressive," "antibody suppressing," "anticholinesterase" "kidney disease treating," "antidepressant") formulations comprising a phorbol ester and one or more adjunctive agent(s) having disease treating activity. Within such combinatorial formulations, a phorbol ester of Formula I and the adjunctive agent(s) having disease treating activity will be present in a combined formulation in disease treating ("AIDS treating," "HIV preventing," "HIV treating," "HIV reservoir activating," "Th1 cytokine increasing," "ERK phosphorylation inducing," "apoptosis inducing," "chemotherapeutic," "anti-tumor," "cancer treating," "remission inducing," "remission maintaining," "chemoprotective," "anti-inflammatory," "neutrophil stimulating," "erythropoiesis stimulating," "bone resorbtion inhibiting," "bone strengthening," "antiemetic," "pain relieving," "radiation protective," "anti-swelling," "cytoprotective," "anti-mucositis," "epithelial stimulating," "anti-fibrotic," "platelet stimulating," "stroke treating," "anti-clotting," "anticholesterolemic," "vasodilating," "antihypertensive," "Parkinson's disease treating," "dopamine increasing," "catechol-O-methyl transferase inhibiting," "aromatic L-amino acid decarboxylase inhibiting," "dopamine agonist," "neuroprotective," "anticholinergic," "prostate hypertrophy treating", "type II 5-alpha reductase inhibitor," "muscle relaxant," "anti-rheumatoid," "anti-inflammatory," "immunosuppressing," "TNF inhibiting," "antibiotic," "calcineurin inhibitor," "pyrimidine synthesis inhibitor," "5-LO inhibitor," "antifolate," "IL-1 receptor antagonist," "T cell costimulation inhibitor," "autoimmune disorder treating," "myasthemia gravis treating," "continence increasing," "antibody suppressing," "anticholinesterase" "kidney disease treating," "antidepressant")) effective amounts, alone or in combination. In exemplary embodiments, a phorbol ester compound of Formula I and a non-phorbol ester agent(s) will each be present in a disease treating/preventing amount (i.e., in singular dosage which will alone elicit a detectable alleviation of symptoms in the subject). Alternatively, the combinatorial formulation may comprise one or both the phorbol ester compound of Formula I and the non-phorbol ester agents in sub-therapeutic singular dosage amount(s), wherein the combinatorial formulation comprising both agents features a combined dosage of both agents that is collectively effective in eliciting a cytopathic disease or condition symptom alleviating response. Thus, one or both of the phorbol ester of Formula I and non-phorbol ester agents may be present in the formulation, or administered in a coordinate administration protocol, at a sub-therapeutic dose, but collectively in the formulation or method they elicit a detectable decrease in symptoms of cytopathic disease in the subject. For example, in some embodiments, the combinatorial formulation may include one or more compounds from a highly active antiretroviral therapy protocol (HAART protocols) in combination with a phorbol ester, among other combinations. Other combinatorial formulations may, for example, include a phorbol ester and/or compounds effective in treating the opportunistic infections of AIDS as well as compounds from HAART protocols. In other embodiments, the combinatorial formulation may include one or more additional chemotherapeutic agents. In a further embodiment, the combinatorial formulation may include one or more additional chemoprotective agents. In other embodiments, the combinatorial formulation may include one or more radioprotective agents. In yet another embodiment, the combinatorial formulation may include one or more neuroprotective agents. In a further embodiment, the combinatorial formulation may include one or more anti-inflammatory agents or other secondary or additional therapeutic agents as described herein.

[0203] To practice coordinate administration methods of the invention, a phorbol ester compound of Formula I may be administered, simultaneously or sequentially, in a coordinate treatment protocol with one or more of the secondary or adjunctive therapeutic agents contemplated herein. Thus, in certain embodiments a compound is administered coordinately with a non-phorbol ester agent, or any other secondary or adjunctive therapeutic agent contemplated herein, using separate formulations or a combinatorial formulation as described above (i.e., comprising both a phorbol ester compound of Formula I or related or derivative compound, and a non-phorbol ester therapeutic agent). This coordinate administration may be done simultaneously or sequentially in either order, and there may be a time period while only one or both (or all) active therapeutic agents individually and/or collectively exert their biological activities.

[0204] In one embodiment, such coordinate treatment methods may, for example, follow or be derived from various highly active antiretroviral therapy protocols (HAART protocols) and include regimens such as, but not limited to, two nucleoside analogue reverse transcriptase inhibitors plus one or more protease inhibitor or non-nucleoside analogue reverse transcriptase inhibitor with a phorbol ester of Formula I, among other combinations. Other coordinate treatment methods may, for example, include a phorbol ester and/or treatments for opportunistic infections as well as compounds from HAART protocols. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary AIDS symptom decreasing, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects, as well as indirect effects.

[0205] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary HIV treating agents, or other indicated or adjunctive therapeutic agents, e.g., selected from, for example, protease inhibitors, including, but not limited to, saquinavir, indinavir, ritonavir, nelfinavir, atazanavir, darunavir, fosamprenavir, tipranavir and amprenavir; nucleoside reverse transcriptase inhibitors including but not limited to, zidovudine, didanosine, stavudine, lamivudine, zalcitabine, emtricitabine, tenofovir disoproxil fumarate, AVX754 and abacavir; non-nucleoside reverse transcriptase inhibitors including, but not limited to, nevaripine, delavirdine, calanolide A, TMC125 and efavirenz; combination drugs including, but not limited to, efavirenz/emtricitabine/tenofovir disoproxil fumarate, lamivudine/zidovudine, abacavir/lamivudine, abacavir/lamivudine/zidovudine, emtricitabine/tenofovir disoproxil fuma-

rate, sulfamethoxazole/trimethoprim, and lopinavir/ritonavir; entry and fusion inhibitors, including, but not limited to, enfuvirtide, AMD070, BMS-488043, fozivudine tidoxil, GSK-873,140, PRO 140, PRO 542, Peptide T, TNX-355, and UK-427,857; treatments for opportunistic infections and other conditions associated with AIDS and HIV including, but not limited to, acyclovir, adefovir dipivoxil, aldesleukin, amphotericin b, azithromycin, calcium hydroxylapatite, clarithromycin, doxorubicin, dronabinol, entecavir, epoetin alfa, etoposide, fluconazole, ganciclovir, immunoglobulins, interferon alfa-2, isoniazid, itraconazole, megestrol, paclitaxel, peginterferon alfa-2, pentamidine, poly-1-lactic acid, ribavirin, rifabutin, rifampin, somatropin, testosterone, trimetrexate, and valganciclovir; integrase inhibitors including, but not limited to, GS 9137, MK-0518; microbicides, including, but not limited to, BMS-378806, C31G, carbopol 974P, carrageenan, cellulose sulfate, cyanovirin-N, dextran sulfate, hydroxyethyl cellulose, PRO 2000, SPL7013, tenofovir, and UC-781, and IL-2.

[0206] In another embodiment, such coordinate treatment methods may, for example, follow or be derived from various chemotherapeutic protocols. Other coordinate treatment methods may, for example, include a phorbol ester and/or treatments for additional symptoms of neoplastic diseases. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary neoplastic disease symptom decreasing, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects as well as indirect effects.

[0207] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary cancer treating agents, or other indicated or adjunctive therapeutic agents, e.g. doxorubicin, vitamin D3, cytarabine, cytosine arabinoside, daunorubicin, cyclophosphamide, gemtuzumab ozogamicin, idarubicin, mercaptopurine, mitoxantrone, thioguanine, aldesleukin, asparaginase, carboplatin, etoposide phosphate, fludarabine, methotrexate, etoposide, dexamethasone, and choline magnesium trisalicylate.

[0208] In another embodiment, such coordinate treatment methods may, for example, follow or be derived from various palliative protocols for chemotherapy patients. Coordinate treatment methods may, for example, include a phorbol ester and/or treatments for additional side effects of chemotherapy. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary chemotherapeutic side effect alleviating, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects as well as indirect effects.

[0209] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary chemotherapeutic side affect alleviating compounds or other indicated or adjunctive therapeutic agents, e.g. pegfilgrastim, epoeitn alfa, darbepoetin alfa, alendronate sodium, risedronate, ibandronate, G-CSF, 5-HT_3 receptor antagonists, NK_1 antagonists, olanzapine, corticosteroids, dopamine antagonists, serotonin antagonists, benzodiazepines, aprepitant, and cannabinoids.

[0210] In another embodiment, such coordinate treatment methods may, for example, follow or be derived from various palliative protocols for radiation therapy patients. Coordinate treatment methods may, for example, include a phorbol ester and/or treatments for additional side effects of radiation therapy. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary radiotherapy side effect alleviating, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects as well as indirect effects.

[0211] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary radiotherapy side affect alleviating compounds or other indicated or adjunctive therapeutic agents, e.g. steroids, amifostine, chlorhexidine, benzydamine, sucralfate, keratinocyte growth factor (KGF), palifermin, Cu/Zn superoxide dismutase, Interleukin 11, or prostaglandins.

[0212] In another embodiment, such coordinate treatment methods may, for example, follow or be derived from various protocols for the treatment of stroke. Coordinate treatment methods may, for example, include a phorbol ester and/or treatments for prevention or treatment of damage caused by a stroke. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary stroke preventing or treating agent, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects as well as indirect effects.

[0213] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary stroke treating compounds or other indicated or adjunctive therapeutic

agents, e.g. tissue plasminogen activator, an anticoagulant, a statin, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitor, beta-blocker, calcium channel blocker, or diuretic. In addition, adjunctive or secondary therapies may be used in the treatment of stroke or the effects of stroke such as, but not limited to, carotid endarterectomy, angioplasty, stent placement, craniotomy, endovascular coil emobilization, or patent foramen ovale closure.

[0214] In another embodiment, such coordinate treatment methods may, for example, follow or be derived from various protocols for the treatment of Parkinson's disease. Coordinate treatment methods may, for example, include a phorbol ester and/or treatments for prevention or treatment of Parkinson's disease. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary Parkinson's disease preventing or treating agent, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects as well as indirect effects.

[0215] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary Parkinson's disease treating compounds or other indicated or adjunctive therapeutic agents, e.g. levodopa, tolcapone, carbidopa, dopamine agonist, inhibitors, pyridoxine, amantidine, pyridoxine, seleyiline, rasagiline, or anticholinergics. In addition, adjunctive or secondary therapies may be used in the treatment of Parkinson's disease such as, but not limited to, deep brain stimulation or lesion formation.

[0216] In another embodiment, such coordinate treatment methods may, for example, follow or be derived from various protocols for the treatment of prostate hypertrophy. Coordinate treatment methods may, for example, include a phorbol ester and/or treatments for prevention or treatment of prostate hypertrophy. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary prostate hypertrophy preventing or treating agent, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects as well as indirect effects.

[0217] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary prostate hypertrophy treating compounds or other indicated or adjunctive therapeutic agents, e.g. finasteride, dutasteride, terazosin, doxazosin, tamsulosin, or an alpha blacker. In addition, adjunctive or secondary therapies may be used in the treatment of prostate hypertrophy such as, but not limited to, transurethral resection of the prostate, transurethral incision of the prostate, laser surgery, or prostatectomy.

[0218] In another embodiment, such coordinate treatment methods may, for example, follow or be derived from various protocols for the treatment of rheumatoid arthritis. Coordinate treatment methods may, for example, include a phorbol ester and/or treatments for the prevention or treatment of rheumatoid arthritis. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary rheumatoid arthritis preventing or treating agent, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects as well as indirect effects.

[0219] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary rheumatoid arthritis treating compounds or other indicated or adjunctive therapeutic agents, e.g. non-steroidal anti-inflammatory agent, steroid, disease-modifying anti-rheumatic drug, an immunosuppressant, TNF-α inhibitor, anakinra, abatacept, adalimumab, azathioprine,
chloroquine, hydroxychloroquine, ciclosporin, D-penicillamine, etanercept, golimumab, gold salts, infliximab, leflunomide, methotrexate, minocycline, sulfasalazine, rituximab, or tocilizumab.

[0220] In another embodiment, such coordinate treatment methods may, for example, follow or be derived from various protocols for the treatment of autoimmune disease. Coordinate treatment methods may, for example, include a phorbol ester and/or treatments for the prevention or treatment of myasthemia gravis. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary myasthemia gravis preventing or treating agent, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects as well as indirect effects.

[0221] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary myasthemia gravis treating compounds or other indicated or adjunctive therapeutic agents, e.g. anticholinesterase, corticosteroid, or immunosuppressive agent.

[0222] In another embodiment, such coordinate treatment methods may, for example, follow or be derived from various

protocols for the treatment of kidney disease. Coordinate treatment methods may, for example, include a phorbol ester and/or treatments for the prevention or treatment of kidney disease and symptoms of kidney disease. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary kidney disease preventing or treating agent, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects as well as indirect effects.

[0223] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary kidney disease treating compounds or other indicated or adjunctive therapeutic agents, e.g. anticholinergic, topical estrogen, imipramine or duloxetine.

[0224] In another embodiment, such coordinate treatment methods may, for example, follow or be derived from various protocols for the treatment of urinary incontinence. Coordinate treatment methods may, for example, include a phorbol ester and/or treatments for the prevention or treatment of urinary incontinence. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary urinary incontinence preventing or treating agent, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects as well as indirect effects.

[0225] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary urinary incontinence treating compounds or other indicated or adjunctive therapeutic agents, e.g. anticholinergic, topical estrogen, imipramine or duloxetine.

[0226] As noted above, in all of the various embodiments of the invention contemplated herein, the disease treating methods and formulations may employ a phorbol ester compound of Formula I in any of a variety of forms, including any one or combination of the subject compound's pharmaceutically acceptable salts, solvates, isomers, enantiomers, polymorphs, solvates, hydrates, and/or prodrugs. In exemplary embodiments of the invention, TPA is employed within the therapeutic formulations and methods for illustrative purposes.

[0227] The pharmaceutical compositions of the present invention may be administered by any means that achieve their intended therapeutic or prophylactic purpose. Suitable routes of administration for the compositions of the invention include, but are not limited to, conventional delivery routes, devices and methods including injectable methods such as, but not limited to, intravenous, intramuscular, intraperitoneal, intraspinal, intrathecal, intracerebroventricular, intraarterial, subcutaneous and intranasal routes.

[0228] The compositions of the present invention may further include a pharmaceutically acceptable carrier appropriate for the particular mode of administration being employed. Dosage forms of the compositions of the present invention include excipients recognized in the art of pharmaceutical compounding as being suitable for the preparation of dosage units as discussed above. Such excipients include, without intended limitation, binders, fillers, lubricants, emulsifiers, suspending agents, sweeteners, flavorings, preservatives, buffers, wetting agents, disintegrants, effervescent agents and other conventional excipients and additives.

[0229] If desired, the compositions of the invention can be administered in a controlled release form by use of a slow release carrier, such as a hydrophilic, slow release polymer. Exemplary controlled release agents in this context include, but are not limited to, hydroxypropyl methyl cellulose, having a viscosity in the range of about 100 cps to about 100,000 cps or other biocompatible matrices such as cholesterol.

[0230] Some phorbol ester compositions of Formula I of the invention are designed for parenteral administration, e.g. to be administered intravenously, intramuscularly, subcutaneously or intraperitoneally, including aqueous and non-aqueous sterile injectable solutions which, like many other contemplated compositions of the invention, may optionally contain anti-oxidants, buffers, bacteriostats and/or solutes which render the formulation isotonic with the blood of the mammalian subject; and aqueous and non-aqueous sterile suspensions which may include suspending agents and/or thickening agents. The formulations may be presented in unit-dose or multi-close containers. Additional compositions and formulations of the invention may include polymers for extended release following parenteral administration. The parenteral preparations may be solutions, dispersions or emulsions suitable for such administration. The subject agents may also be formulated into polymers for extended release following parenteral administration. Pharmaceutically acceptable formulations and ingredients will typically be sterile or readily sterilizable, biologically inert, and easily administered. Such polymeric materials are well known to those of ordinary skill in the pharmaceutical compounding arts. Parenteral preparations typically contain buffering agents and preservatives, and injectable fluids that are pharmaceutically and physiologically acceptable such as water, physiological saline, balanced salt solutions, aqueous dextrose, glycerol or the like. Extemporaneous injection solutions, emulsions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose, as described herein above, or an appropriate fraction thereof, of the active ingredient(s).

[0231] In more detailed embodiments, compositions of the invention may comprise a phorbol ester compound of Formula I encapsulated for delivery in microcapsules, microparticles, or microspheres, prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly (methylmethacylate) microcapsules, respectively; in colloidal drug delivery systems (for example, liposomes, albumin

microspheres, microemulsions, nano-particles and nanocapsules): or within macroemulsions.

[0232] As noted above, in certain embodiments the methods and compositions of the invention may employ pharmaceutically acceptable salts, e.g., acid addition or base salts of the above-described phorbol ester compounds of Formula I and/or related or derivative compounds. Examples of pharmaceutically acceptable addition salts include inorganic and organic acid addition salts. Suitable acid addition salts are formed from acids which form non-toxic salts, for example, hydrochloride, hydrobromide, hydroiodide, sulphate, hydrogen sulphate, nitrate, phosphate, and hydrogen phosphate salts. Additional pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salts, potassium salts, cesium salts and the like; alkaline earth metals such as calcium salts, magnesium salts and the like; organic amine salts such as triethylamine salts, pyridine salts, picoline salts, ethanolamine salts, triethanolamine salts, dicyclohexylamine salts, N,N'-dibenzylethylenediamine salts and the like; organic acid salts such as acetate, citrate, lactate, succinate, tartrate, maleate, fumarate, mandelate, acetate, dichloroacetate, trifluoroacetate, oxalate, and formate salts; sulfonates such as methanesulfonate, benzenesulfonate, and p-toluenesulfonate salts; and amino acid salts such as arginate, asparaginate, glutamate, tartrate, and gluconate salts. Suitable base salts are formed from bases that form non-toxic salts, for example aluminum, calcium, lithium, magnesium, potassium, sodium, zinc and diethanolamine salts.

[0233] Other detailed embodiments, the methods and compositions of the invention for employ prodrugs of phorbol esters of Formula I. Prodrugs are considered to be any covalently bonded carriers which release the active parent drug in vivo. Examples of prodrugs useful within the invention include esters or amides with hydroxyalkyl or aminoalkyl as a substituent, and these may be prepared by reacting such compounds as described above with anhydrides such as succinic anhydride.

[0234] The invention disclosed herein will also be understood to encompass methods and compositions comprising phorbol esters of Formula I using in vivo metabolic products of the said compounds (either generated in vivo after administration of the subject precursor compound, or directly administered in the form of the metabolic product itself). Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes methods and compositions of the invention employing compounds produced by a process comprising contacting a phorbol ester compound of Formula I with a mammalian subject for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled compound of the invention, administering it parenterally in a detectable dose to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur and isolating its conversion products from the urine, blood or other biological samples.

[0235] The invention disclosed herein will also be understood to encompass diagnostic compositions for diagnosing the risk level, presence, severity, or treatment indicia of, or otherwise managing diseases including, but not limited to, neoplastic diseases including malignant neoplastic diseases such as leukemia, stroke, Parkinson's disease, myasthemia gravis, rheumatoid arthritis, kidney disease, prostate hypertrophy, and an AIDS or a related disease or condition in a mammalian subject, comprising contacting a labeled (e.g., isotopically labeled, fluorescent labeled or otherwise labeled to permit detection of the labeled compound using conventional methods) phorbol ester compound of Formula I to a mammalian subject (e.g., to a cell, tissue, organ, or individual) at risk or presenting with one or more symptom(s) of cancer, stroke, Parkinson's disease, myasthemia gravis, rheumatoid arthritis, kidney disease, prostate hypertrophy, and/or AIDS, and thereafter detecting the presence, location, metabolism, and/or binding state (e.g., detecting binding to an unlabeled binding partner involved in HIV receptor physiology/metabolism or malignant cell receptor physiology/metabolism) of the labeled compound using any of a broad array of known assays and labeling/detection methods. In exemplary embodiments, a phorbol ester compound of Formula I is isotopically-labeled by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. The isotopically-labeled compound is then administered to an individual or other subject and subsequently detected as described above, yielding useful diagnostic and/or therapeutic management data, according to conventional techniques.

EXAMPLES

[0236] The experiments described below demonstrate novel and powerful uses for phorbol esters and derivative compounds as HIV treating drugs that can effectively decrease the symptoms of AIDS. In exemplary clinical trials, individuals who were unresponsive to traditional treatments for HIV and AIDS were responsive to treatments with TPA. The treatment with TPA was allowed as "compassionate" and recovery of some patients was considered life-saving according to the attending physicians. The experiments described below additionally demonstrate the usefulness of phorbol esters and derivative compounds in the treatment of neoplastic diseases, as chemoprotectants, radioprotectants, in the treatment of stroke, Parkinson's disease, prostate hypertrophy, rheumatoid arthritis, kidney disease, urinary incontinence and myasthemia gravis. Phorbol esters have additionally provided unexpected cosmetic results in the form of decreasing the appearance of dark circles and increasing the youthfulness of the skin. These and additional findings are further expanded and elucidated within the following examples.

Example I

Effect of TPA on the Peripheral White Blood Cells (WBC) and Hemoglobin (Hb) Counts in S180 Cell-Injected Mice

[0237] Sarcoma 180 (S180) cells were injected into Kwen-Ming mice. On the third day, the mice were given TPA interperitoneally (i.p.). at 50, 100 or 200 μg/kg/day for 7 days. On the second day after the treatment was completed, blood samples were taken from the tails of the treated mice for WBC and Hb analyses. The WBC counts for the treated groups (50, 100, or 200 ug/kg/day for 7 days) were 16.1±7.4, 18.7±3.0 and $20.7\pm3.4\times10^{9}$/L, respectively; the WBC count for the

control group was $13.6\pm1.8\times10^9$/L. The Hb of the treated groups were 136±11, 149±12 and 149±10 g/L, and the Hb of the control group was 134+−15 g/L. The results indicate that i.p. injection of TPA could increase the peripheral WBC counts in mice in a dose-dependent manner, whereas the Hb levels were not greatly affected in TPA treated mice when compared to the control mice.

Example II

Dose Ranging Study

[0238] Due to the strong local irritation caused by TPA application, TPA was given to patients by intravenous (i.v.) infusion. TPA solution in a sterile syringe was injected into 200 ml of sterile saline and mixed well for i.v. infusion.

[0239] The Toxicity and Side Effects of Different TPA Doses Administered Clinically:

[0240] (1) TPA given at 1 mg/patient/week:

[0241] One mg TPA in solution was mixed well with 200 ml of sterile saline for intravenous infusion which was completed in 1 h at the rate of 16 μg/min. One hour after TPA administration, patients started to have chills which lasted for about 30 min, followed by fever, (the patients' temperature reached 37.5-39.5° C. which lasted for 3-5 h, then returned to normal) with light to heavy perspiration. The above symptoms could be alleviated by giving the patients glucocorticoids. TPA at this close caused a minority of patients to bleed, several patients suffered for a short period of time difficulty in breathing, and Hb was detected in the urine. However, these side effects were short lived and reversible. The cardiac, hepatic, renal and pulmonary functions were all found to be normal.

[0242] (2) TPA given at 0.5 mg/patient×2/week: (two doses a week)

[0243] 0.5 mg of TPA in solution was mixed well with 200 ml of saline for intravenous infusion which was completed in 1 h at the rate of 8 μg/min. The reactions after administration were similar to that of the 1 mg TPA dosage, but to a lesser extent than the 1 mg dose. The patients tolerated the lower dose more easily. Occasionally, Hb was detected in patients' urine. Difficulty in breathing was not observed. The cardiac, hepatic, renal and pulmonary functions were all normal.

[0244] (3) TPA given at 0.25 mg/patient×4/week:

[0245] 0.25 mg of TPA in solution was mixed well with 200 ml of saline for intravenous infusion which was completed in 1 h at the rate of 4 μg/min. After administration, symptoms such as chills and fever were also observed, but to a much lesser extent than with the higher dosages. No Hb was detected in the urine, and no patient suffered difficulty in breathing. The cardiac, hepatic, renal and pulmonary functions were all normal.

Example III

First Clinical Study of HIV+ Patients Treated with TPA

[0246] Twelve symptomatic patients (five males and seven females) between the ages of 35 to 52 all of whom were infected with HIV in 1995 through blood transfusion and were refractory to standard treatments for HIV were treated with TPA. Each patient was administered a weight adjusted dosage of TPA (75 μg/sq m) in 200 ml of sterile saline by i.v. over one hour. This dose was administered once daily for the first three days of treatment. Each patient was then given this dose every other day for days 4 to 18 followed by a six month rest period prior to a second course of treatment according to the same protocol.

[0247] Blood samples were gathered prior to administration of the first dose of TPA and on days 4 and 40 of the treatment cycle. Levels of CD3, CD4 and CD8 in peripheral blood were measured using monoclonal antibodies (Becton Dickson Scientific Co., Franklin Lakes, N.J.) and a flow cytometer (B.D. Bioscience, San Diego, Calif.).

[0248] As can be seen in Table 1, no consistent change or correlation was observed in CD3, CD4, or CD8 levels.

TABLE ONE

CD_4 CD_8 CD_3 TEST RESULTS OF TWELVE HIV PATIENTS

PATIENT NO	TEST TIME	CD_4	CD_8	CD_3
01-1	Before TPA	3	196	341
01-2	Four days after TPA	3	180	299
01-3	Forty two days after TPA	2	111	203
02-1	Before TPA	26	614	687
02-2	Four days after TPA	105	<2000	2616
02-3	Forty two days after TPA	54	700	799
03-1	Before TPA	32	524	543
03-2	Four days after TPA	36	366	427
03-3	Forty two days after TPA	33	374	424
04-1	Before TPA	173	735	975
04-2	Four days after TPA	123	770	941
04-3	Forty two days after TPA	44	493	581
05-1	Before TPA	106	1556	1646
05-2	Four days after TPA	119	1330	1282
05-3	Forty two days after TPA	191	1429	1643
06-1	Before TPA	232	865	1221
06-2	Four days after TPA	179	570	808
06-3	Forty two days after TPA	49	429	537
07-1	Before TPA	10	988	1022
07-2	Four days after TPA	7	570	598
07-3	Forty two days after TPA	1	139	146
08-1	Before TPA	524	725	1332
08-2	Four days after TPA	318	355	739
08-3	Forty two days after TPA	241	527	858
09-1	Before TPA	442	1021	1479
09-2	After TPA	663	<2000	2920
10-1	Before TPA	407	328	778
10-2	After TPA	445	591	1077
11-1	Before TPA	40	322	373
11-2	After TPA	131	724	874
12-1	Before TPA	84	256	375
12-2	After TPA	78	268	362

[0249] As can be seen in Table 2, below, there were similarly inconsistent results in the change of viral load with five patients having an increase in HIV and no change or a reduction in seven others.

TABLE TWO

BLOOD HIV COUNT OF THE TWELVE PATIENTS BEFORE DURING AND AFTER THE TPA TREATMENT

PATIENT NO	TEST TIME	RESULTS (copies/ml)	LOG VALUE	FOOT NOTE
01-1	3 days before TPA	3.36×10^5	5.526	
01-2	4 days after initial TPA	1.41×10^4	6.151	
01-3	15 days after initial TPA	2.02×10^4	4.306	
01-4	25 days after initial TPA	2.60×10^4	4.416	
02-1	3 days before TPA	9.97×10^4	4.999	

TABLE TWO-continued

BLOOD HIV COUNT OF THE TWELVE PATIENTS BEFORE DURING AND AFTER THE TPA TREATMENT

PATIENT NO	TEST TIME	RESULTS (copies/ml)	LOG VALUE	FOOT NOTE
02-2	4 days after initial TPA	7.92×10^6	6.899	
02-3	15 days after initial TPA	6.33×10^6	6.801	
02-4	25 days after initial TPA	8.72×10^6	6.941	
03-1	3 days before TPA	3.77×10^5	5.577	
03-2	4 days after initial TPA	8.13×10^4	4.910	
03-3	15 days after initial TPA	6.11×10^3	3.786	
03-4	25 days after initial TPA	8.59×10^5	5.934	
04-1	3 days before TPA	1.11×10^6	6.045	
04-2	4 days after initial TPA	1.75×10^7	7.243	
04-3	15 days after initial TPA	1.11×10^6	6.614	
04-4	25 days after initial TPA	1.21×10^4	4.084	
05-1	3 days before TPA	2.49×10^4	6.637	
05-2	4 days after initial TPA	9.42×10^5	5.974	
05-3	15 days after initial TPA	2.34×10^7	7.369	
05-4	25 days after initial TPA	5.56×10^6	6.745	
06-1	3 days before TPA	4.57×10^5	5.660	
06-2	4 days after initial TPA	1.44×10^4	4.160	
06-3	15 days after initial TPA	1.88×10^5	5.274	
06-4	7 days after TPA	2.28×10^6	6.357	
07-1	3 days before TPA	2.40×10^5	5.623	
07-2	4 days after initial TPA	1.51×10^5	5.179	
07-3	15th day during TPA	9.74×10^4	4.988	
07-4	25 days after initial TPA	5.30×10^3	3.724	
08-1	3 days before TPA	8.02×10^5	5.904	
08-2	4 days after initial TPA	9.09×10^5	5.959	
08-3	15 days after initial TPA	5.46×10^6	6.737	
08-4	25 days after initial TPA	7.77×10^6	6.890	
09-1	3 days before TPA	undetectable		
09-2	25 days after TPA	undetectable		
10-1	3 days before TPA	1.51×10^4	4.180	Sample taken from the
10-2	25 days after initial TPA	2.79×10^4	4.446	second cycle treatment
11-1	3 days before TPA	1.59×10^5	5.201	Sample taken from the
11-2	25 days after initial TPA	1.25×10^5	5.096	second cycle treatment
12-1	3 days before TPA	1.32×10^4	4.122	Sample taken from the
12-2	25 days after initial TPA	6.27×10^3	3.798	second cycle treatment

[0250] Despite the lack of correlation with viral and CD3, CD4 and CD9 levels, eleven of the patients showed significant improvement following treatment. Eight patients became symptom free and five of them have been in remission for 6 to 12 months. Three additional patients had a decrease in symptoms.

Example IV

Second Clinical Study of HIV+ Patients Treated with TPA

[0251] Nine of the patients in Example III were given a second treatment of TPA. Of these nine, seven were asymptomatic at the beginning of the second trial. A tenth patient (patient #2a) who was symptomatic and had not previously been treated with TPA was added to the study. Each patient was administered a weight adjusted dosage of TPA (75 μg/sq m) in 200 ml of sterile saline intravenously over one hour. This dosage was given to each patient once a day for ten consecutive days followed by a rest period of ten days for three cycles and a total of 30 doses of TPA. Patients 5a, 6a, and 8a stopped taking anti-AIDS drugs one month prior to beginning the TPA treatment and beginning again one month after the third cycle. Patients 1-4a, 7a, and 9a-10a continued taking anti-AIDS drugs throughout the treatment.

[0252] Blood samples were taken three days prior to starting treatment, after completing the first 10 day cycle of TPA infusion and again after the last TPA infusion and CD3, CD4, CD8, WBC, RBC, HGB and platelets were measured.

[0253] As shown in Table 3, there was an increase in CD3 in all patients after the first and third infusion with TPA with the highest value occurring after the third cycle, with the exception of two patients (5a & 10a). There was a trend for increases in the CD8 and in CD4. These results suggest a strengthening of the immune systems with TPA treatment. Varied results were obtained in the HIV count (Table 4). The HIV measurements in some of the patients were below the limits of detection of the method (less than 200) while it increased somewhat in others. There was normal variation in the measurement of WBC, RBC, HGB and platelets (Table 5).

TABLE THREE

CD_4 CD_8 CD_3 TEST RESULTS OF 10 HIV PATIENTS

PATIENT NO	TEST TIME	CD_4	CD_8	CD_3
01-1	Before TPA	5	576	1071
01-2	After first 10-day TPA infusion cycle	7	907	1323
01-3	After third 10-day TPA infusion cycle	19	1129	2037
02a-1	Before TPA	26	307	339
02a-2	After first 10-day TPA infusion cycle	76	335	476
02a-3	After third 10-day TPA infusion cycle	137	543	625
03a-1	Before TPA	295	571	870
03a-2	After first 10-day TPA infusion cycle	460	729	1200
03a-3	After third 10-day TPA infusion cycle	1002	980	2033
04a-1	Before TPA	152	672	896
04a-2	After first 10-day TPA infusion cycle	189	584	823
04a-3	After third 10-day TPA infusion cycle	205	916	1193
05a-1	Before TPA	92	1097	1175
05a-2	After first 10-day TPA infusion cycle	91	1507	1598
05a-3	After third 10-day TPA infusion cycle	94	1127	1257
06a-1	Before TPA	230	378	669
06a-2	After first 10-day TPA infusion cycle	285	429	758
06a-3	After third 10-day TPA infusion cycle	276	466	938
07a-1	Before TPA	567	1736	2258
07a-2	After first 10-day TPA infusion cycle	729	>2000	3148
07a-3	After third 10-day TPA infusion cycle	786	>2000	3347
08a-1	Before TPA	361	569	1023
08a-2	After first 10-day TPA infusion cycle	519	547	1143

TABLE THREE-continued

CD_4 CD_8 CD_3 TEST RESULTS OF 10 HIV PATIENTS

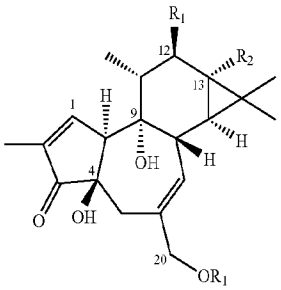
PATIENT NO	TEST TIME	CD_4	CD_8	CD_3
08a-3	After third 10-day TPA infusion cycle	495	733	1295
09a-1	Before TPA	101	533	672
09a-2	After first 10-day TPA infusion cycle	136	574	712
09a-3	After third 10-day TPA infusion cycle	100	1221	1317
10a-1	Before TPA	49	178	240
10a-2	After first 10-day TPA infusion cycle	74	261	333
10a-3	After third 10-day TPA infusion cycle	63	208	308

We claim:

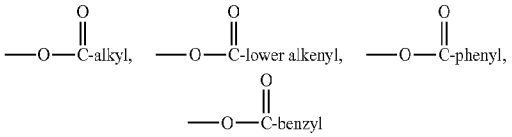
1-48. (canceled)

49. A method of treating or preventing neoplasms in a mammalian subject comprising administering an effective amount of a phorbol ester or derivative of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

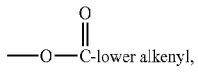
Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,

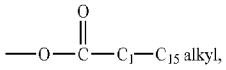


and substituted derivatives thereof, R_3 is selected from hydrogen,

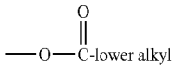


and substituted derivatives thereof; and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent neoplasms in said subject.

50. The method of claim **49**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

51. The method of claim **49**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

52. The method of claim **49**, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

53. The method of claim **49**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

54. The method of claim **49**, wherein the at least one secondary or adjunctive therapeutic agent is selected from the group consisting of doxorubicin, vitamin D3, cytarabine, cytosine arabinoside, daunorubicin, cyclophosphamide, gemtuzumab ozogamicin, idarubicin, mercaptopurine, mitoxantrone, thioguanine, aldesleukin, asparaginase, carboplatin, etoposide phosphate, fludarabine, methotrexate, etoposide, dexamethasone, and choline magnesium trisalicylate.

55. The method of claim **49**, wherein two secondary or adjunctive therapeutic agents are administered to said subject.

56. The method of claim **55**, wherein the two secondary or adjunctive therapeutic agents are dexamethasone and choline magnesium trisalicylate.

57. The method of claim **49**, wherein said effective amount comprises between about 10 and 1500 μg of said phorbol ester or derivative compound of Formula I every day.

58. The method of claim **49**, wherein said effective amount comprises between about 150 to 500 μg of said phorbol ester or derivative compound of Formula I every day.

59. The method of claim **49** wherein the neoplasm is caused by a hematological malignancy/bone marrow disorder.

60. The method of claim **59**, wherein the hematological malignancy/bone marrow disorder is leukemia.

61. The method of claim **60**, wherein the leukemia is acute myeloid leukemia.

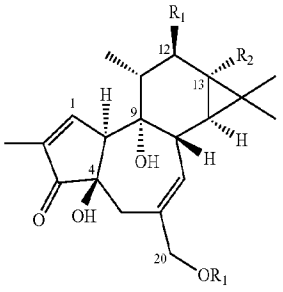
62. The method of claim **49**, wherein the neoplasm is a solid tumor.

63. The method of claim **49**, wherein the neoplasm is a relapsing neoplasm.

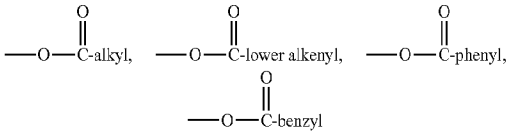
64. The method of claim **49**, wherein the neoplasm is refractory.

65. A method for preventing or treating one or more symptoms or conditions of neoplastic disease in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

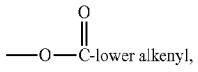
Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,

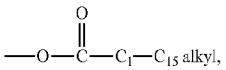


and substituted derivatives thereof, R_3 is hydrogen,

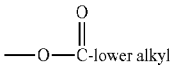


and substituted derivatives thereof; and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula to treat or prevent symptoms of neoplastic disease in said subject.

66. The method of claim **65**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

67. The method of claim **65**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 2-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

68. The method of claim **65**, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

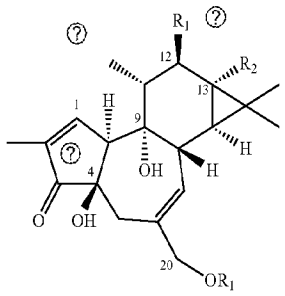
69. The method of claim **68**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

70. The method of claim **68**, wherein the at least one secondary or adjunctive therapeutic agent is selected from the group consisting of: doxorubicin, vitamin D3, cytarabine, cytosine arabinoside, daunorubicin, cyclophosphamide, gemtuzumab ozogamicin, idarubicin, mercaptopurine, mitoxantrone, thioguanine, aldesleukin, asparaginase, carboplatin, etoposide phosphate, fludarabine, methotrexate, etoposide, dexamethasone, and choline magnesium trisalicylate.

71. The method of claim **68**, wherein the one or more symptoms or conditions of neoplastic disease are anemia, chronic fatigue, excessive or easy bleeding, easy bruising, shortness of breath, petechiae, recurrent fever, swollen gums, slow healing of cuts, bone and joint discomfort, recurrent infections, weight loss, itching, night sweats, lymph node swelling, fever, abdominal pain and discomfort, disturbances in vision, coughing, loss of appetite, pain in the chest, difficulty swallowing, swelling, a need to urinate frequently, difficulty starting urination, difficulty holding back urine, weak or interrupted flow of urine, painful or burning urination, difficulty in having an erection, painful ejaculation, blood in urine or semen, frequent pain or stiffness, or weakness.

72. A method for inducing remission in a mammalian subject suffering from neoplastic disease comprising administering to said subject an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject

Formula I



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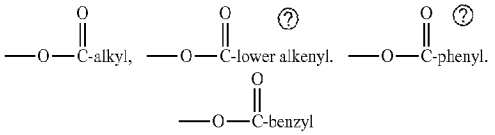
wherein R_1 and R_2 are selected from the group consisting of hydrogen,



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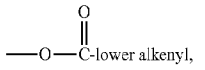
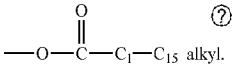
and substituted derivatives thereof; R_3 is hydrogen,



and substituted derivatives thereof; and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester of derivative compound of Formula I to induce remission in said subject.

73. The method of claim **72**, wherein R_1 or R_2 is



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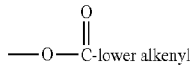
the remaining R_1 or R_2 is



and R_3 is hydrogen and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to induce remission in said subject.

74. The method of claim **72**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

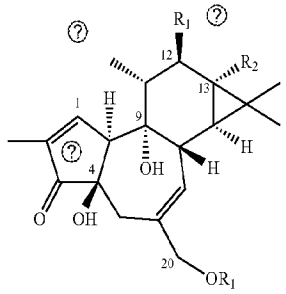
75. The method of claim **72**, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

76. The method of claim **72**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

77. The method of claim **72**, wherein the at least one secondary or adjunctive therapeutic agent is selected from the group consisting of: doxorubicin, vitamin D3, cytarabine, cytosine arabinoside, daunorubicin, cyclophosphamide, gemtuzumab ozogamicin, idarubicin, mercaptopurine, mitoxantrone, thioguanine, aldesleukin, asparaginase, carboplatin, etoposide phosphate, fludarabine, methotrexate, etoposide, dexamethasone, and choline magnesium trisalicylate.

78. A method for inducing apoptosis in a neoplasm in a mammalian subject suffering from neoplastic disease comprising administering to said subject an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject

Formula I



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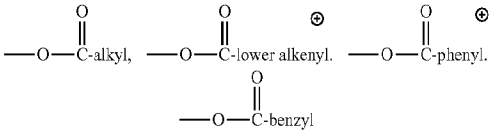
wherein R_1 and R_2 are selected from the group consisting of hydrogen,



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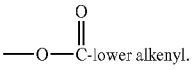
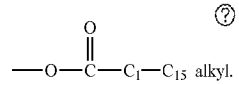
and substituted derivatives thereof, R_3 is hydrogen,



and substituted derivatives thereof; and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation Or coordinate treatment regimen with said phorbol ester of derivative compound of Formula I to induce apoptosis in a neoplasm in said subject.

79. The method of claim **78**, wherein R_1 or R_2 is



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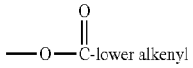
the remaining R_1 or R_2 is



and R_3 is hydrogen and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent malignancy in said subject.

80. The method of claim **78**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

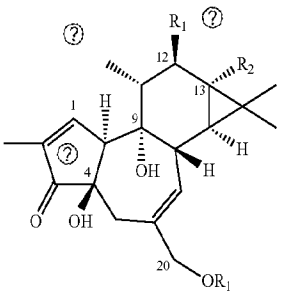
81. The method of claim **78**, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

82. The method of claim **78**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

83. The method of claim **82**, wherein the at least one secondary or adjunctive therapeutic agent is selected from the group consisting of: doxorubicin, vitamin D3, cytarabine, cytosine arabinoside, daunorubicin, cyclophosphamide, gemtuzumab ozogamicin, idarubicin, mercaptopurine, mitoxantrone, thioguanine, aldesleukin, asparaginase, carboplatin, etoposide phosphate, fludarabine, methotrexate, etoposide, dexamethasone, and choline magnesium trisalicylate.

84. A composition for preventing or treating neoplastic disease in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

Formula I



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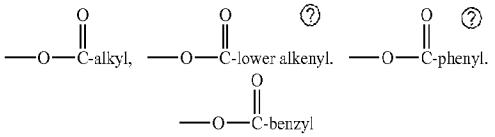
wherein R_1 and R_2 are selected from the group consisting of hydrogen,



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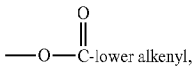
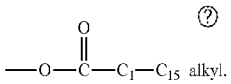
and substituted derivatives thereof, R_3 is hydrogen,



and substituted derivatives thereof; and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent a neoplasm in said subject.

85. The composition of claim **84**, wherein R_1 or R_2 is



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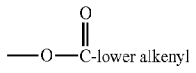
the remaining R_1 or R_2 is



and R_3 is hydrogen.

86. The composition of claim **84**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

87. The composition of claim **84**, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

88. The composition of claim **84**, wherein the at least one secondary or adjunctive therapeutic agent is selected from the group consisting of: doxorubicin, vitamin D3, cytarabine, cytosine arabinoside, daunorubicin, cyclophosphamide, gemtuzumab ozogamicin, idarubicin, mercaptopurine, mitoxantrone, thioguanine, aldesleukin, asparaginase, carbo-

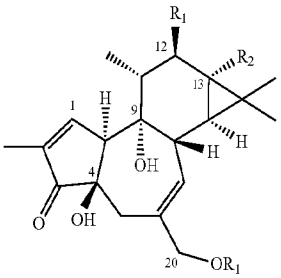
platin, etoposide phosphate, fludarabine, methotrexate, etoposide, dexamethasone, and choline magnesium trisalicylate.

89. The composition of claim **84**, wherein the composition contains at least two secondary or adjunctive therapeutic agents.

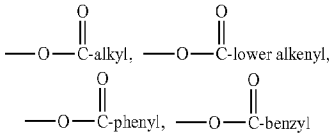
90. The composition of claim **89**, wherein the at least two secondary or adjunctive therapeutic agents are dexamethasone and choline magnesium trisalicylate.

91. A method for preventing or treating one or more side effects of chemotherapy in a mammalian subject comprising administering an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

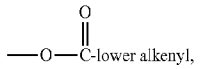
Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,

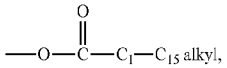


and substituted derivatives thereof, R_3 is hydrogen,

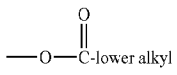


and substituted derivatives thereof.

92. The method of claim **91**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

93. The method of claim **91**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

94. The method of claim **91**, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

95. The method of claim **91**, further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent side effects of chemotherapy treatment to said subject.

96. The method of claim **95**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

97. The method of claim **96**, wherein the at least one secondary or adjunctive therapeutic agent is selected from the group consisting of pegfilgrastim, epoeitn alfa, darbepoetin alfa, alendronate sodium, risedronate, ibandronate, G-CSF, 5-HT3 receptor antagonists, NK1 antagonists, olanzapine, corticosteroids, dopamine antagonists, serotonin antagonists, benzodiazepines, aprepitant, and cannabinoids.

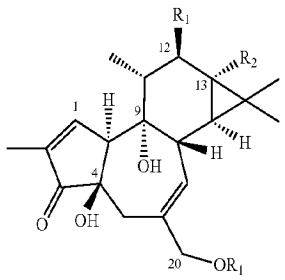
98. The method of claim **91**, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

99. The method of claim **98**, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

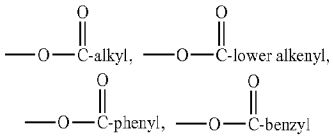
100. The method of claim **91**, wherein the one or more side effects of chemotherapeutic treatment are alopecia, nausea, vomiting, poor appetite, soreness, neutropenia, anemia, thrombocytopenia, dizziness, fatigue, constipation, oral ulcers, itchy skin, peeling, nerve and muscle leprosy, auditory changes, weight loss, diarrhea, immunosuppression, bruising, tendency to bleed easily, heart damage, liver damage, kidney damage, vertigo or encephalopathy.

101. A composition for preventing or treating one or more side effects of chemotherapy in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

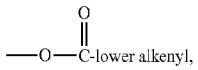
Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,

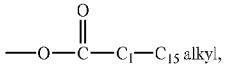


and substituted derivatives thereof, R_3 is hydrogen,

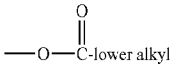


and substituted derivatives thereof.

102. The composition of claim **101**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

103. The composition of claim **101**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenyl acetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

104. The composition of claim **101**, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

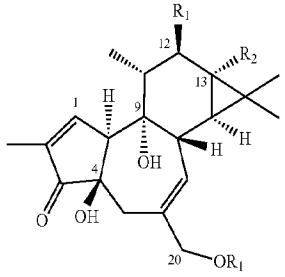
105. The composition of claim **101** further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent a side effect of chemotherapy in said subject.

106. The composition of claim **105**, wherein the at least one secondary or adjunctive therapeutic agent is pegfilgrastim, epoeitn alfa, darbepoetin alfa, alendronate sodium, risedronate, ibandronate, G-CSF, 5-HT3 receptor antagonists, NK1 antagonists, olanzapine, corticosteroids, dopamine antagonists, serotonin antagonists, benzodiazepines, aprepitant, or cannabinoids.

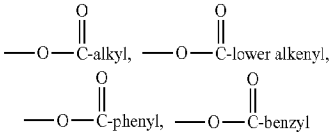
107. The composition of claim **101**, wherein the one or more side effects of chemotherapeutic treatment are alopecia, nausea, vomiting, poor appetite, soreness, neutropenia, anemia, thrombocytopenia, dizziness, fatigue, constipation, oral ulcers, itchy skin, peeling, nerve and muscle leprosy, auditory changes, weight loss, diarrhea, immunosuppression, bruising, tendency to bleed easily, heart damage, liver damage, kidney damage, vertigo or encephalopathy.

108. A method for preventing or treating one or more side effects of radiation therapy in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

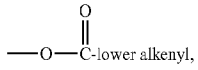
Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,

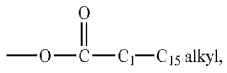


and substituted derivatives thereof, R_3 is hydrogen,

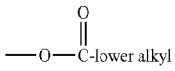


and substituted derivatives thereof.

109. The method of claim **108**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

110. The method of claim **108**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol

12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

111. The method of claim **108**, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

112. The method of claim **108**, further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent side effects of radiation therapy to said subject.

113. The method of claim **112**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

114. The method of claim **113**, wherein the at least one secondary or adjunctive therapeutic agent is selected from the group consisting of steroids, amifostine, chlorhexidine, benzydamine, sucralfate, KGF, palifermin, Cu/Zn superoxide dismutase, Interleukin 11, or prostaglandins.

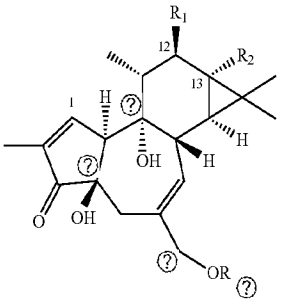
115. The method of claim **108**, wherein the one or more side effects of radiation therapy are moist desquamation, soreness, diarrhea, nausea, vomiting, appetite loss, constipation, itchy skin, peeling, mouth and throat sores, edema, infertility, fibrosis, epilation, or mucosal dryness.

116. The method of claim **108**, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

117. The method of claim **108**, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

118. A composition for preventing or treating one or more side effects of radiation therapy in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

Formula I



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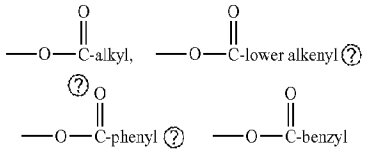
wherein R_1 and R_2 are selected from the group consisting of hydrogen,



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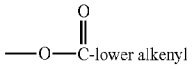
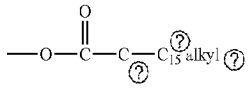
and substituted derivatives thereof, R_3 is hydrogen,



and substituted derivatives thereof.

119. The composition of claim **118**, wherein R_1 or R_2 is



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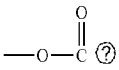
the remaining R_1 or R_2 is



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and R_3 is hydrogen.

120. The composition of claim **118**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 2-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

121. The composition of claim **118**, wherein the phorbol ester is 12-O-tetradecanoyl phorbol-13-acetate.

122. The composition of claim **118** further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent a side effect of radiation therapy in said subject.

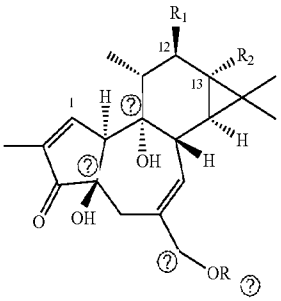
123. The composition of claim **118**, wherein the one or more secondary or adjunctive therapeutic agents are steroids,

amifostine, chlorhexidine, benzydamine, sucralfate, KGF, palifermin, Cu/Zn superoxide dismutase, Interleukin 11, or prostaglandins.

124. The composition of claim **118**, wherein the one or more side effects of radiation therapy are moist desquamation, soreness, diarrhea, nausea, vomiting, appetite loss, constipation, itchy skin, peeling, mouth and throat sores, edema, infertility, fibrosis, epilation, or mucosal dryness.

125. A method for preventing or treating one or more of the effects of stroke in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

Formula I



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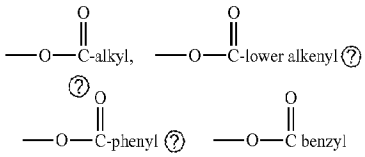
wherein R_1 and R_2 are selected from the group consisting of hydrogen,



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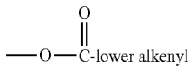
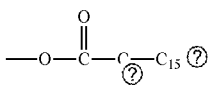
and substituted derivatives thereof, R_3 is hydrogen,



and substituted derivatives thereof.

126. The method of claim **125**, wherein R_1 or R_2 is



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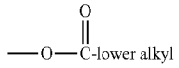
the remaining R_1 or R_2 is



and R_3 is hydrogen.

127. The method of claim **125**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

128. The method of claim **125**, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

129. The method of claim **125**, further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent effects of stroke in said subject.

130. The method of claim **129**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

131. The method of claim **129**, wherein the at least one secondary or adjunctive therapeutic agent is tissue plasminogen activator, an anticoagulant, a statin, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitor, beta-blocker, calcium channel blocker, or diuretic.

132. The method of claim **125**, further comprising surgical intervention in combination with phorbol ester or derivative compound of Formula I to treat or prevent effects of stroke in said subject.

133. The method of claim **132**, wherein the surgical intervention is a carotid endarterectomy, angioplasty, stent placement, craniotomy, endovascular coil emobilization, or patent foramen ovale closure.

134. The method of claim **125**, wherein the one or more effects of stroke are paralysis, spatial impairment, impaired judgment, left-sided neglect, memory loss, aphasia, coordination and balance problems, nausea, vomiting, cognitive impairment, perception impairment, orientation impairment, homonymous hemianopsia, or impulsivity.

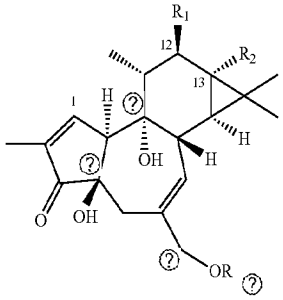
135. The method of claim **125**, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

136. The method of claim **135**, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

137. A composition for the prevention or treatment of one or more effects of stroke in a mammalian subject comprising

an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

Formula I



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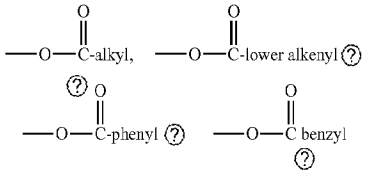
wherein R_1 and R_2 are selected from the group consisting of hydrogen,



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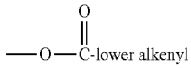
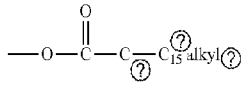
and substituted derivatives thereof, R_3 is hydrogen,



and substituted derivatives thereof.

138. The composition of claim **137**, wherein R_1 or R_2 is



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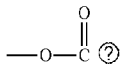
the remaining R_1 or R_2 is



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and R_3 is hydrogen.

139. The composition of claim **138**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

140. The composition of claim **138**, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

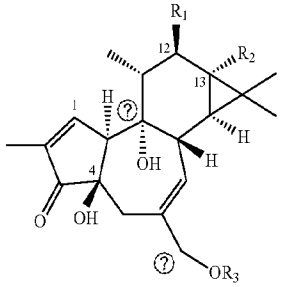
141. The composition of claim **138**, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent an effect of stroke in said subject.

142. The composition of claim **138**, wherein the at least one secondary or adjunctive therapeutic agent is tissue plasminogen activator, an anticoagulant, a statin, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitor, beta-blocker, calcium channel blocker, or diuretic.

143. The composition of claim **138**, wherein the one or more side effects of stroke is paralysis, spatial impairment, impaired judgment, left-sided neglect, memory loss, aphasia, coordination and balance problems, nausea, vomiting, cognitive impairment, perception impairment, orientation impairment, homonymous hemianopsia, or impulsivity.

144. A method for treating or preventing one or more of the symptoms of Parkinson's disease in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

Formula I



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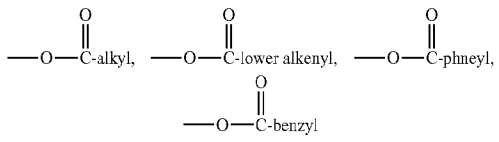
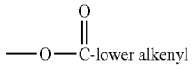
wherein R_1 and R_2 are selected from the group consisting of hydrogen,

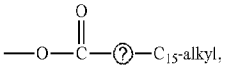


and substituted derivatives thereof, R_3 is hydrogen,



and substituted derivatives thereof.

145. The method of claim **144**, wherein R_1 or R_2 is



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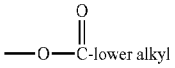
the remaining R_1 or R_2 is



and R_3 is hydrogen.

146. The method of claim **144**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

147. The method of claim **144**, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

148. The method of claim **144**, further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent one or more of the symptoms of Parkinson's disease.

149. The method of claim **148**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

150. The method of claim **148**, wherein the at least one secondary or adjunctive therapeutic agent is levodopa, carbidopa, pyridoxine, seleyiline, rasagiline, tolcapone, dopamine agonist, MAO-B inhibitors, amantidine, or anticholinergics.

151. The method of claim **144**, further comprising surgical intervention in combination with phorbol ester or derivative compound of Formula I to treat or prevent symptoms of Parkinson's disease in said subject.

152. The method of claim **151**, wherein the surgical intervention is deep brain stimulation or lesion formation.

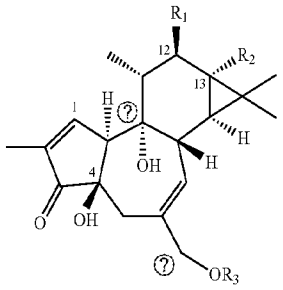
153. The method of claim **144**, wherein the one or more symptoms of Parkinson's disease is tremor at rest, stiffness, bradykinesia, rigidity, speech impairment, cognitive impairment, dementia, mood impairment, drowsiness, insomnia and postural instability.

154. The method of claim **144**, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

155. The method of claim **144**, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

156. A composition for the prevention or treatment of one or more symptoms of Parkinson's disease in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

Formula I



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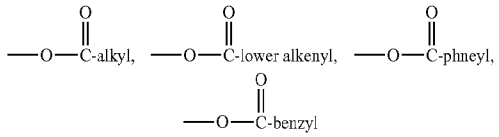
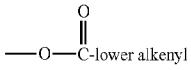
wherein R_1 and R_2 are selected from the group consisting of hydrogen,

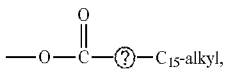


and substituted derivatives thereof, R_3 is hydrogen,



and substituted derivatives thereof.

157. The composition of claim **156**, wherein R_1 or R_2 is



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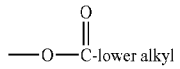
the remaining R_1 or R_2 is



and R_3 is hydrogen.

158. The composition of claim **156**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 3-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

159. The composition of claim **156**, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

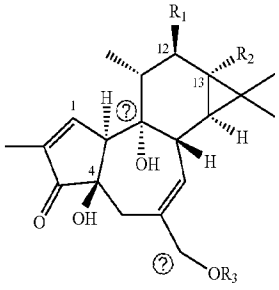
160. The composition of claim **156**, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent an effect of stroke in said subject.

161. The composition of claim **160**, wherein the at least one secondary or adjunctive therapeutic agent is levodopa, carbidopa, pyridoxine, seleyiline, rasagiline, tolcapone, dopamine agonist, MAO-B inhibitors, amantidine, or anticholinergics.

162. The composition of claim **156**, wherein the one or more symptoms of Parkinson's disease is tremor at rest, stiffness, bradykinesia, rigidity, speech impairment, cognitive impairment, dementia, mood impairment, drowsiness, insomnia or postural instability.

163. A method for treating or preventing one or more of the symptoms of prostate hypertrophy in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

Formula I



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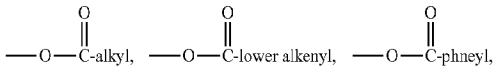
wherein R_1 and R_2 are selected from the group consisting of hydrogen,



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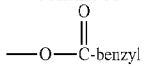
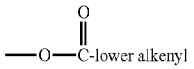
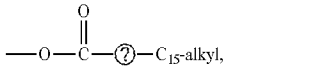


and substituted derivatives thereof, R_3 is hydrogen,



and substituted derivatives thereof.

164. The method of claim **163**, wherein R_1 or R_2 is



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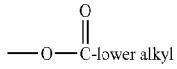
the remaining R_1 or R_2 is



and R_3 is hydrogen.

165. The method of claim **163**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

166. The method of claim **163**, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

167. The method of claim **163**, further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent one or more of the symptoms of prostate hypertrophy.

168. The method of claim **167**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

169. The method of claim **167**, wherein the at least one secondary or adjunctive therapeutic agent is finasteride, dutasteride, terazosin, doxazosin, tamsulosin or an alpha blocker.

170. The method of claim **163**, further comprising surgical intervention in combination with phorbol ester or derivative compound of Formula I to treat or prevent symptoms of prostate hypertrophy disease in said subject.

171. The method of claim **170**, wherein the surgical intervention is transurethral resection of the prostate, transurethral incision of the prostate, laser surgery, or prostatectomy.

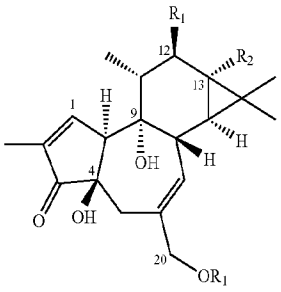
172. The method of claim 163, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

173. The method of claim 163, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

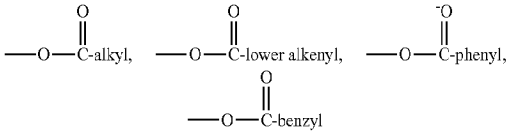
174. The method of claim 163, wherein the one or more symptoms of prostate hypertrophy are dribbling at the end of urination, urinary retention, incomplete emptying of the bladder, incontinence, urinary frequency, pain with urination, bloody urine, slowed or delayed urination, stopping and starting of urine stream, straining to urinate, weak urine stream, or strong and sudden urge to urinate.

175. A composition for the prevention or treatment of one or more symptoms of prostate hypertrophy in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

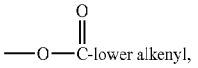
Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,

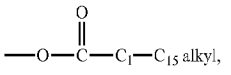


and substituted derivatives thereof, R_3 is hydrogen,

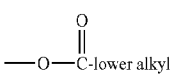


and substituted derivatives thereof.

176. The composition of claim 175, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

177. The composition of claim 175, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,1 diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 3-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

178. The composition of claim 175, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

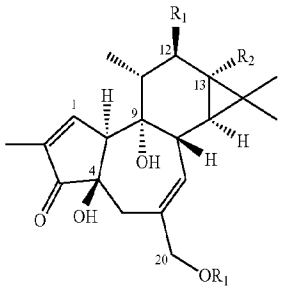
179. The composition of claim 175, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent a symptom of prostate hypertrophy.

180. The composition of claim 179, wherein the at least one secondary or adjunctive therapeutic agent is finasteride, dutasteride, terazosin, doxazosin, tamsulosin or an alpha blocker.

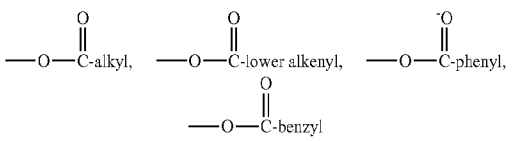
181. The composition of claim 179, wherein the one or more symptoms of prostate hypertrophy are dribbling at the end of urination, urinary retention, incomplete emptying of the bladder, incontinence, urinary frequency, pain with urination, bloody urine, slowed or delayed urination, stopping and starting of urine stream, straining to urinate, weak urine stream, or strong and sudden urge to urinate.

182. A method for treating or preventing one or more of the symptoms of rheumatoid arthritis in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

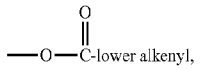
Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,

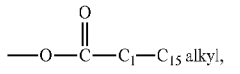


and substituted derivatives thereof, R_3 is hydrogen,

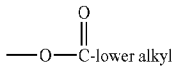


and substituted derivatives thereof.

183. The method of claim **182**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

184. The method of claim **182**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

185. The method of claim **182**, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

186. The method of claim **182**, further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent one or more of the symptoms of rheumatoid arthritis.

187. The method of claim **186**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

188. The method of claim **187**, wherein the at least one secondary or adjunctive therapeutic agent is a non-steroidal anti-inflammatory agent, steroid, disease-modifying anti-rheumatic drug, an immunosuppressant, TNF-α inhibitor, adalimumab, azathioprine, chloroquine, hydroxychloroquine, ciclosporin, D-penicillamine, etanercept, golimumab, gold salts, infliximab, leflunomide, methotrexate, minocycline, sulfasalazine anakinra, abatacept, rituximab, or tocilizumab.

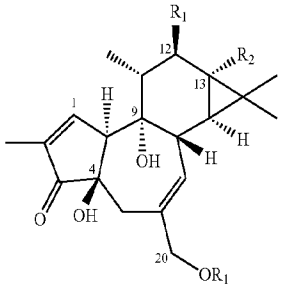
189. The method of claim **182**, wherein the one or more symptoms of rheumatoid arthritis are sore joints, morning stiffness, firm bumps of tissue under the skin of the arms, fatigue, loss of energy, lack of appetite, low-grade fever, or muscle and joint aches.

190. The method of claim **182**, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

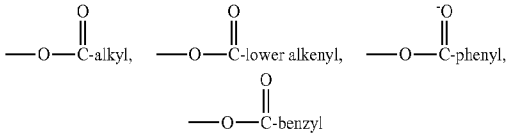
191. The method of claim **182**, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

192. A composition for the prevention or treatment of one or more symptoms of rheumatoid arthritis in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

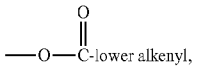
Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,

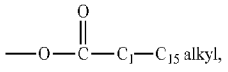


and substituted derivatives thereof, R_3 is hydrogen,

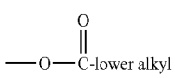


and substituted derivatives thereof.

193. The composition of claim **192**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

194. The composition of claim **192**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol

13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

195. The composition of claim **192**, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

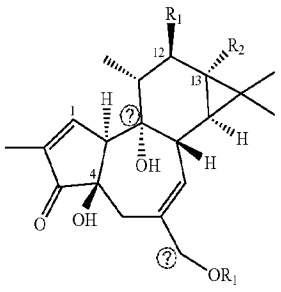
196. The composition of claim **192**, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent a symptom of rheumatoid arthritis.

197. The composition of claim **196**, wherein the at least one secondary or adjunctive therapeutic agent is a non-steroidal anti-inflammatory agent, steroid, disease-modifying anti-rheumatic drug, an immunosuppressant, TNF-α inhibitor, anakinra, abatacept, adalimumab, azathioprine, chloroquine, hydroxychloroquine, ciclosporin, D-penicillamine, etanercept, golimumab, gold salts, infliximab, leflunomide, methotrexate, minocycline, sulfasalazine, rituximab, or tocilizumab.

198. The composition of claim **192**, wherein the one or more symptoms of rheumatoid arthritis are sore joints, morning stiffness, firm bumps of tissue under the skin of the arms, fatigue, loss of energy, lack of appetite, low-grade fever, or muscle and joint aches.

199. A method for treating or preventing one or more of the symptoms of myasthenia gravis in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

Formula I



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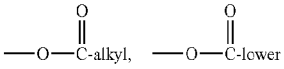
wherein R_1 and R_2 are selected from the group consisting of hydrogen,



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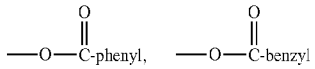
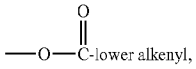
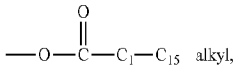


and substituted derivatives thereof, R_3 is hydrogen,

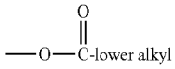


and substituted derivatives thereof.

200. The method of claim **199**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

201. The method of claim **199**, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

202. The method of claim **199** further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent one or more of the symptoms of myasthenia gravis.

203. The method of claim **202**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

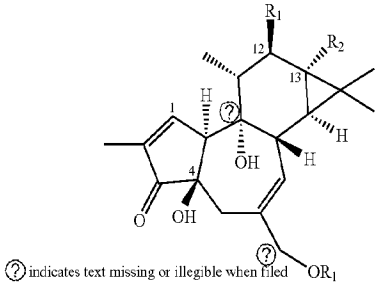
204. The method of claim **202**, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinesterase, corticosteroid, or immunosuppressive agent.

205. The method of claim **199**, wherein the one or more symptoms of myasthemia gravis are ptosis, diplopia, speech impairment, fatigability, muscle weakness, dysphagia, or dysarthria.

206. The method of claim **199**, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

207. The method of claim **199**, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

208. A composition for the prevention or treatment of one or more symptoms of myasthenia gravis in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



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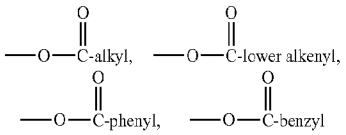
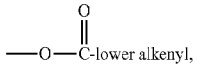
wherein R_1 and R_2 are selected from the group consisting of hydrogen,

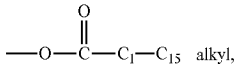


and substituted derivatives thereof, R_3 is hydrogen,

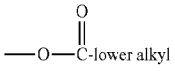


and substituted derivatives thereof.

209. The composition of claim **208**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

210. The composition of claim **208**, wherein the phorbol ester is 12-O-tetradecanoylphorbol 13-acetate.

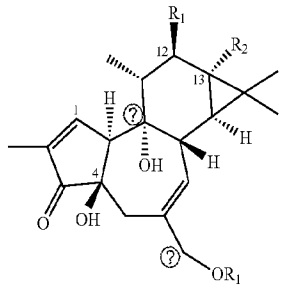
211. The composition of claim **208**, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent a symptom of myasthenia gravis.

212. The composition of claim **211**, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinesterase, corticosteroid, or immunosuppressive agent.

213. The composition of claim **208**, wherein the one or more symptoms of myasthemia gravis are ptosis, diplopia, speech impairment, fatigability, muscle weakness, dysphagia, or dysarthria.

214. A method for treating or preventing symptoms of kidney disease in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

Formula I



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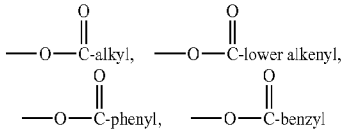
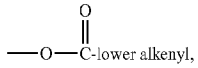
wherein R_1 and R_2 are selected from the group consisting of hydrogen,

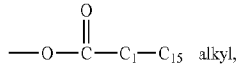


and substituted derivatives thereof, R_3 is hydrogen,

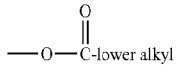


and substituted derivatives thereof.

215. The method of claim **214**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

216. The method of claim **214**, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

217. The method of claim **214**, further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent symptoms of kidney disease.

218. The method of claim **217**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

219. The method of claim **217**, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinergic, topical estrogen, imipramine or duloxetine.

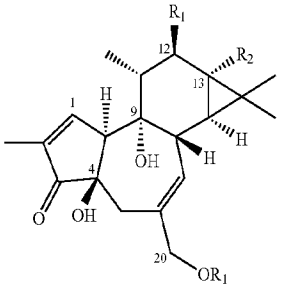
220. The method of claim **214**, wherein the symptom of kidney disease is urinary incontinence, increased excretion of urine, uremia, or oliguria.

221. The method of claim 214, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

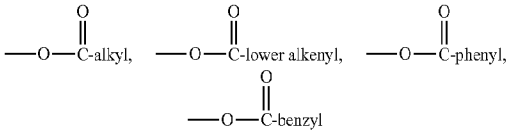
222. The method of claim 214, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

223. A composition for the prevention or treatment of kidney disease in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

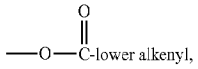
Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,

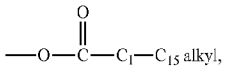


and substituted derivatives thereof, R_3 is hydrogen,

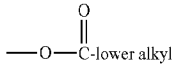


and substituted derivatives thereof.

224. The composition of claim 223, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

225. The composition of claim 223, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

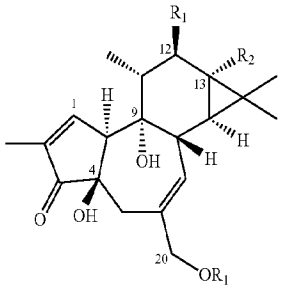
226. The composition of claim 223, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent a symptom of kidney disease.

227. The composition of claim 226, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinergic, topical estrogen, imipramine or duloxetine.

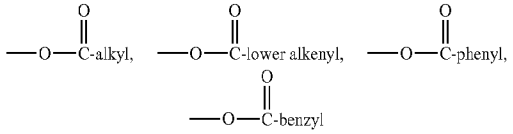
228. The composition of claim 223, wherein the symptom of kidney disease is urinary incontinence, increased excretion of urine, uremia, or oliguria.

229. A method for treating or preventing urinary incontinence in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

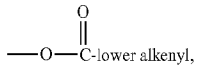
Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,

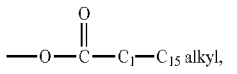


and substituted derivatives thereof, R_3 is hydrogen,

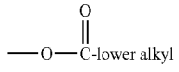


and substituted derivatives thereof.

230. The method of claim 229, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

231. The method of claim 229, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

232. The method of claim 229, further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent symptoms of urinary incontinence.

233. The method of claim 232, wherein the at least one secondary or adjunctive therapeutic agent is administered to

said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

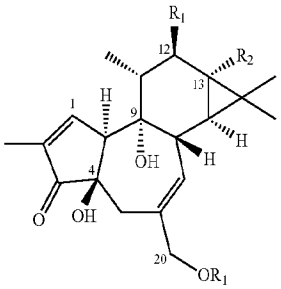
234. The method of claim **232**, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinergic, topical estrogen, imipramine or duloxetine.

235. The method of claim **229**, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

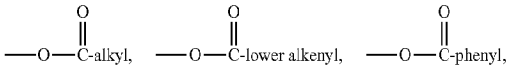
236. The method of claim **229**, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

237. A composition for the prevention or treatment of urinary incontinence in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,



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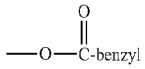
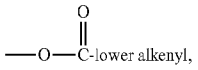
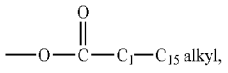


and substituted derivatives thereof, R_3 is hydrogen,

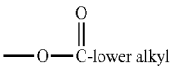


and substituted derivatives thereof.

238. The composition of claim **237**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

239. The composition of claim **237**, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

240. The composition of claim **237**, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent urinary incontinence.

241. The composition of claim **240**, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinergic, topical estrogen, imipramine or duloxetine.

* * * * *

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CORRECTED PUBLICATION

(54) **COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS**

(71) Applicants: **Zheng Tao Han**, Zhengzhou (CN); **Hung-Fong Chen**, Taipei (TW)

(72) Inventors: **Zheng Tao Han**, Zhengzhou (CN); **Hung-Fong Chen**, Taipei (TW)

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(60) Provisional application No. 61/588,165, filed on Jan. 18, 2012, provisional application No. 61/588,162, filed on Jan. 18, 2012, provisional application No. 61/588,167, filed on Jan. 18, 2012, provisional application No. 60/898,810, filed on Jan. 31, 2007.

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(57) **ABSTRACT**

Methods and compositions containing a phorbol ester or a derivative of a phorbol ester are provided for the treatment of chronic and acute conditions. Such conditions may be caused by disease, be symptoms or sequelae of disease. Chronic and acute conditions may be due to viral infections such as HIV and AIDS, neoplastic diseases stroke, kidney disease, urinary incontinence, autoimmune disorders, Parkinson's disease, prostate hypertrophy, aging, or the treatment of such diseases. Additional compositions and methods are provided which employ a phorbol ester or derivative compound in combination with at least one additional agent to yield more effective treatment tools against acute and chronic conditions in mammalian subjects.

COMPOSITIONS AND METHODS OF USE OF PHORBOL ESTERS

RELATED APPLICATIONS

[0001] This application is a United States Continuation-In-Part of U.S. patent application Ser. No. 12/023,753, filed Jan. 31, 2008, which claims priority benefit of U.S. Provisional Patent Application Ser. No. 60/898,810, filed Jan. 31, 2007, U.S. Provisional Patent Application Ser. No. 61/588,162, filed Jan. 18, 2012, U.S. Provisional Patent Application Ser. No. 61/588,165, filed Jan. 18, 2013, and U.S. Provisional Patent Application Ser. No. 61/588,167, each of which is incorporated herein in its entirety by reference.

TECHNICAL FIELD

[0002] The present invention relates generally to the medicinal use of phorbol esters.

BACKGROUND

[0003] Plants have historically served many medicinal purposes. The World Health Organization (WHO) estimates that 4 billion people, 80% of the world population, presently use herbal medicine for some aspect of primary health care. (WHO Fact sheet Fact sheet No 134 December 2008) However, it can be difficult to isolate the specific compound that has the medicinal effect and to reproduce it on a commercial scale. Additionally, while active compounds may be isolated from a plant, the other parts of a plant such as the minerals, vitamins, volatile oils, glycosides, alkaloids, bioflavanoids, and other substances may also be involved in the functioning of the active ingredient, or the medicinal effect for which the plant is known making the use, purification and commercialization of plant based pharmaceutical agents a challenge.

[0004] Phorbol is a natural, plant-derived organic compound of the tigliane family of diterpenes. It was first isolated in 1934 as a hydrolysis product of croton oil derived from the seeds of *Croton tiglium*, a leafy shrub of the Euphorbiaceae family that is native to Southeastern Asia. Various esters of phorbol have important biological properties including the reported ability to mimic diacylglycerols and activate protein kinase C N, Rosenmund C., J Cell Sci; 115:4399-411 (2002)). Some phorbol esters also induce nuclear factor-kappa B (NF-κB). The most notable physiological property of phorbol esters is their reported capacity to act as tumor promoters. (Blumberg, 1988; Goel, G et al., Int, Journal of Toxicology 26, 279-288 (2007)).

[0005] 12-O-tetradecanoylphorbol-13-acetate (TPA), also called phorbol-12-myristate-13-acetate (PMA), is a phorbol ester used in models of carcinogenesis as an inducer for differentiation and/or apoptosis in multiple cell lines and primary cells. TPA has also been reported to cause an increase in circulating white blood cells and neutrophils in patients whose bone marrow function has been depressed by chemotherapy (Han Z. T. et al. Proc. Natl. Acad. Sci. 95, 5363-5365 (1998)) and inhibit the HIV-cytopathic effects on MT-4 cells. (Mekkawy S. et al., Phytochemistry 53, 47-464 (2000)). However, due to a variety of factors, including caustic reactions when contacted with the skin and concerns for its potential toxicity, TPA has not been shown to be an effective tool for treating, managing, or preventing HIV or AIDS or as an adjuvant to chemotherapy. Indeed, as phorbol esters play a key role in activation of protein kinase C (PKC), which triggers various cellular responses resulting in inflammatory responses and tumor development (Goel et al., Int, Journal of Toxicology 26, 279-288 (2007)), phorbol esters would generally be excluded from possible treatment candidates for cancer or inflammatory diseases such as rheumatoid arthritis or conditions that involve inflammatory reactions such as stroke, autoimmune disorders or prostate hypertrophy.

[0006] As modern medicine has developed, survival rates from both chronic and acute disease has increased, generating new challenges in managing both chronic conditions and the sequelae of acute disease and treatment side effects. There is a continuing need for the identification of pharmaceutical agents, including plant based pharmaceutical agents, which can be used to treat disease, prevent damage from acute episodes, manage the symptoms of disease conditions, and manage the side effects of disease treatments. While molecular targeting has produced a number of successful pharmaceutical agents, frequently multiple pathways of signaling are involved, and blocking one pathway can easily be compensated for elsewhere. There is clearly a need for new and more effective treatments and side effect management for individuals suffering from a variety of conditions, particularly chronic or potentially recurring conditions such as cancer, immune disorders, autoimmune disorders, stroke, rheumatoid arthritis, inflammation, uterine fibroids, prostate hypertrophy, urinary incontinence, Parkinson's disease and kidney disease.

SUMMARY

[0007] The present invention relates to compositions containing and methods of using phorbol esters. These compositions and methods are effective in treating chronic or potentially recurring conditions, or to repair the damage left by acute episodes of particular diseases.

[0008] In one embodiment, phorbol esters and derivatives of phorbol esters are used to treat diseases such as HIV and associated conditions such as AIDS. The compositions and methods of the present invention may accomplish the treatment of HIV and associated conditions such as AIDS by any means possible. In some embodiments, the compositions and methods may modify HIV receptor activity in mammalian subjects. In another embodiment, the compositions and methods as described herein may decrease the number of latent HIV reservoirs in an HIV-infected subject. In a further embodiment, the compositions and methods as described herein may enhance HIV activation in latent pro-viral cells. In additional embodiments, they may inhibit HIV-cytopathic effects.

[0009] In another embodiment, compositions containing phorbol esters and phorbol ester derivatives may be used for treating and managing symptoms of HIV and AIDS in mammalian subjects. Targeted symptoms for treatment and management employing the compositions and methods described herein include, but are not limited to, oral lesions, fatigue, skin thrush, fever, lack of appetite, diarrhea, apthous ulcers, malabsorbtion, thrombocytopenia, weight loss, anemia, lymph node enlargement, susceptibility to and severity of secondary conditions such as mycobacterium avium complex, salmonellosis, syphilis, neuroshyphilis, tuberculosis (TB), bacillary angiomatosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, pelvic inflammatory disease, Burkitt's lymphoma, cryptococcal meningitis, histoplasmosis, Kaposi's sarcoma, lymphoma, systemic non-Hodgkin's lymphoma (NHL), primary CNS lymphoma, cryptosporidiosis, isosporiasis, microsporidiosis, pneumocystis carinii pneumonia (PCP), toxoplasmosis, cytomegalovirus (CMV),

hepatitis, herpes simplex, herpes zoster, human papiloma virus (HPV, genital warts, cervical cancer), molluscum contagiosum, oral hairy leukoplakia (OHL), and progressive multifocal leukoencephalopathy (PML).

[0010] In a further embodiment, compounds containing phorbol esters and derivatives of phorbol esters may be used to treat neoplastic diseases. Such neoplasms may be malignant or benign. In some embodiments, neoplasms may be solid or non-solid cancers. In other embodiments, the neoplasms may be relapses. In another embodiment, the neoplasms may be refractory. Exemplary neoplasms include, but are not limited to, hematologic malignancies/bone marrow disorders, including, but not limited to, leukemia, including acute myeloid leukemia (AML), chronic myeloid leukemia (CML), chronic myeloid leukemia blast crisis, myelodysplasia, and myeloproliferative syndrome; lymphoma, including Hodgkin's and non-Hodgkin's lymphoma; subcutaneous adenocarcinoma; ovarian teratocarcinoma; liver cancer; breast cancer; bone cancer; lung cancer; pancreatic, non-small cell lung cancer and prostate cancer. Other neoplastic conditions amenable to treatment using the methods and compositions as described herein include other cancer disorders and conditions, including solid tumors of various types. Successful treatment and/or remission will be determined according to conventional methods, such as determining size reduction of solid tumors, and/or histopathological studies to assess growth, stage, metastatic state or potential, presence or expression levels of histological cancer markers, etc.

[0011] Compositions and methods herein may additionally be used treat symptoms of neoplastic disease including, but not limited to, anemia; chronic fatigue; excessive or easy bleeding, such as bleeding of the nose, gums, and under the skin; easy bruising, particularly bruising with no apparent cause; shortness of breath; petechiae; recurrent fever; swollen gums; slow healing of cuts; bone and joint discomfort; recurrent infections; weight loss; itching; night sweats; lymph node swelling; fever; abdominal pain and discomfort; disturbances in vision; coughing; loss of appetite; pain in the chest; difficulty swallowing; swelling of the face, neck and upper extremities; a need to urinate frequently, especially at night; difficulty starting urination or holding back urine; weak or interrupted flow of urine; painful or burning urination; difficulty in having an erection; painful ejaculation; blood in urine or semen; frequent pain or stiffness in the lower back, hips, or upper thighs; and weakness.

[0012] Compositions and methods herein may further be used to treat the side effects of chemotherapy and radiation therapy which are commonly used as treatments for neoplastic disease. Such side effects include, but not limited to, alopecia, nausea, vomiting, poor appetite, soreness, neutropenia, anemia, thrombocytopenia, dizziness, fatigue, constipation, oral ulcers, itchy skin, peeling, nerve and muscle damage, auditory changes, weight loss, diarrhea, immunosuppression, bruising, heart damage, bleeding, liver damage, kidney damage, edema, mouth and throat sores, infertility, fibrosis, epilation, moist desquamation, mucosal dryness, vertigo and encephalopathy.

[0013] In yet another embodiment, the phorbol esters and derivatives of phorbol esters as described herein may be used to modulate cell signaling pathways. Such modulation may have a variety of results, for example, in some embodiments, the use of compositions containing phorbol esters and derivatives of phorbol esters may increase white blood cell counts in mammalian subjects. In another embodiment, compositions containing phorbol esters and/or phorbol ester derivatives may alter the release of Th1 cytokines in mammalian subjects. In a further embodiment, compositions containing phorbol esters and/or phorbol ester derivatives may alter the release of interleukin 2 (IL-2) in mammalian subjects. In an additional embodiment, compositions containing phorbol esters and/or phorbol ester derivatives may alter the release of interferon in mammalian subjects. In yet another embodiment, compositions containing phorbol esters and/or phorbol ester derivatives may alter the rate of ERK phosphorylation.

[0014] In a further embodiment, the phorbol esters and derivatives of phorbol esters as described herein may be used in the prevention and treatment of stroke and damage due to stroke. Effects of stroke that may be prevented or treated by using the phorbol esters and derivatives of phorbol esters as described herein include, but are not limited to, paralysis, spatial impairment, impaired judgment, left-sided neglect, memory loss, aphasia, coordination and balance problems, nausea, vomiting, cognitive impairment, perception impairment, orientation impairment, homonymous hemianopsia and impulsivity.

[0015] In yet another embodiment, the phorbol esters and derivatives of phorbol esters as described herein may be used in the treatment of rheumatoid arthritis. Symptoms of rheumatoid arthritis that may be prevented or treated by the phorbol esters and derivatives of phorbol esters as described herein include, but are not limited to, sore joints, morning stiffness, firm bumps of tissue under the skin of the arms, fatigue, loss of energy, lack of appetite, low-grade fever or muscle and joint aches.

[0016] In additional embodiments, the phorbol esters and derivatives of phorbol esters as described herein may be used in the treatment of prostate hypertrophy. The compositions and methods as described herein may be used to prevent or treat symptoms of prostate hypertrophy including, but not limited to, dribbling at the end of urination, urinary retention, incomplete emptying of the bladder, incontinence, excessive urinary frequency, pain with urination, bloody urine, delayed urination, straining to urinate, weak urine stream or strong and sudden urge to urinate.

[0017] In a further embodiment, the phorbol esters and derivatives of phorbol esters as described herein may be used in the treatment of kidney disease.

[0018] In an additional embodiment, the phorbol esters and derivatives of phorbol esters as described herein may be used in the treatment of urinary incontinence.

[0019] In another embodiment, the phorbol esters and derivative of phorbol esters as described herein may be used in the treatment of uterine fibroids.

[0020] In another embodiment, the phorbol esters and derivative of phorbol esters as described herein may be used in the treatment of dementia.

[0021] In another embodiment, the phorbol esters and derivative of phorbol esters as described herein may be used in the treatment of diabetes.

[0022] In an embodiment, the phorbol esters and derivatives of phorbol esters as described herein may be used to decrease visible signs of aging in individuals.

[0023] In an additional embodiment, the phorbol esters and derivatives of phorbol esters as described herein may be used to decrease swelling around the eyes.

[0024] In a further embodiment, the phorbol esters and derivatives of phorbol esters as described herein may be used in the treatment of autoimmune disorders including, but not

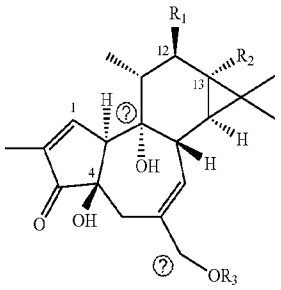
limited to, myasthenia gravis. Symptoms of myasthenia gravis that may be prevented or treated by use of the compositions and methods described herein include, but are not limited to, ptosis, diplopia, speech impairment, fatiguability, muscle weakness, dysphagia or dysarthria.

[0025] In an additional embodiment, the phorbol esters and derivatives of phorbol esters as described herein may be used in the treatment and prevention of central nervous system disorders such as Parkinson's disease. Symptoms of Parkinson's disease that may be treated or prevented by the use of the compositions and methods described herein include, but are not limited to, tremor at rest, stiffness, bradykinesia, rigidity, speech impairment, cognitive impairment, dementia, mood impairment, drowsiness, insomnia and postural instability.

[0026] In yet another embodiment, the phorbol esters and derivatives of phorbol esters as described herein may be used in the treatment and prevention of carpal tunnel syndrome.

[0027] The invention achieves the foregoing and satisfies additional objects and advantages by providing novel and surprisingly effective methods and compositions for modulating cell signaling pathways and/or treating diseases and symptoms of diseases or conditions using compositions containing a phorbol ester or derivative composition of the Formula I, below:

Formula I



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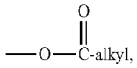
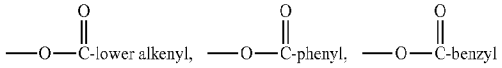
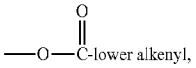
wherein R_1 and R_2 may be hydrogen;



wherein the alkyl group contains 1 to 15 carbon atoms;

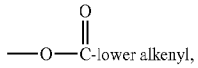


and substituted derivatives thereof and R_3 may be hydrogen or

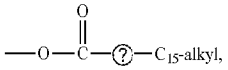


and substituted derivatives thereof.

[0028] In some embodiments, at least one of R_1 and R_2 are other than hydrogen and R_3 is hydrogen or



and substituted derivatives thereof. In another embodiment, either R_1 or R_2 is



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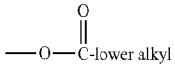
the remaining R_1 or R_2 is

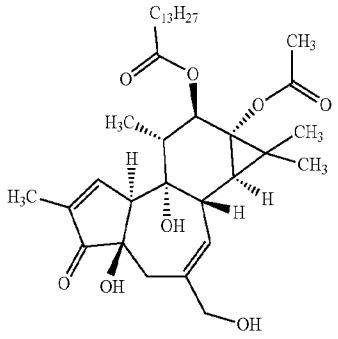


and R_3 is hydrogen.

[0029] The alkyl, alkenyl, phenyl and benzyl groups of the formulas herein may be unsubstituted or substituted with halogens, preferably, chlorine, fluorine or bromine; nitro; amino; and/or similar type radicals.

[0030] In a further embodiment, the invention achieves these objects and satisfies additional objects and advantages by providing novel and surprisingly effective methods and compositions for modulating cell signaling pathways and/or treating diseases or conditions associated with diseases using an exemplary phorbol ester composition such as 12-O-tetradecanoylphorbol-13-acetate (TPA) of Formula II, below:

Formula II



[0031] Useful phorbol esters and related compounds and derivatives within the formulations and methods of the invention include, but are not limited to, other pharmaceutically acceptable active salts of said compounds, as well as active isomers, enantiomers, polymorphs, glycosylated derivatives, solvates, hydrates, and/or prodrugs of said compounds. Exemplary forms of phorbol esters for use within the compositions and methods of the invention include, but are not limited to, phorbol 13-butyrate; phorbol 12-decanoate; phorbol 13-decanoate; phorbol 12,13-diacetate; phorbol 13,20-diacetate; phorbol 12,13-dibenzoate; phorbol 12,13-dibu-

tyrate; phorbol 12,13-didecanoate; phorbol 12,13-dihexanoate; phorbol 12,13-dipropionate; phorbol 12-myristate; phorbol 13-myristate; phorbol 12-myristate-13-acetate (also known as TPA or PMA); phorbol 12,13,20-triacetate; 12-deoxyphorbol 13-angelate; 12-deoxyphorbol 13-angelate 20-acetate; 12-deoxyphorbol 13-isobutyrate; 12-deoxyphorbol 13-isobutyrate-20-acetate; 12-deoxyphorbol 13-phenylacetate; 12-deoxyphorbol 13-phenylacetate 20-acetate; 12-deoxyphorbol 13-tetradecanoate; phorbol 12-tigliate 13-decanoate; 12-deoxyphorbol 13-acetate; phorbol 12-acetate; and phorbol 13-acetate.

[0032] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the invention include, but are not limited to, subjects with HIV and AIDS, as well as subjects with symptoms, or secondary or opportunistic diseases associated with HIV and AIDS, such as oral lesions, fatigue, skin thrush, fever, lack of appetite, diarrhea, apthous ulcers, malabsorption, thrombocytopenia, weight loss, anemia, lymph node enlargement, mycobacterium avium complex, salmonellosis, syphilis, neuroshyphilis, tuberculosis (TB), bacillary angiomatosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, pelvic inflammatory disease, Burkitt's lymphoma, cryptococcal meningitis, histoplasmosis, Kaposi's sarcoma, lymphoma, systemic non-Hodgkin's lymphoma (NHL), primary CNS lymphoma, cryptosporidiosis, isosporiasis, microsporidiosis, pneumocystis carinii pneumonia (PCP), toxoplasmosis, cytomegalovirus (CMV), hepatitis, herpes simplex, herpes zoster, human papiloma virus (HPV, genital warts, cervical cancer), molluscum contagiosum, oral hairy leukoplakia (OHL), and progressive multifocal leukoencephalopathy (PML).

[0033] Additional mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include, but are not limited to, subjects suffering from neoplastic diseases including malignant neoplastic diseases such as solid and non-solid cancers. Non-solid cancers may include, hematologic malignancies/bone marrow disorders, including, but not limited to, leukemia, including acute myeloid leukemia (AML), chronic myeloid leukemia (CML), chronic myeloid leukemia blast crisis, myelodysplasia, myeloproliferative syndrome. Solid cancers may include, but are not limited to, lymphoma, including Hodgkin's and non-Hodgkin's lymphoma, subcutaneous adenocarcinoma, ovarian teratocarcinoma, lung cancer; bone cancer; breast cancer; liver cancer; pancreatic cancer; oral cancer; non-small cell lung cancer and prostate cancer.

[0034] Subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, further include those suffering from symptoms of such neoplastic diseases such as, but not limited to, anemia; chronic fatigue; excessive or easy bleeding, such as bleeding of the nose, gums, and under the skin; easy bruising, particularly bruising with no apparent cause; shortness of breath; petechiae; recurrent fever; swollen gums; slow healing of cuts; bone and joint discomfort; recurrent infections; weight loss; itching; night sweats; lymph node swelling; fever; abdominal pain and discomfort; disturbances in vision; coughing; loss of appetite; pain in the chest; difficulty swallowing; swelling of the face, neck and upper extremities; a need to urinate frequently, especially at night; difficulty starting urination or holding back urine; weak or interrupted flow of urine; painful or burning urination; difficulty in having an erection; painful ejaculation; blood in urine or semen; frequent pain or stiffness in the lower back, hips, or upper thighs; and weakness. In some embodiments, such cancers may be relapses or refractory.

[0035] Further mammalian subjects that are amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include, but are not limited to, subjects suffering from side effects of chemotherapy or radiation therapy for the treatment of neoplastic diseases including malignant neoplastic diseases such as solid and non-solid cancers. Such side effects include, but are not limited to alopecia, nausea, vomiting, poor appetite, soreness, neutropenia, anemia, thrombocytopenia, dizziness, fatigue, constipation, oral ulcers, itchy skin, peeling, nerve and muscle damage, auditory changes, weight loss, diarrhea, immunosuppression, bruising, heart damage, bleeding, liver damage, kidney damage, edema, mouth and throat sores, infertility, fibrosis, epilation, and moist desquamation, mucosal dryness, vertigo and encephalopathy.

[0036] Additional mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods and compositions of the present invention include, but are not limited to individuals who have suffered a stroke. Subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, additionally include those suffering from the effects of a stroke including, but not limited to, paralysis, spatial impairment, impaired judgment, left-sided neglect, memory loss, aphasia, coordination and balance problems, nausea, vomiting, cognitive impairment, perception impairment, orientation impairment, homonymous hemianopsia and impulsivity.

[0037] Other mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention, include individuals suffering from rheumatoid arthritis. Symptoms of rheumatoid arthritis that may be prevented or treated by the phorbol esters of Formula I, particularly TPA, include, but are not limited to, sore joints, morning stiffness, firm bumps of tissue under the skin of the arms, fatigue, loss of energy, lack of appetite, low-grade fever or muscle and joint aches.

[0038] Additional mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention, include individuals suffering from prostate hypertrophy. The compositions and methods as described herein may be used to prevent or treat symptoms of prostate hypertrophy including, but not limited to, dribbling at the end of urination, urinary retention, incomplete emptying of the bladder, incontinence, excessive urinary frequency, pain with urination, bloody urine, delayed urination, straining to urinate, weak urine stream or strong and sudden urge to urinate.

[0039] Further mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include individuals suffering from kidney disease.

[0040] Further mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include individuals suffering from urinary incontinence.

[0041] Additional mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include individuals with visible signs of aging.

[0042] Other mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include individuals with swelling around the eyes.

[0043] Additional mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include individuals with uterine fibroids.

[0044] Additional mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include individuals with dementia.

[0045] Additional mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include individuals with diabetes.

[0046] Further mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include those suffering from autoimmune disorders including, but not limited to, myasthenia gravis. Symptoms of myasthenia gravis that may be prevented or treated by use of the compositions and methods described herein include, but are not limited to, ptosis, diplopia, speech impairment, fatiguability, muscle weakness, dysphagia or dysarthria.

[0047] Additional mammalian subjects, including humans, amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include individuals with Parkinson's disease. Symptoms of Parkinson's disease that may be treated or prevented by the use of the compositions and methods described herein include, but are not limited to, tremor at rest, stiffness, bradykinesia, rigidity, speech impairment, cognitive impairment, dementia, mood impairment, drowsiness, insomnia and postural instability.

[0048] In yet another embodiment, mammalian subjects with carpal tunnel syndrome may be treated with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention.

[0049] These and other subjects are effectively treated, prophylactically and/or therapeutically, by administering to the subject an effective amount of a phorbol ester of Formula I sufficient to prevent or reduce viral load, decrease latent reservoirs of HIV, increase immune responsiveness, increase the release of Th1 cytokines, prevent or reduce symptoms and conditions associated with HIV and AIDS, decrease and/or eliminate neoplastic cells, increase white blood cell counts, induce remission, maintain remission, prevent or reduce symptoms and conditions associated with malignancies, increase ERK phosphorylation, decrease or eliminate radiation damage, boost the immune system, decrease nausea, decrease or prevent hair loss, increase appetite, decrease soreness, increase energy levels, relieve gastrointestinal distress, decrease bruising, eliminate oral ulcers, decrease or eliminate skin damage due to radiation, increase or maintain neutrophil levels, increase or maintain platelet levels, decrease edema, decrease or eliminate moist desquamation, prevent or treat paralysis, increase spatial awareness, decrease memory loss, decrease aphasia, increase coordination and balance, improve cognition, decrease or eliminate tremors, decrease or eliminate stiffness and rigidity, improve sleep quality, increase stability, improve mobility, improve bladder control, improve appetite, ease muscle or joint aches, improve vision, and/or improve muscle control.

[0050] Therapeutically useful methods and formulations of the invention will effectively use a phorbol ester of Formula I in a variety of forms, as noted above, including any active, pharmaceutically acceptable salts of said compounds, as well as active isomers, enantiomers, polymorphs, solvates, hydrates, prodrugs, and/or combinations thereof. TPA of formula II is employed as an illustrative embodiment of the invention within the examples herein below.

[0051] Within additional aspects of the invention, combinatorial formulations and methods are provided which employ an effective amount of a phorbol ester of Formula I in combination with one or more secondary or adjunctive active agent(s) that is/are combinatorially formulated or coordinately administered with the phorbol ester compound of Formula I to yield an effective response in the subject.

[0052] Exemplary combinatorial formulations and coordinate treatment methods in the treatment of viral cytopathic diseases such as HIV and AIDS employ the phorbol ester compound of Formula I in combination with one or more additional, retroviral, HIV or AIDS treating or other indicated secondary or adjunctive therapeutic agents. Such combinatorial formulations and coordinate treatment methods may, for example, follow or be derived from various highly active antiretroviral therapy protocols (HAART protocols) and include regimens such as, but not limited to, two nucleoside analogue reverse transcriptase inhibitors plus one or more protease inhibitor or non-nucleoside analogue reverse transcriptase inhibitor among other combinations. Other combinatorial formulations and coordinate treatment methods may, for example, include treatments for opportunistic infections as well as the compounds for the HAART protocols. The secondary or adjunctive therapeutic agents used in combination with a phorbol ester, e.g., TPA, in these embodiments may possess direct or indirect antiviral effects, alone or in combination with, e.g. TPA; may exhibit other useful adjunctive therapeutic activity in combination with a phorbol ester, e.g. TPA (such as HIV preventing, HIV treating, HIV reservoir activating, Th1 cytokine increasing activity); or may exhibit adjunctive therapeutic activity useful for treating opportunistic infections associated with HIV alone or in combination with a phorbol ester, e.g. TPA.

[0053] Useful adjunctive therapeutic agents in these combinatorial formulations and coordinate treatment methods include, for example, protease inhibitors, including, but not limited to, saquinavir, indinavir, ritonavir, nelfinavir, atazanavir, darunavir, fosamprenavir, tipranavir and amprenavir; nucleoside reverse transcriptase inhibitors including but not limited to, zidovudine, didanosine, stavudine, lamivudine, zalcitabine, emtricitabine, tenofovir disoproxil fumarate, AVX754 and abacavir; non-nucleoside reverse transcriptase inhibitors including, but not limited to, nevaripine, delavirdine, calanolide A, TMC125 and efavirenz; combination drugs including, but not limited to, efavirenz/emtricitabine/tenofovir disoproxil fumarate, lamivudine/zidovudine, abacavir/lamivudine, abacavir/lamivudine/zidovudine, emtricitabine/tenofovir disoproxil fumarate, sulfamethoxazole/trimethoprim, and lopinavir/ritonavir; entry and fusion inhibitors, including, but not limited to, enfuvirtide, AMD070, BMS-488043, fozivudine tidoxil, GSK-873,140, PRO 140, PRO 542, Peptide T, SCH-D, TNX-355, and UK-427,857; treatments for opportunistic infections and other conditions associated with AIDS and HIV including, but not limited to, acyclovir, adefovir dipivoxil, aldesleukin, amphotericin b, azithromycin, calcium hydroxylapatite,

clarithromycin, doxorubicin, dronabinol, entecavir, epoetin alfa, etoposide, fluconazole, ganciclovir, immunoglobulins, interferon alfa-2, isoniazid, itraconazole, megestrol, paclitaxel, peginterferon alfa-2, pentamidine, poly-1-lactic acid, ribavirin, rifabutin, rifampin, somatropin, testosterone, trimetrexate, and valganciclovir; integrase inhibitors including, but not limited to, GS 9137, MK-0518; microbicides, including, but not limited to, BMS-378806, C31G, carbopol 974P, carrageenan, cellulose sulfate, cyanovirin-N, dextran sulfate, hydroxyethyl cellulose, PRO 2000, SPL7013, tenofovir, UC-781 and IL-2.

[0054] Exemplary combinatorial formulations and coordinate treatment methods in the treatment of neoplastic disease employ a phorbol ester compound of Formula I in combination with one or more additional, neoplastic disease treating or other indicated, secondary or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with a phorbol ester, e.g., TPA, in these embodiments may possess direct or indirect chemotherapeutic effects, alone or in combination with, e.g. TPA; may exhibit other useful adjunctive therapeutic activity in combination with a phorbol ester, e.g. TPA (such as cytotoxic, anti-inflammatory, NF-κB inhibiting, apoptosis inducing, Th1 cytokine increasing activity); or may exhibit adjunctive therapeutic activity useful for treating neoplasms or associated symptoms alone or in combination with, e.g. TPA.

[0055] Useful adjunctive or secondary therapeutic agents in these combinatorial formulations and coordinate treatment methods for the treatment of neoplastic diseases include doxorubicin, vitamin D3, cytarabine, cytosine arabinoside, daunorubicin, cyclophosphamide, gemtuzumab ozogamicin, idarubicin, mercaptopurine, mitoxantrone, thioguanine, aldesleukin, asparaginase, carboplatin, etoposide phosphate, fludarabine, methotrexate, etoposide, dexamethasone, and choline magnesium trisalicylate. In addition, adjunctive or secondary therapies may be used such as, but not limited to, radiation treatment, hormone therapy and surgery.

[0056] Exemplary combinatorial formulations and coordinate treatment methods in the prevention or treatment of side effects from chemotherapy employ a phorbol ester compound of Formula I in combination with one or more additional, chemoprotective or other indicated, secondary or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with the phorbol ester, e.g., TPA, in these embodiments may possess direct or indirect chemoprotective effects, alone or in combination with the phorbol ester, e.g. TPA; may exhibit other useful adjunctive therapeutic activity in combination with a phorbol ester, e.g. TPA (such as anti-inflammatory, neutrophil stimulating, erythropoiesis stimulating, bone resorption inhibiting, bone strengthening, antiemetic, pain relieving); or may exhibit adjunctive therapeutic activity useful for treating or preventing side effects of chemotherapy or associated symptoms alone or in combination with a phorbol ester, e.g. TPA.

[0057] Useful adjunctive or secondary therapeutic agents in these combinatorial formulations and coordinate treatment methods for the prevention or treatment of side effects of chemotherapy in a mammalian subject include, but are not limited to, pegfilgrastim, epoeitn alfa, darbepoetin alfa, alendronate sodium, risedronate, ibandronate, G-CSF, 5-HT_3 receptor antagonists, NK_1 antagonists, olanzapine, corticosteroids, dopamine antagonists, serotonin antagonists, benzodiazepines, aprepitant, and cannabinoids.

[0058] Exemplary combinatorial formulations and coordinate treatment methods in the prevention or treatment of side effects from radiation therapy as contemplated herein employ a phorbol ester compound of Formula I in combination with one or more additional, radiation protective or other indicated, secondary or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with a phorbol ester e.g., TPA, in these embodiments may possess direct or indirect protection from radiation damage, alone or in combination with a phorbol ester, e.g. TPA; may exhibit other useful adjunctive therapeutic activity in combination with the phorbol ester, e.g. TPA (such as anti-swelling, cytoprotective, anti-mucositis, epithelial stimulating, anti-fibrotic, platelet stimulating); or may exhibit adjunctive therapeutic activity useful for treating or preventing side effects of radiation therapy or associated symptoms alone or in combination with, e.g. TPA.

[0059] Useful adjunctive or secondary therapeutic agents in these combinatorial formulations and coordinate treatment methods for the prevention or treatment of side effects of radiation therapy in a mammalian subject include, but are not limited to, steroids, amifostine, chlorhexidine, benzydamine, sucralfate, keratinocyte growth factor (KGF), palifermin, Cu/Zn superoxide dismutase, Interleukin 11, or prostaglandins.

[0060] Exemplary combinatorial formulations and coordinate treatment methods in the treatment of stroke employ a phorbol ester compound of Formula I in combination with one or more additional, stroke preventing, treating or other indicated, secondary or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with a phorbol ester, e.g., TPA, in these embodiments may possess direct or indirect effects on prevention or recovery from stroke, alone or in combination with the phorbol ester, e.g. TPA; may exhibit other useful adjunctive therapeutic activity in combination with, e.g. TPA (such as anti-clotting, anticholesterolemic, vasodilating, antihypertensive); or may exhibit adjunctive therapeutic activity useful for treating or preventing stroke or associated symptoms alone or in combination with, e.g. TPA.

[0061] Useful adjunctive or secondary therapeutic agents in these combinatorial formulations and coordinate treatment methods for the prevention or treatment of stroke in a mammalian subject include, but are not limited to, tissue plasminogen activator, anticoagulant, statin, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitor, beta-blocker, calcium channel blocker, or diuretic. In addition, adjunctive or secondary therapies may be used such as, but not limited to, carotid endarterectomy, angioplasty, stent placement, craniotomy, endovascular coil emobilization, or patent foramen ovale closure.

[0062] Exemplary combinatorial formulations and coordinate treatment methods in the treatment of Parkinson's disease employ the phorbol ester compound of Formula I in combination with one or more additional, Parkinson's disease treating or other indicated, secondary, or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with a phorbol ester, e.g., TPA, in these embodiments may possess direct or indirect anti-Parkinsonian effects, alone or in combination with, e.g. TPA; may exhibit other useful adjunctive therapeutic activity in combination with, e.g. TPA (dopamine increasing, catechol-O-methyl transferase inhibiting, aromatic L-amino acid decarboxylase inhibiting, dopamine agonist, neuroprotective,

anticholinergic); or may exhibit adjunctive therapeutic activity useful for treating or preventing side effects of chemotherapy or associated symptoms alone or in combination with, e.g. TPA.

[0063] Useful adjunctive or secondary therapeutic agents in these combinatorial formulations and coordinate treatment methods for the prevention or treatment of symptoms of Parkinson's disease in a mammalian subject include, but are not limited to, levodopa, tolcapone, carbidopa, dopamine agonist, MAO-B inhibitors, pyridoxine, amantidine, pyridoxine, seleyiline, rasagiline, or anticholinergics. In addition, adjunctive or secondary therapies may be used such as, but not limited to, deep brain stimulation or lesion formation.

[0064] Exemplary combinatorial formulations and coordinate treatment methods in the treatment of prostate hypertrophy employ a phorbol ester compound of Formula I in combination with one or more additional, prostate hypertrophy treating or other indicated, secondary or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with a phorbol ester, e.g., TPA, in these embodiments may possess direct or indirect effects, alone or in combination; may exhibit other useful adjunctive therapeutic activity in combination with, e.g. TPA (type II 5-alpha reductase inhibitor, muscle relaxant); or may exhibit adjunctive therapeutic activity useful for treating or preventing prostate hypertrophy or associated symptoms alone or in combination with, e.g. TPA.

[0065] Useful adjunctive or secondary therapeutic agents in these combinatorial formulations and coordinate treatment methods for the prevention or treatment of prostate hypertrophy in a mammalian subject include, but are not limited to, finasteride, dutasteride, terazosin, doxazosin, tamsulosin, or an alpha blocker. In addition, adjunctive or secondary therapies may be used such as, but not limited to, transurethral resection of the prostate, transurethral incision of the prostate, laser surgery, or prostatectomy.

[0066] Exemplary combinatorial formulations and coordinate treatment methods in the treatment of rheumatoid arthritis employ a phorbol ester compound of Formula I in combination with one or more additional, rheumatoid arthritis treating or other indicated, secondary or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with a phorbol ester, e.g., TPA, in these embodiments may possess direct or indirect effects, alone or in combination with a phorbol ester, e.g. TPA; may exhibit other useful adjunctive therapeutic activity in combination with a phorbol ester, e.g. TPA (such as anti-inflammatory, immunosuppressing, TNF inhibiting, antibiotic, calcineurin inhibitor, pyrimidine synthesis inhibitor, 5-LO inhibitor, antifolate, IL-1 receptor antagonist, T cell costimulation inhibitor); or may exhibit adjunctive therapeutic activity useful for treating or preventing rheumatoid arthritis or associated symptoms alone or in combination with, e.g. TPA.

[0067] Useful adjunctive or secondary therapeutic agents in these combinatorial formulations and coordinate treatment methods for the prevention or treatment of rheumatoid arthritis in a mammalian subject include, but are not limited to, non-steroidal anti-inflammatory agent, steroid, disease-modifying anti-rheumatic drug, an immunosuppressant, TNF-α inhibitor, anakinra, abatacept, adalimumab, azathioprine, chloroquine, hydroxychloroquine, ciclosporin, D-penicillamine, etanercept, golimumab, gold salts, infliximab, leflunomide, methotrexate, minocycline, sulfasalazine, rituximab, or tocilizumab.

[0068] Exemplary combinatorial formulations and coordinate treatment methods in the treatment of autoimmune disorders employ a phorbol ester compound of Formula I in combination with one or more additional, autoimmune disease treating or other indicated, secondary or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with a phorbol ester, e.g., TPA, in these embodiments may possess direct or indirect effects, alone or in combination with the phorbol ester, e.g. TPA; may exhibit other useful adjunctive therapeutic activity in combination with the phorbol ester, e.g. TPA (such as immunosuppressive, antibody suppressing, anticholinesterase); or may exhibit adjunctive therapeutic activity useful for treating or preventing autoimmune disorders including myasthemia gravis or associated symptoms alone or in combination with the phorbol ester, e.g. TPA.

[0069] Useful adjunctive or secondary therapeutic agents in these combinatorial formulations and coordinate treatment methods for the prevention or treatment of autoimmune disorders in a mammalian subject include, but are not limited to, anticholinesterase, corticosteroid, or immunosuppressive agent.

[0070] Exemplary combinatorial formulations and coordinate treatment methods in the treatment of kidney disease employ the phorbol ester compound of Formula I in combination with one or more additional, kidney disease treating or other indicated, secondary or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with, e.g., TPA, in these embodiments may possess direct or indirect effects, alone or in combination with, e.g. TPA, may exhibit other useful adjunctive therapeutic activity in combination with, e.g. TPA (such as anticholinergic, antidepressant); or may exhibit adjunctive therapeutic activity useful for treating or preventing kidney disease or associated symptoms alone or in combination with, e.g. TPA.

[0071] Useful adjunctive or secondary therapeutic agents in these combinatorial formulations and coordinate treatment methods for the prevention or treatment of kidney disease in a mammalian subject include, but are not limited to, anticholinergic, topical estrogen, imipramine or duloxetine.

[0072] Exemplary combinatorial formulations and coordinate treatment methods in the treatment of urinary incontinence employ the phorbol ester compound of Formula I in combination with one or more additional, urinary incontinence treating or other indicated, secondary or adjunctive therapeutic agents. The secondary or adjunctive therapeutic agents used in combination with, e.g., TPA, in these embodiments may possess direct or indirect effects, alone or in combination with, e.g. TPA, may exhibit other useful adjunctive therapeutic activity in combination with, e.g. TPA (such as anticholinergic, antidepressant); or may exhibit adjunctive therapeutic activity useful for treating or preventing urinary incontinence or associated symptoms alone or in combination with, e.g. TPA.

[0073] Useful adjunctive or secondary therapeutic agents in these combinatorial formulations and coordinate treatment methods for the prevention or treatment of urinary incontinence in a mammalian subject include, but are not limited to, anticholinergic, topical estrogen, imipramine or duloxetine.

[0074] The forgoing and additional objects, features, aspects and advantages of the present invention will become apparent from the following detailed description.

DETAILED DESCRIPTION

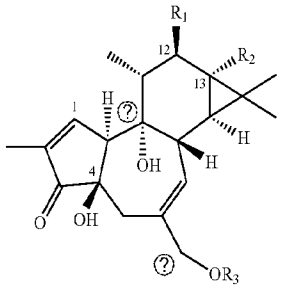
[0075] Novel methods and compositions have been identified for use in treating chronic or recurring conditions, or to repair the damage left by episodes of illness or treatment of illness in mammalian subjects, including humans.

[0076] In various embodiments, the methods and compositions are effective to prevent or treat HIV and AIDS and related conditions, diseases caused by HIV and AIDS, symptoms of HIV and AIDS, and/or diseases acquired because of HIV or AIDS infection. In other embodiments, the methods and compositions are effective to prevent or treat neoplastic diseases and symptoms of such diseases. Such neoplastic diseases may or may not be malignant. In some embodiments, the neoplastic diseases may be solid or non-solid cancers. In other embodiments, the cancers may be refractory or relapses. In additional embodiments, the methods and compositions are effective in preventing or ameliorating damage or side effects from chemotherapeutic agents. In further embodiments, the methods and compositions as described herein are effective in preventing or ameliorating damage or side effects from radiation therapy. In other embodiments, the methods and compositions as described herein are effective in preventing or treating damage from stroke. In additional embodiments, the methods and compositions as described herein are effective in treating rheumatoid arthritis. In other embodiments, the methods and compositions as described herein are effective in decreasing the signs of aging. In another embodiment, the methods and compositions as described herein are effective in treating prostate hypertrophy. In additional embodiments, the methods and compositions as described herein are effective in treating autoimmune disorders. In further embodiments, the methods and compositions a described herein are effective in treating urinary incontinence. In other embodiments, the methods and compositions as described herein are effective in treating kidney disease. In additional embodiments, the methods and compositions as described herein are effective in treating Parkinson's disease.

[0077] The composition and methods as described herein may prevent or reduce viral load, decrease latent reservoirs of HIV, increase immune responsiveness, increase the release of Th1 cytokines, prevent or reduce symptoms and conditions associated with HIV and AIDS, decrease and/or eliminate neoplastic cells, increase white blood cell counts, induce remission, maintain remission, prevent or reduce symptoms and conditions associated with malignancies, increase ERK phosphorylation, decrease or eliminate radiation damage, boost the immune system, decrease nausea, decrease or prevent hair loss, increase appetite, decrease soreness, increase energy levels, relieve gastrointestinal distress, decrease bruising, eliminate oral ulcers, decrease or eliminate skin damage due to radiation, increase or maintain neutrophil levels, increase or maintain platelet levels, decrease edema, decrease or eliminate moist desquamation, prevent or treat paralysis, increase spatial awareness, decrease memory loss, decrease aphasia, increase coordination and balance, improve cognition, decrease or eliminate tremors, decrease or eliminate stiffness and rigidity, improve sleep quality, increase stability, improve mobility, improve bladder control, increase continence, improve appetite, ease muscle or joint aches, improve vision, and/or improve muscle control, and strengthening in the immune system.

[0078] Formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I as more fully described in U.S. patent application Ser. No. 12/023,753, filed Jan. 31, 2008, which claims priority benefit of U.S. Provisional patent application Ser. No. 60/898,810, filed Jan. 31, 2007, each of which is incorporated herein in its entirety by reference,

Formula I



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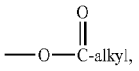
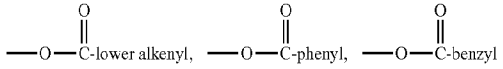
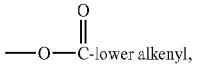
wherein R_1 and R_2 may be hydrogen;



wherein the alkyl group contains 1 to 15 carbon atoms;



and substituted derivatives thereof and R_3 may be hydrogen or



including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as novel HIV and AIDS treating compounds.

[0079] Viral load decreasing formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as novel viral load decreasing agents.

[0080] Immune responsiveness increasing formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as immune stimulatory compounds.

[0081] Th1 cytokine increasing formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as novel Th1 cytokine increasing agents.

[0082] Formulations and methods provided herein additionally employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof in the treatment of neoplastic diseases.

[0083] Apoptosis inducing formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as chemotherapeutic agents that induce apoptosis in neoplasms.

[0084] Remission inducing formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as anti-neoplasm agents.

[0085] Formulations and methods provided herein further employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof in the prevention or treatment of side effects from chemotherapy.

[0086] Formulations and methods provided herein additionally employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof in the prevention or treatment of side effects from radiation therapy.

[0087] Stroke treating formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as anti-stroke agents.

[0088] Rheumatoid arthritis treating formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as anti-rheumatoid agents.

[0089] Anti-Parkinsonian formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as anti-Parkinsonian agents.

[0090] Formulations and methods provided herein also employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof in the treatment of prostate hypertrophy.

[0091] Formulations and methods provided herein additionally employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof in the treatment of autoimmune disorders.

[0092] Formulations and methods provided herein further employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof in the treatment of carpal tunnel syndrome.

[0093] Formulations and methods provided herein additionally employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof in the treatment of kidney disease.

[0094] Continence inducing formulations and methods provided herein employ a phorbol ester or derivative compound of Formula I, above, including all active pharmaceutically acceptable compounds of this description as well as various foreseen and readily provided complexes, salts, solvates, isomers, enantiomers, polymorphs and prodrugs of these compounds and combinations thereof as continence increasing agents.

[0095] A broad range of mammalian subjects, including human subjects, are amenable to treatment using the formulations and methods of the invention. These subjects include, but are not limited to, individuals suffering from diseases or conditions including neoplastic diseases and viral diseases such as HIV and AIDS, as well as individuals suffering from Parkinson's disease, stroke, rheumatoid arthritis, side effects from chemotherapy, side effects from radiation therapy, prostate hypertrophy, urinary incontinence, Myasthemia gravis, and kidney disease.

[0096] Subjects amenable to treatment include HIV+ human and other mammalian subjects presenting with oral lesions, fatigue, skin thrush, fever, lack of appetite, diarrhea, apthous ulcers, malabsorption, thrombocytopenia, weight loss, anemia, lymph node enlargement, susceptibility to and severity of secondary conditions such as mycobacterium avium complex, salmonellosis, syphilis, neuroshyphilis, tuberculosis (TB), bacillary angiomatosis, aspergillosis, can-

didiasis, coccidioidomycosis, listeriosis, pelvic inflammatory disease, Burkitt's lymphoma, cryptococcal meningitis, histoplasmosis, Kaposi's sarcoma, lymphoma, systemic non-Hodgkin's lymphoma (NHL), primary CNS lymphoma, cryptosporidiosis, isosporiasis, microsporidiosis, pneumocystis carinii pneumonia (PCP), toxoplasmosis, cytomegalovirus (CMV), hepatitis, herpes simplex, herpes zoster, human papiloma virus (HPV, genital warts, cervical cancer), molluscum contagiosum, oral hairy leukoplakia (OHL), and progressive multifocal leukoencephalopathy (PML).

[0097] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for treating HIV/AIDS and/or related disorders. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent (s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the treatment of HIV/AIDS and related conditions.

[0098] Acquired immune deficiency syndrome or acquired immunodeficiency syndrome (AIDS or Aids) is a collection of symptoms and infections resulting from damage to the immune system caused by infection with the human immunodeficiency virus (HIV). The damage to the immune system leaves individuals prone to opportunistic infections and tumors. Although treatments for AIDS and HIV exist to slow the virus's progression and the severity of the symptoms, there is no known cure.

[0099] HIV is a retrovirus that primarily infects components of the human immure system such as CD4+ T cells, macrophages and dendritic cells. When CD4+ T cells are destroyed and their total count decreases to below 200 CD4+ T cells/μL of blood or the percentage of CD4+ T-cell as a fraction of the total lymphocytes falls to less than 14%, cellular immunity is lost, leading to AIDS.

[0100] It is currently believed that a change in the T_h1 and T_h2 cytokine balance can contribute to immune dysregulation associated with HIV infection. T_h1 cells produce cytokines that stimulate proliferation of cytotoxic T cells. T_h2 cells produce cytokines that are responsible for activation of the humoral immune responses in healthy people. Progression from HIV infection to AIDS is characterized by a decrease in levels of T_h1 cytokines IL-2, IL-12 and IFN-γ with a concomitant increase in levels of T_h2 cytokines IL-4, IL-5 and IL-10. (Clerci, Immunology Today, v. 14, No. 3, p. 107-110, 1993; Becker, Virus Genes 28:1, 5-18 (2004)). Resistance to HIV infection and/or resistance to progression to AIDS may therefore be dependent on a $T_h1>T_h2$ dominance.

[0101] A fraction of CD4+ memory T cells contain integrated transcriptionally inactive proviruses for HIV. These latent reservoirs may be activated to produce active infectious virus following activation by specific antigens or cytokines. The half life of these CD4 memory T cells is at least 44 months making it extremely difficult to eliminate HIV and requiring extended continuation of antiretroviral therapy even when HIV levels in the peripheral blood are undetectable.

[0102] Prostratin, 12-deoxyphorbol 13-acetate, a non-tumor promoting phorbol ester, has reportedly shown some effectiveness for inhibiting HIV induced cell killing and viral replication. Prostratin reportedly activated viral expression in latently-infected cell lines, but had little or no effect on chronically-infected cell lines. (Gulakowski, et al., Antiviral Research v. 33, 87-97 (1997); Williams, et al., JBC v. 279, No. 40, P. 42008-42017 (2004)). Prostratin represents a distinct subclass of protein kinase C activators which has unique biological activities that differ from tumor-promoting phorbol esters such as TPA.

[0103] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention additionally include, but are not limited to, mammalian subjects with neoplastic diseases including solid and non-solid cancers, including hematologic malignancies/bone marrow disorders, such as leukemia, including acute myeloid leukemia (AML), chronic myeloid leukemia (CML), chronic myeloid leukemia blast crisis, myelodysplasia, myeloproliferative syndrome; lymphoma, including Hodgkin's and non-Hodgkin's lymphoma; subcutaneous adenocarcinoma; ovarian teratocarcinoma; and prostate cancer. In some embodiments, such cancers may be relapses or refractory.

[0104] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for treating neoplastic diseases. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the treatment of neoplastic diseases and symptoms of such diseases.

[0105] Neoplastic disease is any growth or tumor caused by abnormal and uncontrolled cell division; it may spread to other parts of the body through the lymphatic system or the blood stream. Such growths may be malignant or benign, solid or non-solid.

[0106] In some embodiments, the neoplastic diseases may be a hematological neoplasm/bone marrow disorder such as acute myeloid leukemia (AML). AML (also called acute myelogenous leukemia, acute myeloblastic leukemia, acute granulocytic leukemia, and acute nonlymphocytic leukemia) is the most common type of acute leukemia in adults. In AML, stem cells produced by the bone marrow usually develop into a type of immature white blood cell called myeloblasts (or myeloid blasts). In individuals suffering from AML, these myeloblasts do not mature into healthy white blood cells. Additionally, stem cells in individuals with AML may develop into abnormal red blood cells or platelets. The lack of normal blood cells increases incidences of infection, anemia, and easy bleeding. Additionally, the leukemia cells can spread outside the blood to other parts of the body, including the central nervous system (brain and spinal cord), skin, and gums.

[0107] The average age of a patient with AML is over 64 years of age. Patients over the age of 60 treated for AML with

standard chemotherapeutics have a remission rate of less than 20%. Additionally, patients who develop AML after an antecedent hematologic disorder or prior leukemogenic chemotherapy/radiation therapy have similarly poor outcomes.

[0108] Chemotherapy is the treatment of cancer with an anti-neoplastic drug or combination of such drugs. Chemotherapy works by impairing the reproduction of rapidly splitting cells, a property common in cancerous cells. However it does not actively distinguish between healthy cells that are also rapidly splitting and cancerous cells and it has a number of side effects such as, but not limited to, alopecia, nausea, vomiting, poor appetite, soreness, neutropenia, anemia, thrombocytopenia, dizziness, fatigue, constipation, oral ulcers, itchy skin, peeling, nerve and muscle leprosy, auditory changes, problems with blood, weight loss, diarrhea, immunosuppression, bruising, tendency to bleed easily, heart damage, liver damage, kidney damage, vertigo and encephalopathy.

[0109] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention additionally include, but are not limited to, mammalian subjects undergoing chemotherapy.

[0110] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for preventing or treating side effects due to chemotherapy. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of side effects due to chemotherapy.

[0111] Radiation therapy uses high-energy radiation to shrink tumors and kill cancer cells. It may be applied externally, internally, or systemically. It can cause acute or chronic side effects. Acute side effects occur during treatment, and chronic side effects occur months or even years after treatment ends. The side effects that develop depend on the area of the body being treated, the dose given per day, the total dose given, the patient's general medical condition, and other treatments given at the same time. (National Cancer Institute, 2011). Common side effects of radiation therapy are moist desquamation, soreness, diarrhea, nausea, vomiting, appetite loss, constipation, itchy skin, peeling, mouth and throat sores, edema, infertility, fibrosis, epilation, and mucosal dryness.

[0112] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention additionally include, but are not limited to, mammalian subjects undergoing radiation therapy.

[0113] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for preventing or treating side effects due to radiation therapy. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of side effects due to radiation therapy.

[0114] Rheumatoid arthritis affects about 1% of the U.S. population. While the cause is unknown, it is currently believed to be caused by a combination of genetic and environmental factors. It is a chronic form of arthritis that typically occurs in joints on both sides of the body and is also considered an autoimmune disease. In rheumatoid arthritis, the immune system attaches the synovium leading to fluid buildup in the joints, causing pain and frequently systemic inflammation. While symptoms present differently in different people, it generally causes joint pain, stiffness—particularly in the morning or after sitting for long periods of time, joint swelling, fever, muscle aches, inflammation of the joints, and rheumatoid nodules.

[0115] Mammalian subjects amenable to treatment with phorbol esters of Formula. I, particularly TPA, according to the methods of the present invention additionally include, but are not limited to, mammalian subjects with rheumatoid arthritis.

[0116] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for preventing or treating symptoms of rheumatoid arthritis. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of rheumatoid arthritis and symptoms thereof.

[0117] It is estimated that 4 to 6 million people worldwide suffer from Parkinson's disease, a chronic and progressive neurodegenerative brain disorder. It is believed to have both genetic and environmental triggers, but the exact cause is unknown. May symptoms of Parkinson's disease result from a lack of dopamine and low norepinephrine levels. It is also characterized by the presence of Lewy bodies though their exact function is unknown. Parkinson's disease is characterized by tremors, bradykinesia, rigidity, speech impairment, postural instability and dementia.

[0118] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include, but are not limited to, mammalian subjects with Parkinson's disease.

[0119] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for preventing or treating Parkinson's

disease. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of Parkinson's disease and symptoms thereof.

[0120] Worldwide, stroke is the second leading cause of death, responsible for 4.4 million (9 percent) of the total 50.5 million deaths each year. (http://www.theuniversityhospital.com/stroke/stats.htm_University Hospital, Newark N.J., 2011) Ninety percent of stroke survivors suffer some type of impairment and it is the leading cause of disability among adults in the U.S. A stroke occurs when a blood vessel in the brain is blocked or bursts. Without oxygen, brain cells begin to die causing sudden numbness, tingling, weakness or loss of movement in the face, am or leg. It can also cause sudden vision changes, trouble speaking, confusion, problems with walking or balance and a sudden, severe headache. After a stroke, an individual may suffer from paralysis, spatial impairment, impaired judgment, left-sided neglect, memory loss, aphasia, coordination and balance problems, nausea, vomiting, cognitive impairment, perception impairment, orientation impairment, homonymous hemianopsia and impulsivity.

[0121] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include, but are not limited to, mammalian subjects who have suffered or are at risk for a stroke.

[0122] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for preventing or treating the effects of a stroke. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of stroke and symptoms thereof.

[0123] Prostate hypertrophy causes symptoms in more than half of men in their sixties and as many as 90 percent in their seventies and eighties. As the prostate enlarges, the layer of tissue surrounding it stops it from expanding, causing the gland to press against the urethra. The bladder wall becomes thicker and irritable and begins to contract even when it contains small amounts of urine, causing more frequent urination. Eventually, the bladder weakens and loses the ability to empty itself. (NIH Publication No. 07-3012, 2006) The most common symptoms of prostate hypertrophy are a hesitant, interrupted, weak stream; urgency and leaking or dribbling; and more frequent urination, especially at night. Additional symptoms include dribbling at the end of urination, urinary retention, incomplete emptying of the bladder, incontinence, urinary frequency, pain with urination, bloody urine, slowed or delayed urination, or straining to urinate.

[0124] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include, but are not limited to, mammalian subjects who have suffered or are at risk for prostate hypertrophy.

[0125] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for preventing or treating prostate hypertrophy. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of prostate hypertrophy and symptoms thereof.

[0126] Autoimmune disorders are conditions that occur when the immune system mistakenly attacks and destroys healthy body tissue. In individuals with an autoimmune disorder, the immune system can't tell the difference between healthy body tissue and antigens. The result is an immune response that destroys normal body tissues. In Myasthemia Gravis, antibodies are directed against the body's own proteins. The autoantibodies most commonly act against the nicotinic acetylcholine receptor (nAChR), the receptor in the motor end plate for the neurotransmitter acetylcholine that stimulates muscular contraction. (Patrick J, Lindstrom J. Autoimmune response to acetylcholine receptor. Science (1973) 180:871-2.) Symptoms of myasthemia gravis include ptosis, diplopia, speech impairment, fatigability, muscle weakness, dysphagia, or dysarthria.

[0127] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include, but are not limited to, mammalian subjects who have or are at risk for autoimmune disorders.

[0128] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for preventing or treating autoimmune disorders including myasthemia gravis. In exemplary embodiments. TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of autoimmune disorders including myasthemia gravis and symptoms thereof.

[0129] Carpal tunnel syndrome occurs when the median nerve, which runs from the forearm into the palm of the hand, becomes pressed or squeezed at the wrist. Sometimes, thickening from irritated tendons or other swelling narrows the tunnel and causes the median nerve to be compressed. The result may be pain, weakness, or numbness in the hand and wrist, radiating up the arm. Although painful sensations may indicate other conditions, carpal tunnel syndrome is the most common and widely known of the entrapment neuropathies in which the body's peripheral nerves are compressed or traumatized. (NIH Publication No. 03-4898, 2002)

[0130] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include, but are not limited to, mammalian subjects who have or are at risk for carpal tunnel syndrome.

[0131] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for preventing or treating carpal tunnel syndrome. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent (s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of carpal tunnel syndrome.

[0132] Chronic kidney disease are conditions that damage the kidneys and decrease their ability to regulate the balance of water and electrolytes, discharge metabolic waste and secreting hormones essential to human body. Symptoms of kidney disease include urinary incontinence, increased excretion of urine, uremia, and oliguria.

[0133] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include, but are not limited to, mammalian subjects who have or are at risk for kidney disease.

[0134] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for preventing or treating kidney disease. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of kidney disease and symptoms thereof.

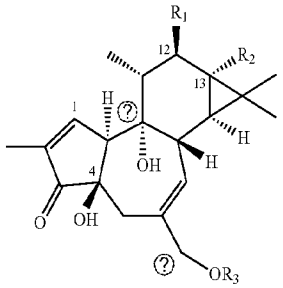
[0135] Urinary incontinence is a common and often embarrassing problem. The severity can range from occasionally leaking urine when coughing or sneezing, to losing complete control. Urinary incontinence may be caused by a variety of conditions including infection, pregnancy, aging, bladder stones, prostate cancer, bladder cancer, obstruction, prostatitis, hysterectomy, and medication. It may be transitory or permanent.

[0136] Mammalian subjects amenable to treatment with phorbol esters of Formula I, particularly TPA, according to the methods of the present invention include, but are not limited to, mammalian subjects who have or are at risk for urinary incontinence.

[0137] Within the methods and compositions of the invention, one or more phorbol ester compound(s) of Formula I as disclosed herein is/are effectively formulated or administered as an agent effective for preventing or treating urinary incontinence. In exemplary embodiments, TPA is demonstrated for illustrative purposes to be an effective agent in pharmaceutical formulations and therapeutic methods, alone or in combination with one or more adjunctive therapeutic agent(s). The present disclosure further provides additional, pharmaceutically acceptable phorbol ester compounds in the form of a native or synthetic compound, including complexes, derivatives, salts, solvates, isomers, enantiomers, polymorphs, and prodrugs of the compounds disclosed herein, and combinations thereof, which are effective as therapeutic agents within the methods and compositions of the invention in the prevention or treatment of urinary incontinence and symptoms thereof.

[0138] Phorbol is a natural, plant-derived polycyclic alcohol of the tigliane family of diterpenes. It was first isolated in 1934 as the hydrolysis product of croton oil derived from the seeds of *Croton tiglium*. It is well soluble in most polar organic solvents and in water. Esters of phorbol have the general structure of Formula I, below:

Formula I



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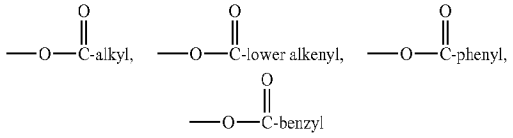
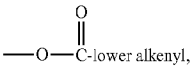
wherein R_1 and R_2 are selected from the group consisting of hydrogen;



wherein the alkyl group contains 1 to 15 carbon atoms, and substituted derivatives thereof and R_3 may be hydrogen,



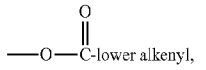
or substituted derivatives thereof.

[0139] The term "lower alkyl" or "lower alkenyl" as used herein means moieties containing 1-7 carbon atoms. In the compounds of the Formula I, the alkyl or alkenyl groups may be straight or branched chain. In some embodiments, either or both R_1 or R_2, are a long chain carbon moiety (i.e., Formula I is decanoate or myristate).

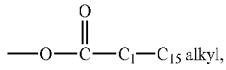
[0140] The alkyl, alkenyl, phenyl and benzyl groups of the formulas herein may be unsubstituted or substituted with halogens, preferably, chlorine, fluorine or bromine; nitro; amino and similar type radicals.

[0141] Organic and synthetic forms of phorbol esters, including any preparations or extracts from herbal sources such as *croton tiglium*, are contemplated as useful compositions comprising phorbol esters (or phorbol ester analogs, related compounds and/or derivatives) for use within the embodiments herein. Useful phorbol esters and/or related compounds for use within the embodiments herein will typically have a structure as illustrated in Formula I, although functionally equivalent analogs, complexes, conjugates, and derivatives of such compounds will also be appreciated by those skilled in the art as within the scope of the invention.

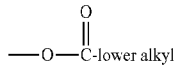
[0142] In more detailed embodiments, illustrative structural modifications according to Formula I above will be selected to provide useful candidate compounds for treating and/or preventing HIV and AIDS and/or neoplastic diseases, wherein: at least one of R_1 and R_2 are other than hydrogen and R_3 is selected from the group consisting of hydrogen



[0143] and substituted derivatives thereof. In another embodiment, either R_1 or R_2 is



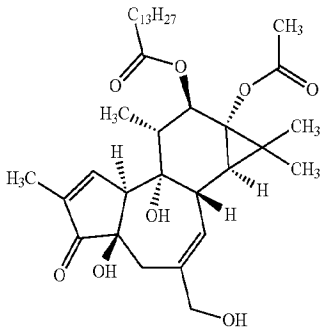
the remaining R_1 or R_2 is



and R_3 is hydrogen.

[0144] An exemplary embodiment of a phorbol ester compound of Formula I useful in the treatment of cytopathic diseases such as HIV and AIDS and/or neoplastic diseases, particularly AML, is found in phorbol 12-myristate-13-acetate (also known as PMA or 12-O-tetradecanoyl-phorbol-13-acetate (TPA)) shown in Formula II, below.

Formula II



[0145] Additional useful phorbol esters and related compounds and derivatives within the formulations and methods of the invention include, but are not limited to, other pharmaceutically acceptable active salts of said compounds, as well as active isomers, enantiomers, polymorphs, glycosylated derivatives, solvates, hydrates, and/or prodrugs of said compounds. Further exemplary forms of phorbol esters for use within the compositions and methods of the invention include, but are not limited to, phorbol 13-butyrate; phorbol 12-decanoate; phorbol 13-decanoate; phorbol 12,13-diacetate; phorbol 13,20-diacetate; phorbol 12,13-dibenzoate; phorbol 12,13-dibutyrate; phorbol 12,13-didecanoate; phorbol 12,13-dihexanoate; phorbol 12,13-dipropionate; phorbol 12-myristate; phorbol 13-myristate; phorbol 12,13,20-triacetate; 12-deoxyphorbol 13-angelate; 12-deoxyphorbol 13-angelate 20-acetate; 12-deoxyphorbol 13-isobutyrate; 12-deoxyphorbol 13-isobutyrate-20-acetate; 12-deoxyphorbol 13-phenylacetate; 12-deoxyphorbol 13-phenylacetate 20-acetate; 12-deoxyphorbol 13-tetradecanoate; phorbol 12-tigliate 13-decanoate; 12-deoxyphorbol 13-acetate; phorbol 12-acetate; and phorbol 13-acetate.

[0146] Phorbol ester compositions herein comprise HIV- and AIDS-treating compositions comprising an anti-AIDS effective amount of a phorbol ester compound of Formula I, which is effective for prophylaxis and/or treatment of HIV, AIDS, and/or HIV-related symptoms, including opportunistic infections, in a mammalian subject. An "anti-HIV", "anti-AIDS", or "AIDS treating" effective amount of the active compound is therapeutically effective, in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more symptoms of AIDS in a subject, and/or to alleviate one or more symptom(s) or condition(s) associated with HIV infection in the subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to alleviate symptoms of AIDS or other HIV-related conditions in human and other mammalian subjects vulnerable to HIV infection.

[0147] Phorbol ester compositions herein additionally may comprise chemotherapeutic compositions comprising an anti-neoplastic effective amount of a phorbol ester or derivative compound of Formula I, which is effective for maintenance and treatment of malignancies or symptoms caused by cancer in a mammalian subject. A "chemotherapeutic", "anti-tumor," "cancer treating", "apoptosis inducing", "remission inducing", "remission maintaining" effective amount of the active compound is therapeutically effective, in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more symptoms of malignancy in a subject, and/or to alleviate one or more symptom(s) or condition(s) associated with malignancy in the subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to alleviate symptoms of neoplastic disease related conditions in human and other mammalian subjects vulnerable to malignancies.

[0148] Compositions as described herein comprise chemoprotective compositions comprising an effective amount of a phorbol ester compound of Formula I to prevent or alleviate the side effects of chemotherapy. A "chemoprotective," "anti-inflammatory," "neutrophil stimulating," "erythropoiesis stimulating," "bone resorbtion inhibiting," "bone strengthening," "antiemetic," "pain relieving" effective amount of the active compound is therapeutically effective, in a single or multiple unit dosage form, over a specified period of thera-

peutic intervention, to measurably alleviate one or more of the side effects of chemotherapy in a subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to alleviate side effects of chemotherapy in human and other mammalian subjects undergoing chemotherapy.

[0149] Compositions as described herein comprise radiation therapy protective compositions comprising an effective amount of a phorbol ester compound of Formula I to prevent or alleviate the side effects of radiation therapy. A "radiation protective," "radioprotective," "anti-swelling," "cytoprotective," "anti-mucositis," "epithelial stimulating," "anti-fibrotic," "platelet stimulating" effective amount of the active compound is therapeutically effective, in single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more of the side effects of chemotherapy in a subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to alleviate side effects of radiation therapy in human and other mammalian subjects undergoing radiation therapy.

[0150] Compositions as described herein comprise stroke treating compositions comprising a stroke damage alleviating or preventing effective amount of a phorbol ester compound of Formula I, which is effective for prophylaxis and/or treatment of stroke or stroke related symptoms or sequelae in a mammalian subject. A "stroke treating," "anti-clotting," "anticholesterolemic," "vasodilating," "antihypertensive," or "neuroprotective" effective amount of the active compound is therapeutically effective, in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more symptoms or sequelae of stroke in the subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to prevent or alleviate symptoms of stroke or sequelae of stroke in human and other mammalian subjects vulnerable to or who have suffered a stroke.

[0151] Compositions as described herein further comprise Parkinson's disease treating compositions comprising an effective amount of a phorbol ester compound of Formula I which is effective for prophylaxis and/or treatment of Parkinson's disease or related symptoms in a mammalian subject. A "Parkinson's disease treating," "dopamine increasing," "catechol-O-methyl transferase inhibiting," "aromatic L-amino acid decarboxylase inhibiting," "dopamine agonist," "neuroprotective," or "anticholinergic" effective amount of the active compound is therapeutically effective in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate or prevent one or more of the symptoms of Parkinson's disease in the subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to prevent or alleviate symptoms of Parkinson's disease in human and other mammalian subjects suffering from or at risk for Parkinson's disease.

[0152] Compositions as described herein additionally comprise prostate hypertrophy treating compositions comprising an effective amount of a phorbol ester of a compound of Formula I, which is effective for prophylaxis and/or treatment of prostate hypertrophy or related symptoms or sequelae in a mammalian subject. A "prostate hypertrophy treating", "type II 5-alpha reductase inhibitor," or "muscle relaxant" effective amount of the active compound is therapeutically effective, in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more symptoms or sequelae of prostate hypertrophy in the subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to prevent or alleviate symptoms of prostate hypertrophy or sequelae in human and other mammalian subjects who have or are at risk for prostate hypertrophy.

[0153] Compositions as described herein further comprise rheumatoid arthritis treating compositions comprising anti-rheumatoid effective amounts of a phorbol ester of a compound of Formula I, which is effective for prophylaxis and/or treatment of rheumatoid arthritis or related symptoms in a mammalian subject. A "anti-rheumatoid," "anti-inflammatory," "immunosuppressing," "TNF inhibiting," "antibiotic," "calcineurin inhibitor," "pyrimidine synthesis inhibitor," "5-LO inhibitor," "antifolate," "IL-1 receptor antagonist," or "T cell costimulation inhibitor" effective amount of the active compound is therapeutically effective, in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more symptoms of rheumatoid arthritis in the subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to prevent or alleviate symptoms of rheumatoid arthritis in human and other mammalian subjects who have or are at risk for rheumatoid arthritis.

[0154] Compositions as described herein additionally comprise autoimmune disease treating compositions comprising an autoimmune disease treating effective amount of a phorbol ester of a compound of Formula I, which is effective for prophylaxis and/or treatment of an autoimmune disease such as myasthemia gravis or related symptoms or sequelae in a mammalian subject. An "autoimmune disorder treating," "myasthemia gravis treating," "immunosuppressive," "antibody suppressing," or "anticholinesterase" effective amount of the active compound is therapeutically effective, in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more symptoms or sequelae of autoimmune disease, specifically myasthemia gravis in the subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to prevent or alleviate symptoms of myasthemia gravis in human and other mammalian subjects who have or are at risk for myasthemia gravis.

[0155] Compositions as described herein additionally comprise kidney disease treating compositions comprising an effective amount of a phorbol ester of a compound of Formula I, which is effective for prophylaxis and/or treatment of kidney disease or related symptoms or sequelae in a mammalian subject. A "kidney disease treating," "anticholinergic," or "antidepressant" effective amount of the active compound is therapeutically effective, in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more symptoms or sequelae of kidney disease, including incontinence in the subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to prevent or alleviate symptoms of kidney disease in human and other mammalian subjects who have or are at risk for kidney disease.

[0156] Compositions as described herein additionally comprise urinary incontinence treating compositions comprising an effective amount of a phorbol ester of a compound of Formula I, which is effective for prophylaxis and/or treatment of urinary incontinence in a mammalian subject. A "continence increasing," "anticholinergic," "antibiotic," or "antide-

pressant" effective amount of the active compound is therapeutically effective, in a single or multiple unit dosage form, over a specified period of therapeutic intervention, to measurably alleviate one or more symptoms of urinary incontinence in the subject. Within exemplary embodiments, the compositions of the invention are effective in treatment methods to prevent or alleviate symptoms of urinary incontinence in human and other mammalian subjects who have or are at risk for kidney disease.

[0157] Phorbol ester treating, including chemotherapeutic, chemoprotectant, radioprotectant, stroke mitigating, Parkinson's disease treating, prostate hypertrophy treating, rheumatoid arthritis treating, anti-aging, kidney disease treating, continence increasing, autoimmune disease treating, and HIV treating, compositions of the invention typically comprise an effective amount or unit dosage of a phorbol ester compound of Formula I, which may be formulated with one or more pharmaceutically acceptable carriers, excipients, vehicles, emulsifiers, stabilizers, preservatives, buffers, and/or other additives that may enhance stability, delivery, absorption, half-life, efficacy, pharmacokinetics, and/or pharmacodynamics, reduce adverse side effects, or provide other advantages for pharmaceutical use. Effective amounts of a phorbol ester compound or related or derivative compound of Formula I (e.g., a unit close comprising an effective concentration/amount of TPA, or of a selected pharmaceutically acceptable salt, isomer, enantiomer, solvate, polymorph and/or prodrug of TPA) will be readily determined by those of ordinary skill in the art, depending on clinical and patient-specific factors. Suitable effective unit dosage amounts of the active compounds for administration to mammalian subjects, including humans, may range from about 10 to about 1500 μg, about 20 to about 1000 μg, about 25 to about 750 μg, about 50 to about 500 μg, about 150 to about 500 μg, about 125 μg to about 500 μg, about 180 to about 500 μg, about 190 to about 500 μg, about 220 to about 500 μg, about 240 to about 500 μg, about 260 to about 500 μg, about 290 to about 500 μg. In certain embodiments, the disease treating effective dosage of a phorbol ester compound or related or derivative compound of Formula I may be selected within narrower ranges of, for example, 10 to 25 μg, 30-50 μg, 75 to 100 μg, 100 to 300 μg, or 150 to 500 μg. These and other effective unit dosage amounts may be administered in a single dose, or in the form of multiple daily, weekly or monthly doses, for example in a dosing regimen comprising from 1 to 5, or 2 to 3, doses administered per day, per week, or per month. In one exemplary embodiment, dosages of 10 to 30 μg, 30 to 50 μg, 50 to 100 μg, 100 to 300 μg, or 300 to 500 μg, are administered one, two, three, four, or five times per day. In more detailed embodiments, dosages of 50-100 μg, 100-300 μg, 300-400 μg, or 400-600 μg are administered once or twice daily. In a further embodiment, dosages of 50-100 μg, 100-300 μg, 300-400 μg, or 400-600 μg are administered every other day. In alternate embodiments, dosages are calculated based on body weight, and may be administered, for example, in amounts from about 0.5 $\mu g/m^2$ to about 300 $\mu g/m^2$ per day, about 1 $\mu g/m^2$ to about 200 $\mu g/m^2$, about 1 $\mu g/m^2$ to about 187.5 $\mu g/m^2$ per day, about 1 $\mu g/m^2$ per day to about 175 $\mu g/m^2$ per day, about 1 $\mu g/m^2$ per day to about 157 $\mu g/m^2$ per day about 1 $\mu g/m^2$ to about 125 $\mu g/m^2$ per day, about 1 $\mu g/m^2$ to about 75 $\mu g/m^2$ per day, 1 $\mu g/m^2$ to about 50 $\mu g/m^2$ per clay, 2 $\mu g/m^2$ to about 50 $\mu g/m^2$ per day, 2 $\mu g/m^2$ to about 30 $\mu g/m^2$ per day or 3 $\mu g/m^2$ to about 30 $\mu g/m^2$ per day.

[0158] In other embodiments, dosages may be administered less frequently, for example, 0.5 $\mu g/m^2$ to about 300 $\mu g/m^2$ every other day, about 1 $\mu g/m^2$ to about 200 $\mu g/m^2$, about 1 $\mu g/m^2$ to about 187.5 $\mu g/m^2$ every other day, about 1 $\mu g/m^2$ to about 175 $\mu g/m^2$ every other day, about 1 $\mu g/m^2$ per day to about 157 $\mu g/m^2$ every other day about 1 $\mu g/m^2$ to about 125 $\mu g/m^2$ every other day, about 1 $\mu g/m^2$ to about 75 $\mu g/m^2$ every other day, 1 $\mu g/m^2$ to about 50 $\mu g/m^2$ every other day, 2 $\mu g/m^2$ to about 50 $\mu g/m^2$ every other day, 2 $\mu g/m^2$ to about 30 $\mu g/m^2$ per day or 3 $\mu g/m^2$ to about 30 $\mu g/m^2$ per day. In additional embodiments, dosages may be administered 3 times/week, 4 times/week, 5 times/week, only on weekdays, only in concert with other treatment regimens, on consecutive days, or in any appropriate dosage regimen depending on clinical and patient-specific factors

[0159] The amount, timing and mode of delivery of compositions of the invention comprising a cytopathic disease treating effective amount of a phorbol ester compound of Formula I (AIDS treating, HIV preventing, HIV treating, HIV reservoir activating, Th1 cytokine increasing, ERK phosphorylation inducing, chemotherapeutic, anti-tumor, cancer treating, remission inducing, remission maintaining, apoptosis inducing effective amount) will be routinely adjusted on an individual basis, depending on such factors as weight, age, gender, and condition of the individual, the acuteness of the cytopathic disease and/or related symptoms, whether the administration is prophylactic or therapeutic, and on the basis of other factors known to effect drug delivery, absorption, pharmacokinetics, including half-life, and efficacy.

[0160] An effective dose or multi-dose treatment regimen for the instant disease treating (alternatively, "AIDS treating", "HIV treating", "HIV preventing", "HIV reservoir activating", or "Th1 cytokine increasing", "ERK phosphorylation inducing", "chemotherapeutic", "anti-tumor", "cancer treating", "apoptosis inducing", "remission inducing", "remission maintaining", "chemoprotective," "anti-inflammatory," "neutrophil stimulating," "erythropoiesis stimulating," "bone resorbtion inhibiting," "bone strengthening," "antiemetic," "pain relieving," "radiation protective," "anti-swelling," "cytoprotective," "anti-mucositis," "epithelial stimulating," "anti-fibrotic," "platelet stimulating," "stroke treating," "anti-clotting," "anticholesterolemic," "vasodilating," "antihypertensive," "Parkinson's disease treating," "dopamine increasing," "catechol-O-methyl transferase inhibiting," "aromatic L-amino acid decarboxylase inhibiting," "dopamine agonist," "neuroprotective," "anticholinergic," "prostate hypertrophy treating", "type II 5-alpha reductase inhibitor," "muscle relaxant," "anti-rheumatoid," "anti-inflammatory," "immunosuppressing," "TNF inhibiting," "antibiotic," "calcineurin inhibitor," "pyrimidine synthesis inhibitor," "5-LO inhibitor," "antifolate," "IL-1 receptor antagonist," "T cell costimulation inhibitor," "autoimmune disorder treating," "myasthemia gravis treating," "immunosuppressive," "antibody suppressing," "anticholinesterase" "kidney disease treating," "continence increasing," "antidepressant") formulations of the invention will ordinarily be selected to approximate a minimal dosing regimen that is necessary and sufficient to substantially prevent or alleviate the symptoms of the disease including AIDS or neoplastic diseases such as cancer and related opportunistic diseases, stroke, autoimmune disease, kidney disease, urinary incontinence, Parkinson's disease, carpal tunnel syndrome, or prostate hypertrophy, in the subject, and/or to substantially prevent or alleviate one or more symptoms associated with AIDS, neoplastic diseases such as

cancer, stroke, autoimmune disease, aging, urinary incontinence, kidney disease, Parkinson's disease, carpal tunnel syndrome, prostate hypertrophy, chemotherapy treatment, or radiation treatment in the subject. A dosage and administration protocol will often include repeated dosing therapy over a course of several days or even one or more weeks or years. An effective treatment regime may also involve prophylactic dosage administered on a day or multi-dose per day basis lasting over the course of days, weeks, months or even years.

[0161] Various assays and model systems can be readily employed to determine the therapeutic effectiveness of the treatment of cytopathic diseases. For example in the treatment of HIV or AIDS effectiveness may be demonstrated by a decrease in viral load, an increase in CD4 counts, an increase in CD3 counts, an increase in IL-2 and IFN production, a decrease in IL-4 and IL-10 production, and a decrease or elimination of the symptoms of AIDS among other methods of determining effectiveness known to those of skill in the art.

[0162] Effectiveness of the compositions and methods of the invention may be demonstrated, for example, through blood tests for HIV antibodies, viral load, CD4 levels, CD8 counts, and CD3 counts. Normal levels of CD4 are usually between 600 and 1200 per microliter, or 32-68% of lymphocytes. Individuals with a CD4 count of less than 350 have a weakened immune system. Those with a CD4 count of less than 200 are considered to have AIDS. CD8 levels in a healthy individual are generally between 150-1000 per microliter. CD3 levels in a healthy individual are generally between about 885-2270 per microliter. Levels of CD3, CD4 and CD8 cells may be measured, for example, using flow cytometry. Effective amounts of the compositions of the invention will increase levels of CD3, CD4 and CD8 positive cells by at least 10%, 20%, 30%, 50% or greater reduction, up to a 75-90%, or 95% or greater. Effective amounts will also move the CD3, CD4 and CD8 profile of an individual towards the optimal category for each type of glycoprotein.

[0163] Individuals may also be evaluated using a $beta_2$-microglobulin ($beta_2$-M) test. $Beta_2$-microglobulin is a protein released into the blood when a cell dies. A rising $beta_2$-M blood level can be used to measure the progression of AIDS. Effective amounts of a composition of the present invention will lead to a decrease or cessation of increase in the amount of $beta_2$-M.

[0164] Effectiveness may further be demonstrated using a complete blood count (CBC). The measurements taken in a CBC include a white blood cell count (WBC), a red blood cell count (RBC), the red cell distribution width, the hematocrit, and the amount of hemoglobin. Specific AIDS-related signs in a CBC include a low hematocrit, a sharp decrease in the number of blood platelets, and a low level of neutrophils. An effective amount of a composition of the present invention will increase the levels measured in a complete blood count by 10%, 20%, 30%, 50% or greater increase, up to a 75-90%, or 95% or greater. Effective amounts will also move the blood protein of an individual towards the optimal category for each type of protein.

[0165] Effectiveness of the compositions and methods of the invention may also be demonstrated by a decrease in the symptoms of HIV or AIDS including, but not limited to, oral lesions, fatigue, skin thrush, fever, lack of appetite, diarrhea, apthous ulcers, malabsorption, thrombocytopenia, weight loss, anemia, and lymph node enlargement.

[0166] Effectiveness of the compositions and methods of the invention may also be demonstrated by a decrease in the susceptibility to and severity of secondary or opportunistic conditions such as mycobacterium avium complex, salmonellosis, syphilis, neuroshyphilis, tuberculosis (TB), bacillary angiomatosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, pelvic inflammatory disease, Burkitt's lymphoma, cryptococcal meningitis, histoplasmosis, Kaposi's sarcoma, lymphoma, systemic non-Hodgkin's lymphoma (NHL), primary CNS lymphoma, cryptosporidiosis, isosporiasis, microsporidiosis, pneumocystis carinii pneumonia (PCP), toxoplasmosis, cytomegalovirus (CMV), hepatitis, herpes simplex, herpes zoster, human papiloma virus (HPV, genital warts, cervical cancer), molluscum contagiosum, oral hairy leukoplakia (OHL), and progressive multifocal leukoencephalopathy (PML).

[0167] Effectiveness may further be demonstrated by reduction of detectable HIV in the HIV-infected subject; maintaining a normal T cell count; or maintaining normal p24 antigen levels.

[0168] Effectiveness in the treatment of neoplastic diseases may also be determined by a number of methods such as, but not limited to, ECOG Performance Scale, the Karnofsky Performance Scale, microscopic examination of blood cells, bone marrow aspiration and biopsy, cytogenetic analysis, biopsy, immunophenotyping, blood chemistry studies, a complete blood count, lymph node biopsy, peripheral blood smear, visual analysis of a tumor or lesion, or any other method of evaluating and/or diagnosing malignancies and tumor progression known to those of skill in the art.

[0169] For example, effectiveness of the compositions and methods herein in the treatment of hematologic malignancies/bone marrow disorders may be evaluated using, an absolute neutrophil count (ANC). A normal ANC is between 1,500 to 8,000/mm^3. Individuals suffering from hematologic malignancies/bone marrow disorders frequently have an ANC below 1500/mm^3, and may even reach levels below 500/mm^3. Effective amounts of the compositions and methods herein will increase an individual's ANC by 10%, 20%, 30%, 50% or greater increase, up to a 75-90%, or 95% or greater. Effective amounts may increase ANC levels above 1500/mm^3.

[0170] Effectiveness of the compositions and methods herein in the treatment of hematologic malignancies/bone marrow disorders may further be evaluated using, for example, a platelet count. A platelet count is normally between 150,000 to 450,000 platelets per microliter (×10−6/Liter). Individuals suffering from hematologic malignancies/bone marrow disorder may have platelet counts below 100,000 per microliter. Effective amounts of the compositions and methods herein will increase an individual's platelet count by 10%, 20%, 30%, 50% or greater increase, up to a 75-90%, or 95% or greater. Effective amounts may increase platelet levels above 100,000 per microliter.

[0171] Effectiveness of the compositions and methods herein in the treatment of hematologic malignancies/bone marrow disorders may additionally be evaluated, for example, by measuring the number of myeloblasts. Myeloblasts normally represent less than 5% of the cells in the bone marrow but should not be present in circulating blood. Effective amounts of the compositions and methods herein will decrease the number of myeloblasts by 10%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease. Effective amounts may decrease myeloblasts to below 5%.

[0172] Effectiveness of the compositions and methods herein in the treatment of hematologic malignancies/bone marrow disorders may further be evaluated by examining myeloblasts for the presence of Auer rods. Effective amounts of the compositions of the present invention will decrease the number of Auer rods visible by 10%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease up to the complete elimination of Auer rods.

[0173] Effectiveness of the compositions and methods of the invention may also be demonstrated by a decrease in the symptoms of subjects suffering from neoplastic disease including, but not limited to, anemia; chronic fatigue; excessive or easy bleeding, such as bleeding of the nose, gums, and under the skin; easy bruising, particularly bruising with no apparent cause; shortness of breath; petechiae; recurrent fever; swollen gums; slow healing of cuts; bone and joint discomfort; recurrent infections; weight loss; itching; night sweats; lymph node swelling; fever; abdominal pain and discomfort; disturbances in vision; coughing; loss of appetite; pair in the chest; difficulty swallowing; swelling of the face, neck and upper extremities; a need to urinate frequently, especially at night; difficulty starting urination or holding back urine; weak or interrupted flow of urine; painful or burning urination; difficulty in having an erection; painful ejaculation; blood in urine or semen; frequent pain or stiffness in the lower back, hips, or upper thighs; and weakness.

[0174] Effectiveness of the compositions and methods of the invention may also be demonstrated by a decrease in the symptoms of chemotherapeutic treatment including, but not limited to, alopecia, nausea, vomiting, poor appetite, soreness, neutropenia, anemia, thrombocytopenia, dizziness, fatigue, constipation, oral ulcers, itchy skin, peeling, nerve and muscle leprosy, auditory changes, problems with blood, weight loss, diarrhea, immunosuppression, bruising, tendency to bleed easily, heart damage, liver damage, kidney damage, vertigo and encephalopathy.

[0175] Effectiveness of the compositions and methods of the invention may also be demonstrated by a decrease in the symptoms that accompany radiation therapy including, but not limited to, moist desquamation, soreness, diarrhea, nausea, vomiting, appetite loss, constipation, itchy skin, peeling, mouth and throat sores, edema, infertility, fibrosis, epilation, and mucosal dryness in comparison to others who have received similar radiotherapy treatments.

[0176] Effectiveness in the treatment of rheumatoid arthritis may be demonstrated, for example, through the use of a variety of animal models including collagen-induced arthritis, as described below in Example 30, pristane induced arthritis, adjuvant induced arthritis, streptococcal cell wall induced arthritis, ovalbumin induced arthritis, antigen induced arthritis, or the air-pouch model.

[0177] Effectiveness of the compositions and methods of the invention in the treatment of rheumatoid arthritis may also be demonstrated by a decrease in the symptoms of rheumatoid arthritis including, but not limited to, joint pain, stiffness—particularly in the morning or after sitting for long periods of time, joint swelling, fever, muscle aches, inflammation of the joints, and rheumatoid nodules.

[0178] Effectiveness of the compositions and methods of the invention in the treatment of rheumatoid arthritis may also be demonstrated by a change in the erythrocyte sedimentation rate. Individuals with rheumatoid arthritis frequently have elevated levels of erythrocyte sedimentation. An effective amount of the compositions of the invention would decrease the levels of erythrocyte sedimentation by 10%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease over the initial diagnostic levels of erythrocyte sedimentation. Effectiveness may also be demonstrated by a change in the levels of rheumatoid factor and anti-cyclic citrullinated antibodies.

[0179] Effectiveness of the compositions and methods of the invention in the treatment of Parkinson's disease may be demonstrated by a decrease in the symptoms of Parkinson's including, but not limited to, tremors, bradykinesia, rigidity, speech impairment, postural instability and dementia. Effectiveness of the phorbol ester compounds of the present invention in the treatment of Parkinson's disease may further be demonstrated by an increase in dopamine and/or norepinephrine levels. Such levels may increase 10%, 20%, 30%, 50% or greater increase, up to a 75-90%, or 95% or greater of normal levels.

[0180] Effectiveness of the compositions and methods of the invention in the treatment of Parkinson's disease may further be demonstrated by a decrease in the presence of Lewy bodies. Effectiveness may also demonstrated through the use of animal models, such as MPTP induced Parkinson's, rotenone induced Parkinson's, surgically induced Parkinson's, paraquat induced Parkinson's, 6-OHDA induced Parkinson's, or α-synuclein overexpressing mice. The use of the compositions and methods of the invention will decrease the symptoms of Parkinson's disease expressed in these models by 0%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease over control animals.

[0181] Effectiveness of the compositions and methods of the invention in the treatment of stroke may be demonstrated using a variety of model systems including temporary middle cerebral artery occlusion as shown in Example 22, permanent middle cerebral artery occlusion as shown in Example 21, endovascular filament middle cerebral artery occlusion, embolic middle cerebral artery occlusion as shown in Example 20, endothelin-1-induced constriction of arteries and veins, or cerebrocortical photothrombosis. Use of the phorbol ester compositions of the present invention will decrease the symptoms exhibited by the model systems by 0%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease over control animals.

[0182] Effectiveness of the compositions and methods of the invention in the treatment of stroke may further be demonstrated by a decrease in the symptoms exhibited in individuals who have suffered a stroke. Such symptoms include, but are not limited to, paralysis, spatial impairment, impaired judgment, left-sided neglect, memory loss, aphasia, coordination and balance problems, nausea, vomiting, cognitive impairment, perception impairment, orientation impairment, homonymous hemianopsia and impulsivity. Use of the phorbol ester compositions of the present invention will decrease the symptoms exhibited by individuals by 0%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease over initial states.

[0183] Effectiveness of the compositions and methods of the invention in the treatment of prostate hypertrophy may be demonstrated by a decrease in the symptoms associated with prostate hypertrophy including, but not limited to, hesitant, interrupted, weak stream; urgency and leaking or dribbling; more frequent urination; dribbling at the end of urination; urinary retention; incomplete emptying of the bladder; incontinence; urinary frequency; pain with urination; bloody urine; slowed or delayed urination; or straining to urinate. Use of the

phorbol ester compositions of the present invention will decrease the symptoms exhibited by individuals by 0%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease over initial states.

[0184] Effectiveness of the compositions and methods of the invention in the treatment of prostate hypertrophy may additionally be demonstrated through the use of various tests such as post-void residual urine test, pressure flow studies or a cytoscopy. Use of the phorbol ester compositions of the present invention will decrease the amount of residual urine, or increase the pressure flow by 0%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater over the results prior to treatment with a phorbol ester compound.

[0185] Effectiveness of the compositions and methods of the invention in the treatment of Myasthemia gravis may be demonstrated by a decrease in the symptoms associated with Myasthemia gravis including, but not limited to, ptosis, diplopia, speech impairment, fatigability, muscle weakness, dysphagia, or dysarthria. Use of the phorbol ester compositions of the present invention will decrease the symptoms exhibited by individuals by 0%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease over initial states.

[0186] Effectiveness of the compositions and methods of the invention in the treatment of Myasthemia gravis may also be determined using the Tensilon test or the ice test, nerve conduction studies, Single Fibre EMG, or detection of serum antibodies to the acetylcholine receptor. Effectiveness can additionally be determined using animal models of Myasthemia gravis such as by immunizing animals with torpedo californica acetylcholine receptors (AChR) in complete Freund's adjuvant. Use of the phorbol ester compositions of the present invention will decrease the symptoms exhibited by individuals by 0%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease over initial states and/or controls.

[0187] Effectiveness of the compositions and methods of the invention in the treatment of Carpal Tunnel syndrome maybe demonstrated by a decrease in symptoms associated with carpal tunnel syndrome including, but not limited to, pain, weakness, or numbness in the hand and wrist, radiating up the arm. Use of the phorbol ester compositions of the present invention will decrease the symptoms exhibited by individuals by 0%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease over initial states.

[0188] Effectiveness of the compositions and methods of the invention in the treatment of kidney disease may be demonstrated by a decrease in symptoms associated with kidney disease including, but not limited to, urinary incontinence, increased excretion of urine, uremia, or oliguria. Use of the phorbol ester compositions of the present invention will decrease the symptoms exhibited by individuals by 0%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease over initial states.

[0189] Effectiveness of the compositions and methods of the invention in the treatment of urinary incontinence may be demonstrated by a decrease in symptoms associated with urinary incontinence. Use of phorbol ester compositions of the present invention will decrease the symptoms exhibited by individuals by 0%, 20%, 30%, 50% or more, up to a 75-90%, 96% or greater decrease over initial states.

[0190] For each of the indicated conditions described herein, test subjects will exhibit a 10%, 20%, 30%, 50% or greater reduction, up to a 75-90%, or 96% or greater, reduction, in one or more symptom(s) caused by, or associated with, die disease, or related diseases or conditions in the subject, compared to placebo-treated or other suitable control subjects.

[0191] Within additional aspects of the invention, combinatorial disease treating ("AIDS treating," "HIV preventing," "HIV treating," "HIV reservoir activating," "Th1 cytokine increasing," "ERK phosphorylation inducing," "apoptosis inducing," "chemotherapeutic," "anti-tumor," "cancer treating," "remission inducing," "remission maintaining," "chemoprotective," "anti-inflammatory," "neutrophil stimulating," "erythropoiesis stimulating," "bone resorbtion inhibiting," "bone strengthening," "antiemetic," "pain relieving," "radiation protective," "anti-swelling," "cytoprotective," "anti-mucositis," "epithelial stimulating," "anti-fibrotic," "platelet stimulating," "stroke treating," "anti-clotting," "anticholesterolemic," "vasodilating" "antihypertensive," "incontinence increasing," "Parkinson's disease treating," "dopamine increasing," "catechol-O-methyl transferase inhibiting," "aromatic L-amino acid decarboxylase inhibiting," "dopamine agonist," "neuroprotective," "anticholinergic," "prostate hypertrophy treating", "type II 5-alpha reductase inhibitor," "muscle relaxant," "anti-rheumatoid," "anti-inflammatory," "immunosuppressing," "TNF inhibiting," "antibiotic," "calcineurin inhibitor," "pyrimidine synthesis inhibitor," "5-LO) inhibitor," "antifolate," "IL-1 receptor antagonist," "T cell co stimulation inhibitor," "autoimmune disorder treating," "myasthemia gravis treating," "antibody suppressing," "anticholinesterase" "kidney disease treating," "antidepressant") formulations and coordinate administration methods are provided which employ an effective amount of a phorbol ester compound of Formula I and one or more secondary or adjunctive agent(s) that is/are combinatorially formulated or coordinately administered with the phorbol ester compound of Formula I to yield a combined, multi-active disease treating composition or coordinate treatment method.

[0192] Exemplary combinatorial formulations and coordinate treatment methods in this context employ the phorbol ester of Formula I in combination with the one or more secondary anti-AIDS agent(s), or with one or more adjunctive therapeutic agent(s) that is/are useful for treatment or prophylaxis of the targeted (or associated) disease, condition and/or symptom(s) in the selected combinatorial formulation or coordinate treatment regimen. For most combinatorial formulations and coordinate treatment methods of the invention, a phorbol ester compound of Formula I or related or derivative compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or coordinately useful to treat HIV/AIDS and/or one or more symptom(s) of a opportunistic or secondary disease or condition in the subject. Exemplary combinatorial formulations and coordinate treatment methods in this context employ a phorbol ester compound of Formula I in combination with one or more secondary or adjunctive therapeutic agents selected from, e.g., protease inhibitors, including, but not limited to, saquinavir, indinavir, ritonavir, nelfinavir, atazanavir, darunavir, fosamprenavir, tipranavir and amprenavir; nucleoside reverse transcriptase inhibitors including but not limited to, zidovudine, didanosine, stavudine, lamivudine, zalcitabine, emtricitabine, tenofovir disoproxil fumarate, AVX754 and abacavir; non-nucleoside reverse transcriptase inhibitors including, but not limited to, nevaripine, delavird-

ine, calanolide A, TMC125 and efavirenz; combination drugs including, but not limited to, efavirenz/emtricitabine/tenofovir disoproxil fumarate, lamivudine/zidovudine, abacavir/lamivudine, abacavir/lamivudine/zidovudine, emtricitabine/tenofovir disoproxil fumarate, sulfamethoxazole/trimethoprim, and lopinavir/ritonavir; entry and fusion inhibitors, including, but not limited to, enfuvirtide, AMD070, BMS-488043, fozivudine tidoxil, GSK-873,140, PRO 140, PRO 542, Peptide T, SCH-D, TNX-355, and UK-427,857; treatments for opportunistic infections and other conditions associated with AIDS and HIV including, but not limited to, acyclovir, adefovir dipivoxil, aldesleukin, amphotericin b, azithromycin, calcium hydroxylapatite, clarithromycin, doxorubicin, dronabinol, entecavir, epoetin alfa, etoposide, fluconazole, ganciclovir, immunoglobulins, interferon alfa-2, isoniazid, itraconazole, megestrol, paclitaxel, peginterferon alfa-2, pentamidine, poly-1-lactic acid, ribavirin, rifabutin, rifampin, somatropin, testosterone, trimetrexate, and valganciclovir; integrase inhibitors including, but not limited to, GS 9137, MK-0518; microbicides, including, but not limited to, BMS-378806, C31G, carbopol 974P, carrageenan, cellulose sulfate, cyanovirin-N, dextran sulfate, hydroxyethyl cellulose, PRO 2000, SPL7013, tenofovir, UC-781, and IL-2.

[0193] Additional exemplary combinatorial formulations and coordinate treatment methods may additionally employ the phorbol ester of Formula I in combination with one or more secondary anti-tumor agent(s), or with one or more adjunctive therapeutic agent(s) that is/are useful for treatment or prophylaxis of the targeted (or associated) disease, condition and/or symptom(s) in the selected combinatorial formulation or coordinate treatment regimen. For most combinatorial formulations and coordinate treatment methods of the invention, a phorbol ester compound of Formula I or related or derivative compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or coordinately useful to treat neoplastic diseases and one or more symptom(s) of a secondary disease or condition in the subject. Exemplary combinatorial formulations and coordinate treatment methods in this context employ a phorbol ester compound of Formula I in combination with one or more secondary or adjunctive therapeutic agents selected from, e.g., chemotherapeutic agents, anti-inflammatory agents, doxorubicin, vitamin D3, cytarabine, cytosine arabinoside, daunorubicin, cyclophosphamide, gemtuzumab ozogamicin, idarubicin, mercaptopurine, mitoxantrone, thioguanine, aldesleukin, asparaginase, carboplatin, etoposide phosphate, fludarabine, methotrexate, etoposide, dexamethasone, and choline magnesium trisalicylate. In addition, adjunctive or secondary therapies may be used such as, but not limited to, radiation treatment, hormone therapy and surgery.

[0194] Exemplary combinatorial formulations and coordinate treatment methods in the prevention or treatment of side effects from chemotherapy employ the phorbol ester compound of Formula I in combination with one or more additional, chemoprotective or other indicated, secondary or adjunctive therapeutic agents that is/are useful for treatment or prophylaxis of the targeted disease, condition and/or symptom(s). For most combinatorial formulations and coordinate treatment methods of the invention, a phorbol ester compound of Formula I or related or derivative compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or coordinately useful to prevent or treat side effects of chemotherapy in the subject. Exemplary combinatorial formulations and coordinate treatment methods in this context employ a phorbol ester compound of Formula I in combination with one or more secondary or adjunctive therapeutic agents selected from, pegfilgrastim, epoeitn alfa, darbepoetin alfa, alendronate sodium, risedronate, ibandronate, G-CSF, 5-HT_3 receptor antagonists, NK_1 antagonists, olanzapine, corticosteroids, dopamine antagonists, serotonin antagonists, benzodiazepines, aprepitant, and cannabinoids.

[0195] Exemplary combinatorial formulations and coordinate treatment methods in the prevention or treatment of side effects from radiation therapy employ the phorbol ester compound of Formula I in combination with one or more additional, radioprotective or other indicated, secondary or adjunctive therapeutic agents that is/are useful for treatment or prophylaxis of the targeted condition and/or symptom(s). For most combinatorial formulations and coordinate treatment methods of the invention, a phorbol ester compound of Formula I or related or derivative compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or coordinately useful to prevent or treat side effects of radiation therapy in the subject. Exemplary combinatorial formulations and coordinate treatment methods in this context employ a phorbol ester compound of Formula I in combination with one or more secondary or adjunctive therapeutic agents selected from steroids, amifostine, chlorhexidine, benzydamine, sucralfate, keratinocyte growth factor (KGF), palifermin, Cu/Zn superoxide dismutase. Interleukin 11, or prostaglandins.

[0196] Exemplary combinatorial formulations and coordinate treatment methods in the prevention or treatment of stoke employ the phorbol ester compound of Formula I in combination with one or more additional, neuroprotective or other indicated, secondary or adjunctive therapeutic agents that is/are useful for treatment or prophylaxis of the targeted disease, condition and/or symptom(s). For most combinatorial formulations and coordinate treatment methods of the invention, a phorbol ester compound of Formula I or related or derivative compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or coordinately useful to prevent or treat stroke, or the effects of stroke. Exemplary combinatorial formulations and coordinate treatment methods in this context employ a phorbol ester compound of Formula I in combination with one or more secondary or adjunctive therapeutic agents selected from tissue plasminogen activator, an anticoagulant, a statin, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitor, beta-blocker, calcium channel blocker, or diuretic.

[0197] Exemplary combinatorial formulations and coordinate treatment methods in the prevention or treatment of Parkinson's disease employ the phorbol ester compound of Formula I in combination with one or more additional, neuroprotective or other indicated, secondary or adjunctive therapeutic agents that is/are useful for treatment or prophylaxis of the targeted disease, condition and/or symptom(s). For most

combinatorial formulations and coordinate treatment methods of the invention, a phorbol ester compound of Formula I or related or derivative compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or coordinately useful to prevent or treat Parkinson's disease. Exemplary combinatorial formulations and coordinate treatment methods in this context employ a phorbol ester compound of Formula I in combination with one or more secondary or adjunctive therapeutic agents selected from MAO-B inhibitors, pyridoxine, amantidine, pyridoxine, seleyiline, rasagiline, or anticholinergics.

[0198] Exemplary combinatorial formulations and coordinate treatment methods in the prevention or treatment of prostate hypertrophy employ the phorbol ester compound of Formula I in combination with one or more indicated, secondary or adjunctive therapeutic agents that is/are useful for treatment or prophylaxis of the targeted disease, condition and/or symptom(s). For most combinatorial formulations and coordinate treatment methods of the invention, a phorbol ester compound of Formula I or related or derivative compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or coordinately useful to prevent or treat prostate hypertrophy. Exemplary combinatorial formulations and coordinate treatment methods in this context employ a phorbol ester compound of Formula I in combination with one or more secondary or adjunctive therapeutic agents selected from finasteride, dutasteride, terazosin, doxazosin, tamsulosin, or an alpha blocker.

[0199] Exemplary combinatorial formulations and coordinate treatment methods in the prevention or treatment of rheumatoid arthritis employ the phorbol ester compound of Formula I in combination with one or more additional, anti-rheumatoid or other indicated, secondary or adjunctive therapeutic agents that is/are useful for treatment or prophylaxis of the targeted disease, condition and/or symptom(s). For most combinatorial formulations and coordinate treatment methods of the invention, a phorbol ester compound of Formula I or related or derivative compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or coordinately useful to prevent or treat rheumatoid arthritis. Exemplary combinatorial formulations and coordinate treatment methods in this context employ a phorbol ester compound of Formula I in combination with one or more secondary or adjunctive therapeutic agents selected from non-steroidal anti-inflammatory agent, steroid, disease-modifying anti-rheumatic drug, an immunosuppressant, TNF-α inhibitor, anakinra, abatacept, adalimumab, azathioprine, chloroquine, hydroxychloroquine, ciclosporin, D-penicillamine, etanercept, golimumab, gold salts, infliximab, leflunomide, methotrexate, minocycline, sulfasalazine, rituximab, or tocilizumab.

[0200] Exemplary combinatorial formulations and coordinate treatment methods in the prevention or treatment of myasthemia gravis employ the phorbol ester compound of Formula I in combination with one or more indicated, secondary or adjunctive therapeutic agents that is/are useful for treatment or prophylaxis of the targeted disease, condition and/or symptom(s). For most combinatorial formulations and coordinate treatment methods of the invention, a phorbol ester compound of Formula I or related or derivative compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or coordinately useful to prevent or treat myasthemia gravis. Exemplary combinatorial formulations and coordinate treatment methods in this context employ a phorbol ester compound of Formula I in combination with one or more secondary or adjunctive therapeutic agents selected from anticholinesterase, corticosteroid, or immunosuppressive agent.

[0201] Exemplary combinatorial formulations and coordinate treatment methods in the prevention or treatment of kidney disease employ the phorbol ester compound of Formula I in combination with one or more anti-incontinent or other indicated, secondary or adjunctive therapeutic agents that is/are useful for treatment or prophylaxis of the targeted disease, condition and/or symptom(s). For most combinatorial formulations and coordinate treatment methods of the invention, a phorbol ester compound of Formula I or related or derivative compound is formulated, or coordinately administered, in combination with one or more secondary or adjunctive therapeutic agent(s), to yield a combined formulation or coordinate treatment method that is combinatorially effective or coordinately useful to prevent or treat kidney disease. Exemplary combinatorial formulations and coordinate treatment methods in this context employ anticholinergic, topical estrogen, imipramine or duloxetine.

[0202] In certain embodiments the invention provides combinatorial disease treating ("AIDS treating," "HIV preventing," "HIV treating," "HIV reservoir activating," "Th1 cytokine increasing," "ERK phosphorylation inducing," "apoptosis inducing," "chemotherapeutic," "anti-tumor," "cancer treating," "remission inducing," "remission maintaining," "chemoprotective," "anti-inflammatory," "neutrophil stimulating," "erythropoiesis stimulating," "bone resorbtion inhibiting," "bone strengthening," "antiemetic," "pain relieving," "radiation protective," "anti-swelling," "cytoprotective," "anti-mucositis," "epithelial stimulating," "anti-fibrotic," "platelet stimulating," "stroke treating," "anti-clotting," "anticholesterolemic," "vasodilating," "antihypertensive," "Parkinson's disease treating," "dopamine increasing," "catechol-O-methyl transferase inhibiting," "aromatic L-amino acid decarboxylase inhibiting," "dopamine agonist," "neuroprotective," "anticholinergic," "prostate hypertrophy treating", "type II 5-alpha reductase inhibitor," "muscle relaxant," "anti-rheumatoid," "anti-inflammatory," "immunosuppressing," "TNF inhibiting," "antibiotic," "calcineurin inhibitor," "pyrimidine synthesis inhibitor," "5-LO inhibitor," "antifolate," "IL-1 receptor antagonist," "T cell costimulation inhibitor," "autoimmune disorder treating," "myasthemia gravis treating," "immunosuppressive," "antibody suppressing," "anticholinesterase" "kidney disease treating," "antidepressant") formulations comprising a phorbol ester and one or more adjunctive agent(s) having disease treating activity. Within such combinatorial formulations, a phorbol ester of Formula I and the adjunctive agent(s) having disease treating activity will be present in a combined formulation in disease treating ("AIDS treating," "HIV preventing," "HIV treating," "HIV reservoir activating," "Th1 cytokine increasing," "ERK phosphorylation inducing," "apoptosis inducing," "chemotherapeutic," "anti-tumor," "cancer treating," "remission

inducing," "remission maintaining," "chemoprotective," "anti-inflammatory," "neutrophil stimulating," "erythropoiesis stimulating," "bone resorbtion inhibiting," "bone strengthening," "antiemetic," "pain relieving," "radiation protective," "anti-swelling," "cytoprotective," "anti-mucositis," "epithelial stimulating," "anti-fibrotic," "platelet stimulating," "stroke treating," "anti-clotting," "anticholesterolemic," "vasodilating," "antihypertensive," "Parkinson's disease treating," "dopamine increasing," "catechol-O-methyl transferase inhibiting," "aromatic L-amino acid decarboxylase inhibiting," "dopamine agonist," "neuroprotective," "anticholinergic," "prostate hypertrophy treating", "type II 5-alpha reductase inhibitor," "muscle relaxant," "anti-rheumatoid," "anti-inflammatory," "immunosuppressing," "TNF inhibiting," "antibiotic," "calcineurin inhibitor," "pyrimidine synthesis inhibitor," "5-LO inhibitor," "antifolate," "IL-1 receptor antagonist," "T cell costimulation inhibitor," "autoimmune disorder treating," "myasthemia gravis treating," "continence increasing," "antibody suppressing," "anticholinesterase" "kidney disease treating," "antidepressant")) effective amounts, alone or in combination. In exemplary embodiments, a phorbol ester compound of Formula I and a non-phorbol ester agent(s) will each be present in a disease treating/preventing amount (i.e., in singular dosage which will alone elicit a detectable alleviation of symptoms in the subject). Alternatively, the combinatorial formulation may comprise one or both the phorbol ester compound of Formula I and the non-phorbol ester agents in sub-therapeutic singular dosage amount(s), wherein the combinatorial formulation comprising both agents features a combined dosage of both agents that is collectively effective in eliciting a cytopathic disease or condition symptom alleviating response. Thus, one or both of the phorbol ester of Formula I and non-phorbol ester agents may be present in the formulation, or administered in a coordinate administration protocol, at a sub-therapeutic dose, but collectively in the formulation or method they elicit a detectable decrease in symptoms of cytopathic disease in the subject. For example, in some embodiments, the combinatorial formulation may include one or more compounds from a highly active antiretroviral therapy protocol (HAART protocols) in combination with a phorbol ester, among other combinations. Other combinatorial formulations may, for example, include a phorbol ester and/or compounds effective in treating the opportunistic infections of AIDS as well as compounds from HAART protocols. In other embodiments, the combinatorial formulation may include one or more additional chemotherapeutic agents. In a further embodiment, the combinatorial formulation may include one or more additional chemoprotective agents. In other embodiments, the combinatorial formulation may include one or more radioprotective agents. In yet another embodiment, the combinatorial formulation may include one or more neuroprotective agents. In a further embodiment, the combinatorial formulation may include one or more anti-inflammatory agents or other secondary or additional therapeutic agents as described herein.

[0203] To practice coordinate administration methods of the invention, a phorbol ester compound of Formula I may be administered, simultaneously or sequentially, in a coordinate treatment protocol with one or more of the secondary or adjunctive therapeutic agents contemplated herein. Thus, in certain embodiments a compound is administered coordinately with a non-phorbol ester agent, or any other secondary or adjunctive therapeutic agent contemplated herein, using separate formulations or a combinatorial formulation as described above (i.e., comprising both a phorbol ester compound of Formula I or related or derivative compound, and a non-phorbol ester therapeutic agent). This coordinate administration may be done simultaneously or sequentially in either order, and there may be a time period while only one or both (or all) active therapeutic agents individually and/or collectively exert their biological activities.

[0204] In one embodiment, such coordinate treatment methods may, for example, follow or be derived from various highly active antiretroviral therapy protocols (HAART protocols) and include regimens such as, but not limited to, two nucleoside analogue reverse transcriptase inhibitors plus one or more protease inhibitor or non-nucleoside analogue reverse transcriptase inhibitor with a phorbol ester of Formula I, among other combinations. Other coordinate treatment methods may, for example, include a phorbol ester and/or treatments for opportunistic infections as well as compounds from HAART protocols. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary AIDS symptom decreasing, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects, as well as indirect effects.

[0205] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary HIV treating agents, or other indicated or adjunctive therapeutic agents, e.g., selected from, for example, protease inhibitors, including, but not limited to, saquinavir, indinavir, ritonavir, nelfinavir, atazanavir, darunavir, fosamprenavir, tipranavir and amprenavir; nucleoside reverse transcriptase inhibitors including but not limited to, zidovudine, didanosine, stavudine, lamivudine, zalcitabine, emtricitabine, tenofovir disoproxil fumarate, AVX754 and abacavir; non-nucleoside reverse transcriptase inhibitors including, but not limited to, nevaripine, delavirdine, calanolide A, TMC125 and efavirenz; combination drugs including, but not limited to, efavirenz/emtricitabine/tenofovir disoproxil fumarate, lamivudine/zidovudine, abacavir/lamivudine, abacavir/lamivudine/zidovudine, emtricitabine/tenofovir disoproxil fumarate, sulfamethoxazole/trimethoprim, and lopinavir/ritonavir; entry and fusion inhibitors, including, but not limited to, enfuvirtide, AMD070, BMS-488043, fozivudine tidoxil, GSK-873,140, PRO 140, PRO 542, Peptide T, TNX-355, and UK-427,857; treatments for opportunistic infections and other conditions associated with AIDS and HIV including, but not limited to, acyclovir, adefovir dipivoxil, aldesleukin, amphotericin b, azithromycin, calcium hydroxylapatite, clarithromycin, doxorubicin, dronabinol, entecavir, epoetin alfa, etoposide, fluconazole, ganciclovir, immunoglobulins, interferon alfa-2, isoniazid, itraconazole, megestrol, paclitaxel, peginterferon alfa-2, pentamidine, poly-1-lactic acid, ribavirin, rifabutin, rifampin, somatropin, testosterone, trimetrexate, and valganciclovir; integrase inhibitors including, but

not limited to, GS 9137, MK-0518; microbicides, including, but not limited to, BMS-378806. C31G, carbopol 974P, carrageenan, cellulose sulfate, cyanovirin-N, dextran sulfate, hydroxyethyl cellulose, PRO 2000, SPL7013, tenofovir, and UC-781, and IL-2.

[0206] In another embodiment, such coordinate treatment methods may, for example, follow or be derived from various chemotherapeutic protocols. Other coordinate treatment methods may, for example, include a phorbol ester and/or treatments for additional symptoms of neoplastic diseases. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary neoplastic disease symptom decreasing, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects as well as indirect effects.

[0207] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary cancer treating agents, or other indicated or adjunctive therapeutic agents, e.g. doxorubicin, vitamin D3, cytarabine, cytosine arabinoside, daunorubicin, cyclophosphamide, gemtuzumab ozogamicin, idarubicin, mercaptopurine, mitoxantrone, thioguanine, aldesleukin, asparaginase, carboplatin, etoposide phosphate, fludarabine, methotrexate, etoposide, dexamethasone, and choline magnesium trisalicylate.

[0208] In another embodiment, such coordinate treatment methods may, for example, follow or be derived from various palliative protocols for chemotherapy patients. Coordinate treatment methods may, for example, include a phorbol ester and/or treatments for additional side effects of chemotherapy. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary chemotherapeutic side effect alleviating, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects as well as indirect effects.

[0209] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary chemotherapeutic side affect alleviating compounds or other indicated or adjunctive therapeutic agents, e.g. pegfilgrastim, epoeitn alfa, darbepoetin alfa, alendronate sodium, risedronate, ibandronate, G-CSF, 5-HT_3 receptor antagonists, NK_1 antagonists, olanzapine, corticosteroids, dopamine antagonists, serotonin antagonists, benzodiazepines, aprepitant, and cannabinoids.

[0210] In another embodiment, such coordinate treatment methods may, for example, follow or be derived from various palliative protocols for radiation therapy patients. Coordinate treatment methods may, for example, include a phorbol ester and/or treatments for additional side effects of radiation therapy. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary radiotherapy side effect alleviating, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects as well as indirect effects.

[0211] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary radiotherapy side affect alleviating compounds or other indicated or adjunctive therapeutic agents, e.g. steroids, amifostine, chlorhexidine, benzydamine, sucralfate, keratinocyte growth factor (KGF), palifermin, Cu/Zn superoxide dismutase, Interleukin 11, or prostaglandins.

[0212] In another embodiment, such coordinate treatment methods may, for example, follow or be derived from various protocols for the treatment of stroke. Coordinate treatment methods may, for example, include a phorbol ester and/or treatments for prevention or treatment of damage caused by a stroke. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary stroke preventing or treating agent, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects as well as indirect effects.

[0213] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary stroke treating compounds or other indicated or adjunctive therapeutic agents, e.g. tissue plasminogen activator, an anticoagulant, a statin, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitor, beta-blocker, calcium channel blocker, or diuretic. In addition, adjunctive or secondary therapies may be used in the treatment of stroke or the effects of stroke such as, but not limited to, carotid endarterectomy, angioplasty, stent placement, craniotomy, endovascular coil emobilization, or patent foramen ovale closure.

[0214] In another embodiment, such coordinate treatment methods may, for example, follow or be derived from various protocols for the treatment of Parkinson's disease. Coordinate treatment methods may, for example, include a phorbol ester and/or treatments for prevention or treatment of Parkin-

son's disease. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary Parkinson's disease preventing or treating agent, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects as well as indirect effects.

[0215] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary Parkinson's disease treating compounds or other indicated or adjunctive therapeutic agents, e.g. levodopa, tolcapone, carbidopa, dopamine agonist, inhibitors, pyridoxine, amantidine, pyridoxine, seleyiline, rasagiline, or anticholinergics. In addition, adjunctive or secondary therapies may be used in the treatment of Parkinson's disease such as, but not limited to, deep brain stimulation or lesion formation.

[0216] In another embodiment, such coordinate treatment methods may, for example, follow or be derived from various protocols for the treatment of prostate hypertrophy. Coordinate treatment methods may, for example, include a phorbol ester and/or treatments for prevention or treatment of prostate hypertrophy. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary prostate hypertrophy preventing or treating agent, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects as well as indirect effects.

[0217] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary prostate hypertrophy treating compounds or other indicated or adjunctive therapeutic agents, e.g. finasteride, dutasteride, terazosin, doxazosin, tamsulosin, or an alpha blacker. In addition, adjunctive or secondary therapies may be used in the treatment of prostate hypertrophy such as, but not limited to, transurethral resection of the prostate, transurethral incision of the prostate, laser surgery, or prostatectomy.

[0218] In another embodiment, such coordinate treatment methods may, for example, follow or be derived from various protocols for the treatment of rheumatoid arthritis. Coordinate treatment methods may, for example, include a phorbol ester and/or treatments for the prevention or treatment of rheumatoid arthritis. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary rheumatoid arthritis preventing or treating agent, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects as well as indirect effects.

[0219] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary rheumatoid arthritis treating compounds or other indicated or adjunctive therapeutic agents, e.g. non-steroidal anti-inflammatory agent, steroid, disease-modifying anti-rheumatic drug, an immunosuppressant, TNF-α inhibitor, anakinra, abatacept, adalimumab, azathioprine,

chloroquine, hydroxychloroquine, ciclosporin, D-penicillamine, etanercept, golimumab, gold salts, infliximab, leflunomide, methotrexate, minocycline, sulfasalazine, rituximab, or tocilizumab.

[0220] In another embodiment, such coordinate treatment methods may, for example, follow or be derived from various protocols for the treatment of autoimmune disease. Coordinate treatment methods may, for example, include a phorbol ester and/or treatments for the prevention or treatment of myasthemia gravis. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary myasthemia gravis preventing or treating agent, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects as well as indirect effects.

[0221] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary myasthemia gravis treating compounds or other indicated or adjunctive therapeutic agents, e.g. anticholinesterase, corticosteroid, or immunosuppressive agent.

[0222] In another embodiment, such coordinate treatment methods may, for example, follow or be derived from various protocols for the treatment of kidney disease. Coordinate treatment methods may, for example, include a phorbol ester and/or treatments for the prevention or treatment of kidney disease and symptoms of kidney disease. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary kidney disease preventing or treating agent, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the sub-

ject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects as well as indirect effects.

[0223] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary kidney disease treating compounds or other indicated or adjunctive therapeutic agents, e.g. anticholinergic, topical estrogen, imipramine or duloxetine.

[0224] In another embodiment, such coordinate treatment methods may, for example, follow or be derived from various protocols for the treatment of urinary incontinence. Coordinate treatment methods may, for example, include a phorbol ester and/or treatments for the prevention or treatment of urinary incontinence. A distinguishing aspect of all such coordinate treatment methods is that the phorbol ester compound of Formula I exerts at least some activity, which yields a favorable clinical response in conjunction with a complementary urinary incontinence preventing or treating agent, or distinct, clinical response provided by the secondary or adjunctive therapeutic agent. Often, the coordinate administration of the phorbol ester compound of Formula I with the secondary or adjunctive therapeutic agent will yield improved therapeutic or prophylactic results in the subject beyond a therapeutic effect elicited by the phorbol ester compound of Formula I, or the secondary or adjunctive therapeutic agent administered alone. This qualification contemplates both direct effects as well as indirect effects.

[0225] Within exemplary embodiments, a phorbol ester compound of Formula I will be coordinately administered (simultaneously or sequentially, in combined or separate formulation(s)), with one or more secondary urinary incontinence treating compounds or other indicated or adjunctive therapeutic agents, e.g. anticholinergic, topical estrogen, imipramine or duloxetine.

[0226] As noted above, in all of the various embodiments of the invention contemplated herein, the disease treating methods and formulations may employ a phorbol ester compound of Formula I in any of a variety of forms, including any one or combination of the subject compound's pharmaceutically acceptable salts, solvates, isomers, enantiomers, polymorphs, solvates, hydrates, and/or prodrugs. In exemplary embodiments of the invention, TPA is employed within the therapeutic formulations and methods for illustrative purposes.

[0227] The pharmaceutical compositions of the present invention may be administered by any means that achieve their intended therapeutic or prophylactic purpose. Suitable routes of administration for the compositions of the invention include, but are not limited to, conventional delivery routes, devices and methods including injectable methods such as, but not limited to, intravenous, intramuscular, intraperitoneal, intraspinal, intrathecal, intracerebroventricular, intraarterial, subcutaneous and intranasal routes.

[0228] The compositions of the present invention may further include a pharmaceutically acceptable carrier appropriate for the particular mode of administration being employed. Dosage forms of the compositions of the present invention include excipients recognized in the art of pharmaceutical compounding as being suitable for the preparation of dosage units as discussed above. Such excipients include, without intended limitation, binders, fillers, lubricants, emulsifiers, suspending agents, sweeteners, flavorings, preservatives, buffers, wetting agents, disintegrants, effervescent agents and other conventional excipients and additives.

[0229] If desired, the compositions of the invention can be administered in a controlled release form by use of a slow release carrier, such as a hydrophilic, slow release polymer. Exemplary controlled release agents in this context include, but are not limited to, hydroxypropyl methyl cellulose, having a viscosity in the range of about 100 cps to about 100,000 cps or other biocompatible matrices such as cholesterol.

[0230] Some phorbol ester compositions of Formula I of the invention are designed for parenteral administration, e.g. to be administered intravenously, intramuscularly, subcutaneously or intraperitoneally, including aqueous and non-aqueous sterile injectable solutions which, like many other contemplated compositions of the invention, may optionally contain anti-oxidants, buffers, bacteriostats and/or solutes which render the formulation isotonic with the blood of the mammalian subject; and aqueous and non-aqueous sterile suspensions which may include suspending agents and/or thickening agents. The formulations may be presented in unit-dose or multi-close containers. Additional compositions and formulations of the invention may include polymers for extended release following parenteral administration. The parenteral preparations may be solutions, dispersions or emulsions suitable for such administration. The subject agents may also be formulated into polymers for extended release following parenteral administration. Pharmaceutically acceptable formulations and ingredients will typically be sterile or readily sterilizable, biologically inert, and easily administered. Such polymeric materials are well known to those of ordinary skill in the pharmaceutical compounding arts. Parenteral preparations typically contain buffering agents and preservatives, and injectable fluids that are pharmaceutically and physiologically acceptable such as water, physiological saline, balanced salt solutions, aqueous dextrose, glycerol or the like. Extemporaneous injection solutions, emulsions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose, as described herein above, or an appropriate fraction thereof, of the active ingredient(s).

[0231] In more detailed embodiments, compositions of the invention may comprise a phorbol ester compound of Formula I encapsulated for delivery in microcapsules, microparticles, or microspheres, prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly (methylmethacylate) microcapsules, respectively; in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules); or within macroemulsions.

[0232] As noted above, in certain embodiments the methods and compositions of the invention may employ pharmaceutically acceptable salts, e.g., acid addition or base salts of the above-described phorbol ester compounds of Formula I and/or related or derivative compounds. Examples of pharmaceutically acceptable addition salts include inorganic and organic acid addition salts. Suitable acid addition salts are formed from acids which form non-toxic salts, for example, hydrochloride, hydrobromide, hydroiodide, sulphate, hydrogen sulphate, nitrate, phosphate, and hydrogen phosphate salts. Additional pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salts, potas-

sium salts, cesium salts and the like; alkaline earth metals such as calcium salts, magnesium salts and the like; organic amine salts such as triethylamine salts, pyridine salts, picoline salts, ethanolamine salts, triethanolamine salts, dicyclohexylamine salts, N,N'-dibenzylethylenediamine salts and the like; organic acid salts such as acetate, citrate, lactate, succinate, tartrate, maleate, fumarate, mandelate, acetate, dichloroacetate, trifluoroacetate, oxalate, and formate salts; sulfonates such as methanesulfonate, benzenesulfonate, and p-toluenesulfonate salts; and amino acid salts such as arginate, asparaginate, glutamate, tartrate, and gluconate salts. Suitable base salts are formed from bases that form non-toxic salts, for example aluminum, calcium, lithium, magnesium, potassium, sodium, zinc and diethanolamine salts.

[0233] Other detailed embodiments, the methods and compositions of the invention for employ prodrugs of phorbol esters of Formula I. Prodrugs are considered to be any covalently bonded carriers which release the active parent drug in vivo. Examples of prodrugs useful within the invention include esters or amides with hydroxyalkyl or aminoalkyl as a substituent, and these may be prepared by reacting such compounds as described above with anhydrides such as succinic anhydride.

[0234] The invention disclosed herein will also be understood to encompass methods and compositions comprising phorbol esters of Formula I using in vivo metabolic products of the said compounds (either generated in vivo after administration of the subject precursor compound, or directly administered in the form of the metabolic product itself). Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes methods and compositions of the invention employing compounds produced by a process comprising contacting a phorbol ester compound of Formula I with a mammalian subject for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled compound of the invention, administering it parenterally in a detectable dose to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur and isolating its conversion products from the urine, blood or other biological samples.

[0235] The invention disclosed herein will also be understood to encompass diagnostic compositions for diagnosing the risk level, presence, severity, or treatment indicia of, or otherwise managing diseases including, but not limited to, neoplastic diseases including malignant neoplastic diseases such as leukemia, stroke, Parkinson's disease, myasthemia gravis, rheumatoid arthritis, kidney disease, prostate hypertrophy, and an AIDS or a related disease or condition in a mammalian subject, comprising contacting a labeled (e.g., isotopically labeled, fluorescent labeled or otherwise labeled to permit detection of the labeled compound using conventional methods) phorbol ester compound of Formula I to a mammalian subject (e.g., to a cell, tissue, organ, or individual) at risk or presenting with one or more symptom(s) of cancer, stroke, Parkinson's disease, myasthemia gravis, rheumatoid arthritis, kidney disease, prostate hypertrophy, and/or AIDS, and thereafter detecting the presence, location, metabolism, and/or binding state (e.g., detecting binding to an unlabeled binding partner involved in HIV receptor physiology/metabolism or malignant cell receptor physiology/metabolism) of the labeled compound using any of a broad array of known assays and labeling/detection methods. In exemplary embodiments, a phorbol ester compound of Formula I is isotopically-labeled by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. The isotopically-labeled compound is then administered to an individual or other subject and subsequently detected as described above, yielding useful diagnostic and/or therapeutic management data, according to conventional techniques.

EXAMPLES

[0236] The experiments described below demonstrate novel and powerful uses for phorbol esters and derivative compounds as HIV treating drugs that can effectively decrease the symptoms of AIDS. In exemplary clinical trials, individuals who were unresponsive to traditional treatments for HIV and AIDS were responsive to treatments with TPA. The treatment with TPA was allowed as "compassionate" and recovery of some patients was considered life-saving according to the attending physicians. The experiments described below additionally demonstrate the usefulness of phorbol esters and derivative compounds in the treatment of neoplastic diseases, as chemoprotectants, radioprotectants, in the treatment of stroke, Parkinson's disease, prostate hypertrophy, rheumatoid arthritis, kidney disease, urinary incontinence and myasthemia gravis. Phorbol esters have additionally provided unexpected cosmetic results in the form of decreasing the appearance of dark circles and increasing the youthfulness of the skin. These and additional findings are further expanded and elucidated within the following examples.

Example I

Effect of TPA on the Peripheral White Blood Cells (WBC) and Hemoglobin (Hb) Counts in S180 Cell-Injected Mice

[0237] Sarcoma 180 (S180) cells were injected into Kwen-Ming mice. On the third day, the mice were given TPA interperitoneally (i.p.). at 50, 100 or 200 μg/kg/day for 7 days. On the second day after the treatment was completed, blood samples were taken from the tails of the treated mice for WBC and Hb analyses. The WBC counts for the treated groups (50, 100, or 200 ug/kg/day for 7 days) were 16.1±7.4, 18.7±3.0 and 20.7±3.4×10^{9}/L, respectively; the WBC count for the control group was 13.6±1.8×10^{9}/L. The Hb of the treated groups were 136±11, 149±12 and 149±10 g/L, and the Hb of the control group was 134+−15 g/L. The results indicate that i.p. injection of TPA could increase the peripheral WBC counts in mice in a dose-dependent manner, whereas the Hb levels were not greatly affected in TPA treated mice when compared to the control mice.

Example II

Dose Ranging Study

[0238] Due to the strong local irritation caused by TPA application, TPA was given to patients by intravenous (i.v.)

infusion. TPA solution in a sterile syringe was injected into 200 ml of sterile saline and mixed well for i.v. infusion.

[0239] The Toxicity and Side Effects of Different TPA Doses Administered Clinically:

[0240] (1) TPA given at 1 mg/patient/week:

[0241] One mg TPA in solution was mixed well with 200 ml of sterile saline for intravenous infusion which was completed in 1 h at the rate of 16 μg/min. One hour after TPA administration, patients started to have chills which lasted for about 30 min, followed by fever, (the patients' temperature reached 37.5-39.5° C. which lasted for 3-5 h, then returned to normal) with light to heavy perspiration. The above symptoms could be alleviated by giving the patients glucocorticoids. TPA at this close caused a minority of patients to bleed, several patients suffered for a short period of time difficulty in breathing, and Hb was detected in the urine. However, these side effects were short lived and reversible. The cardiac, hepatic, renal and pulmonary functions were all found to be normal.

[0242] (2) TPA given at 0.5 mg/patient×2/week: (two doses a week)

[0243] 0.5 mg of TPA in solution was mixed well with 200 ml of saline for intravenous infusion which was completed in 1 h at the rate of 8 μg/min. The reactions after administration were similar to that of the 1 mg TPA dosage, but to a lesser extent than the 1 mg dose. The patients tolerated the lower dose more easily. Occasionally, Hb was detected in patients' urine. Difficulty in breathing was not observed. The cardiac, hepatic, renal and pulmonary functions were all normal.

[0244] (3) TPA given at 0.25 mg/patient×4/week:

[0245] 0.25 mg of TPA in solution was mixed well with 200 ml of saline for intravenous infusion which was completed in 1 h at the rate of 4 μg/min. After administration, symptoms such as chills and fever were also observed, but to a much lesser extent than with the higher dosages. No Hb was detected in the urine, and no patient suffered difficulty in breathing. The cardiac, hepatic, renal and pulmonary functions were all normal.

Example III

First Clinical Study of HIV+ Patients Treated with TPA

[0246] Twelve symptomatic patients (five males and seven females) between the ages of 35 to 52 all of whom were infected with HIV in 1995 through blood transfusion and were refractory to standard treatments for HIV were treated with TPA. Each patient was administered a weight adjusted dosage of TPA (75 μg/sq m) in 200 ml of sterile saline by i.v. over one hour. This dose was administered once daily for the first three days of treatment. Each patient was then given this dose every other day for days 4 to 18 followed by a six month rest period prior to a second course of treatment according to the same protocol.

[0247] Blood samples were gathered prior to administration of the first dose of TPA and on days 4 and 40 of the treatment cycle. Levels of CD3, CD4 and CD8 in peripheral blood were measured using monoclonal antibodies (Becton Dickson Scientific Co., Franklin Lakes, N.J.) and a flow cytometer (B.D. Bioscience, San Diego, Calif.).

[0248] As can be seen in Table 1, no consistent change or correlation was observed in CD3, CD4, or CD8 levels.

TABLE ONE

CD_4 CD_8 CD_3 TEST RESULTS OF TWELVE HIV PATIENTS

PATIENT NO	TEST TIME	CD_4	CD_8	CD_3
01-1	Before TPA	3	196	341
01-2	Four days after TPA	3	180	299
01-3	Forty two days after TPA	2	111	203
02-1	Before TPA	26	614	687
02-2	Four days after TPA	105	<2000	2616
02-3	Forty two days after TPA	54	700	799
03-1	Before TPA	32	524	543
03-2	Four days after TPA	36	366	427
03-3	Forty two days after TPA	33	374	424
04-1	Before TPA	173	735	975
04-2	Four days after TPA	123	770	941
04-3	Forty two days after TPA	44	493	581
05-1	Before TPA	106	1556	1646
05-2	Four days after TPA	119	1330	1282
05-3	Forty two days after TPA	191	1429	1643
06-1	Before TPA	232	865	1221
06-2	Four days after TPA	179	570	808
06-3	Forty two days after TPA	49	429	537
07-1	Before TPA	10	988	1022
07-2	Four days after TPA	7	570	598
07-3	Forty two days after TPA	1	139	146
08-1	Before TPA	524	725	1332
08-2	Four days after TPA	318	355	739
08-3	Forty two days after TPA	241	527	858
09-1	Before TPA	442	1021	1479
09-2	After TPA	663	<2000	2920
10-1	Before TPA	407	328	778
10-2	After TPA	445	591	1077
11-1	Before TPA	40	322	373
11-2	After TPA	131	724	874
12-1	Before TPA	84	256	375
12-2	After TPA	78	268	362

[0249] As can be seen in Table 2, below, there were similarly inconsistent results in the change of viral load with five patients having an increase in HIV and no change or a reduction in seven others.

TABLE TWO

BLOOD HIV COUNT OF THE TWELVE PATIENTS BEFORE DURING AND AFTER THE TPA TREATMENT

PATIENT NO	TEST TIME	RESULTS (copies/ml)	LOG VALUE	FOOT NOTE
01-1	3 days before TPA	3.36×10^5	5.526	
01-2	4 days after initial TPA	1.41×10^4	6.151	
01-3	15 days after initial TPA	2.02×10^4	4.306	
01-4	25 days after initial TPA	2.60×10^4	4.416	
02-1	3 days before TPA	9.97×10^4	4.999	
02-2	4 days after initial TPA	7.92×10^6	6.899	
02-3	15 days after initial TPA	6.33×10^6	6.801	
02-4	25 days after initial TPA	8.72×10^6	6.941	
03-1	3 days before TPA	3.77×10^5	5.577	
03-2	4 days after initial TPA	8.13×10^4	4.910	
03-3	15 days after initial TPA	6.11×10^3	3.786	
03-4	25 days after initial TPA	8.59×10^5	5.934	
04-1	3 days before TPA	1.11×10^6	6.045	

TABLE TWO-continued

BLOOD HIV COUNT OF THE TWELVE PATIENTS BEFORE DURING AND AFTER THE TPA TREATMENT

PATIENT NO	TEST TIME	RESULTS (copies/ml)	LOG VALUE	FOOT NOTE
04-2	4 days after initial TPA	1.75×10^7	7.243	
04-3	15 days after initial TPA	1.11×10^6	6.614	
04-4	25 days after initial TPA	1.21×10^4	4.084	
05-1	3 days before TPA	2.49×10^4	6.637	
05-2	4 days after initial TPA	9.42×10^5	5.974	
05-3	15 days after initial TPA	2.34×10^7	7.369	
05-4	25 days after initial TPA	5.56×10^6	6.745	
06-1	3 days before TPA	4.57×10^5	5.660	
06-2	4 days after initial TPA	1.44×10^4	4.160	
06-3	15 days after initial TPA	1.88×10^5	5.274	
06-4	7 days after TPA	2.28×10^6	6.357	
07-1	3 days before TPA	2.40×10^5	5.623	
07-2	4 days after initial TPA	1.51×10^5	5.179	
07-3	15th day during TPA	9.74×10^4	4.988	
07-4	25 days after initial TPA	5.30×10^3	3.724	
08-1	3 days before TPA	8.02×10^5	5.904	
08-2	4 days after initial TPA	9.09×10^5	5.959	
08-3	15 days after initial TPA	5.46×10^6	6.737	
08-4	25 days after initial TPA	7.77×10^6	6.890	
09-1	3 days before TPA	undetectable		
09-2	25 days after TPA	undetectable		
10-1	3 days before TPA	1.51×10^4	4.180	Sample taken from the
10-2	25 days after initial TPA	2.79×10^4	4.446	second cycle treatment
11-1	3 days before TPA	1.59×10^5	5.201	Sample taken from the
11-2	25 days after initial TPA	1.25×10^5	5.096	second cycle treatment
12-1	3 days before TPA	1.32×10^4	4.122	Sample taken from the
12-2	25 days after initial TPA	6.27×10^3	3.798	second cycle treatment

[0250] Despite the lack of correlation with viral and CD3, CD4 and CD9 levels, eleven of the patients showed significant improvement following treatment. Eight patients became symptom free and five of them have been in remission for 6 to 12 months. Three additional patients had a decrease in symptoms.

Example IV

Second Clinical Study of HIV+ Patients Treated with TPA

[0251] Nine of the patients in Example III were given a second treatment of TPA. Of these nine, seven were asymptomatic at the beginning of the second trial. A tenth patient (patient #2a) who was symptomatic and had not previously been treated with TPA was added to the study. Each patient was administered a weight adjusted dosage of TPA (75 μg/sq m) in 200 ml of sterile saline intravenously over one hour. This dosage was given to each patient once a day for ten consecutive days followed by a rest period of ten days for three cycles and a total of 30 doses of TPA. Patients 5a, 6a, and 8a stopped taking anti-AIDS drugs one month prior to beginning the TPA treatment and beginning again one month after the third cycle. Patients 1-4a, 7a, and 9a-10a continued taking anti-AIDS drugs throughout the treatment.

[0252] Blood samples were taken three days prior to starting treatment, after completing the first 10 day cycle of TPA infusion and again after the last TPA infusion and CD3, CD4, CD8, WBC, RBC, HGB and platelets were measured.

[0253] As shown in Table 3, there was an increase in CD3 in all patients after the first and third infusion with TPA with the highest value occurring after the third cycle, with the exception of two patients (5a & 10a). There was a trend for increases in the CD8 and in CD4. These results suggest a strengthening of the immune systems with TPA treatment. Varied results were obtained in the HIV count (Table 4). The HIV measurements in some of the patients were below the limits of detection of the method (less than 200) while it increased somewhat in others. There was normal variation in the measurement of WBC, RBC, HGB and platelets (Table 5).

TABLE THREE

CD_4 CD_8 CD_3 TEST RESULTS OF 10 HIV PATIENTS

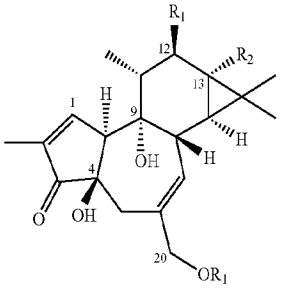
PATIENT NO	TEST TIME	CD_4	CD_8	CD_3
01-1	Before TPA	5	576	1071
01-2	After first 10-day TPA infusion cycle	7	907	1323
01-3	After third 10-day TPA infusion cycle	19	1129	2037
02a-1	Before TPA	26	307	339
02a-2	After first 10-day TPA infusion cycle	76	335	476
02a-3	After third 10-day TPA infusion cycle	137	543	625
03a-1	Before TPA	295	571	870
03a-2	After first 10-day TPA infusion cycle	460	729	1200
03a-3	After third 10-day TPA infusion cycle	1002	980	2033
04a-1	Before TPA	152	672	896
04a-2	After first 10-day TPA infusion cycle	189	584	823
04a-3	After third 10-day TPA infusion cycle	205	916	1193
05a-1	Before TPA	92	1097	1175
05a-2	After first 10-day TPA infusion cycle	91	1507	1598
05a-3	After third 10-day TPA infusion cycle	94	1127	1257
06a-1	Before TPA	230	378	669
06a-2	After first 10-day TPA infusion cycle	285	429	758
06a-3	After third 10-day TPA infusion cycle	276	466	938
07a-1	Before TPA	567	1736	2258
07a-2	After first 10-day TPA infusion cycle	729	>2000	3148
07a-3	After third 10-day TPA infusion cycle	786	>2000	3347
08a-1	Before TPA	361	569	1023
08a-2	After first 10-day TPA infusion cycle	519	547	1143
08a-3	After third 10-day TPA infusion cycle	495	733	1295
09a-1	Before TPA	101	533	672
09a-2	After first 10-day TPA infusion cycle	136	574	712
09a-3	After third 10-day TPA infusion cycle	100	1221	1317
10a-1	Before TPA	49	178	240
10a-2	After first 10-day TPA infusion cycle	74	261	333
10a-3	After third 10-day TPA infusion cycle	63	208	308

We claim:

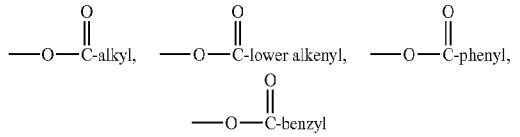
1-48. (canceled)

49. A method of treating or preventing neoplasms in a mammalian subject comprising administering an effective amount of a phorbol ester or derivative of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

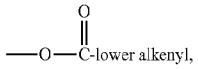
Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,

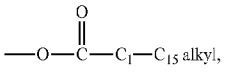


and substituted derivatives thereof, R_3 is selected from hydrogen,

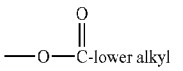


and substituted derivatives thereof; and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent neoplasms in said subject.

50. The method of claim **49**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

51. The method of claim **49**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

52. The method of claim **49**, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

53. The method of claim **49**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

54. The method of claim **49**, wherein the at least one secondary or adjunctive therapeutic agent is selected from the group consisting of doxorubicin, vitamin D3, cytarabine, cytosine arabinoside, daunorubicin, cyclophosphamide, gemtuzumab ozogamicin, idarubicin, mercaptopurine, mitoxantrone, thioguanine, aldesleukin, asparaginase, carboplatin, etoposide phosphate, fludarabine, methotrexate, etoposide, dexamethasone, and choline magnesium trisalicylate.

55. The method of claim **49**, wherein two secondary or adjunctive therapeutic agents are administered to said subject.

56. The method of claim **55**, wherein the two secondary or adjunctive therapeutic agents are dexamethasone and choline magnesium trisalicylate.

57. The method of claim **49**, wherein said effective amount comprises between about 10 and 1500 μg of said phorbol ester or derivative compound of Formula I every day.

58. The method of claim **49**, wherein said effective amount comprises between about 150 to 500 μg of said phorbol ester or derivative compound of Formula I every day.

59. The method of claim **49** wherein the neoplasm is caused by a hematological malignancy/bone marrow disorder.

60. The method of claim **59**, wherein the hematological malignancy/bone marrow disorder is leukemia.

61. The method of claim **60**, wherein the leukemia is acute myeloid leukemia.

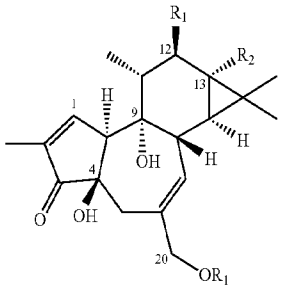
62. The method of claim **49**, wherein the neoplasm is a solid tumor.

63. The method of claim **49**, wherein the neoplasm is a relapsing neoplasm.

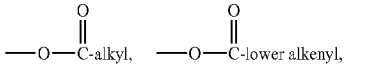
64. The method of claim **49**, wherein the neoplasm is refractory.

65. A method for preventing or treating one or more symptoms or conditions of neoplastic disease in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,



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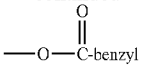
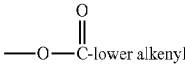
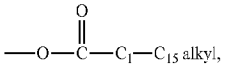


and substituted derivatives thereof, R_3 is hydrogen,

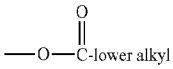


and substituted derivatives thereof; and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula to treat or prevent symptoms of neoplastic disease in said subject.

66. The method of claim **65**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

67. The method of claim **65**, wherein the phorbol ester is phorbol 13-butyrate. phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate. phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 2-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

68. The method of claim **65**, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

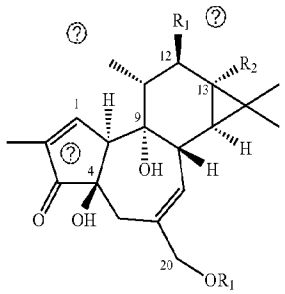
69. The method of claim **68**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

70. The method of claim **68**, wherein the at least one secondary or adjunctive therapeutic agent is selected from the group consisting of: doxorubicin, vitamin D3, cytarabine, cytosine arabinoside, daunorubicin, cyclophosphamide, gemtuzumab ozogamicin, idarubicin, mercaptopurine, mitoxantrone, thioguanine, aldesleukin, asparaginase, carboplatin, etoposide phosphate, fludarabine, methotrexate, etoposide, dexamethasone, and choline magnesium trisalicylate.

71. The method of claim **68**, wherein the one or more symptoms or conditions of neoplastic disease are anemia, chronic fatigue, excessive or easy bleeding, easy bruising, shortness of breath, petechiae, recurrent fever, swollen gums, slow healing of cuts, bone and joint discomfort, recurrent infections, weight loss, itching, night sweats, lymph node swelling, fever, abdominal pain and discomfort, disturbances in vision, coughing, loss of appetite, pain in the chest, difficulty swallowing, swelling, a need to urinate frequently, difficulty starting urination, difficulty holding back urine, weak or interrupted flow of urine, painful or burning urination, difficulty in having an erection, painful ejaculation, blood in urine or semen, frequent pain or stiffness, or weakness.

72. A method for inducing remission in a mammalian subject suffering from neoplastic disease comprising administering to said subject an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject

Formula I



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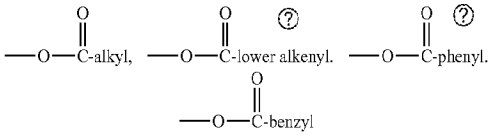
wherein R_1 and R_2 are selected from the group consisting of hydrogen,



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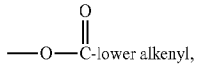
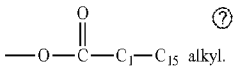
and substituted derivatives thereof; R_3 is hydrogen,



and substituted derivatives thereof; and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester of derivative compound of Formula I to induce remission in said subject.

73. The method of claim **72**, wherein R_1 or R_2 is



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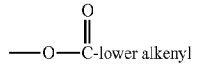
the remaining R_1 or R_2 is



and R_3 is hydrogen and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to induce remission in said subject.

74. The method of claim **72**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

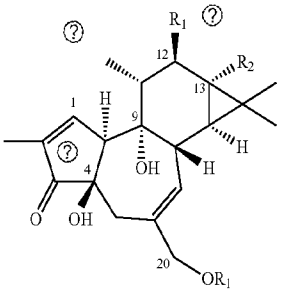
75. The method of claim **72**, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

76. The method of claim **72**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

77. The method of claim **72**, wherein the at least one secondary or adjunctive therapeutic agent is selected from the group consisting of: doxorubicin, vitamin D3, cytarabine, cytosine arabinoside, daunorubicin, cyclophosphamide, gemtuzumab ozogamicin, idarubicin, mercaptopurine, mitoxantrone, thioguanine, aldesleukin, asparaginase, carboplatin, etoposide phosphate, fludarabine, methotrexate, etoposide, dexamethasone, and choline magnesium trisalicylate.

78. A method for inducing apoptosis in a neoplasm in a mammalian subject suffering from neoplastic disease comprising administering to said subject an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof, to said subject

Formula I



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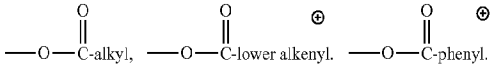
wherein R_1 and R_2 are selected from the group consisting of hydrogen,



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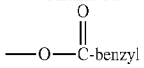

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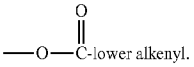
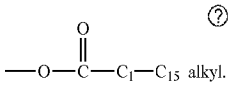
and substituted derivatives thereof, R_3 is hydrogen,



and substituted derivatives thereof; and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation Or coordinate treatment regimen with said phorbol ester of derivative compound of Formula I to induce apoptosis in a neoplasm in said subject.

79. The method of claim **78**, wherein R_1 or R_2 is



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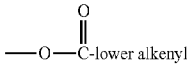
the remaining R_1 or R_2 is



and R_3 is hydrogen and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent malignancy in said subject.

80. The method of claim **78**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

81. The method of claim **78**, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

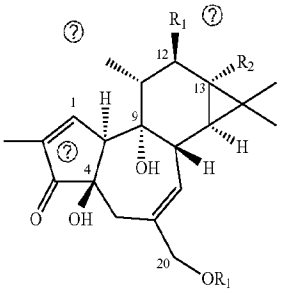
82. The method of claim **78**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

83. The method of claim **82**, wherein the at least one secondary or adjunctive therapeutic agent is selected from the group consisting of: doxorubicin, vitamin D3, cytarabine, cytosine arabinoside, daunorubicin, cyclophosphamide,

gemtuzumab ozogamicin, idarubicin, mercaptopurine, mitoxantrone, thioguanine, aldesleukin, asparaginase, carboplatin, etoposide phosphate, fludarabine, methotrexate, etoposide, dexamethasone, and choline magnesium trisalicylate.

84. A composition for preventing or treating neoplastic disease in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

Formula I



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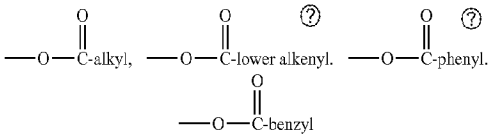
wherein R_1 and R_2 are selected from the group consisting of hydrogen,



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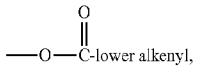
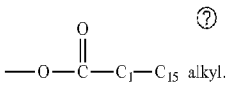
and substituted derivatives thereof, R_3 is hydrogen,



and substituted derivatives thereof; and at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent a neoplasm in said subject.

85. The composition of claim **84**, wherein R_1 or R_2 is



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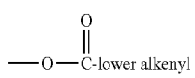
the remaining R_1 or R_2 is



and R_3 is hydrogen.

86. The composition of claim **84**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

87. The composition of claim **84**, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

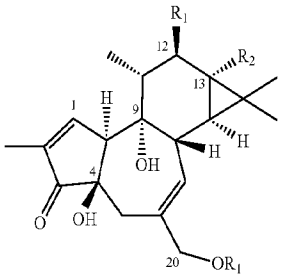
88. The composition of claim **84**, wherein the at least one secondary or adjunctive therapeutic agent is selected from the group consisting of: doxorubicin, vitamin D3, cytarabine, cytosine arabinoside, daunorubicin, cyclophosphamide, gemtuzumab ozogamicin, idarubicin, mercaptopurine, mitoxantrone, thioguanine, aldesleukin, asparaginase, carboplatin, etoposide phosphate, fludarabine, methotrexate, etoposide, dexamethasone, and choline magnesium trisalicylate.

89. The composition of claim **84**, wherein the composition contains at least two secondary or adjunctive therapeutic agents.

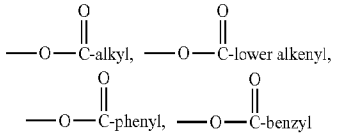
90. The composition of claim **89**, wherein the at least two secondary or adjunctive therapeutic agents are dexamethasone and choline magnesium trisalicylate.

91. A method for preventing or treating one or more side effects of chemotherapy in a mammalian subject comprising administering an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

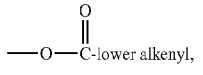
Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,

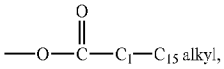


and substituted derivatives thereof, R_3 is hydrogen,

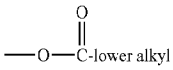


and substituted derivatives thereof.

92. The method of claim **91**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

93. The method of claim **91**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

94. The method of claim **91**, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

95. The method of claim **91**, further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent side effects of chemotherapy treatment to said subject.

96. The method of claim **95**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

97. The method of claim **96**, wherein the at least one secondary or adjunctive therapeutic agent is selected from the group consisting of pegfilgrastim, epoeitn alfa, darbepoetin alfa, alendronate sodium, risedronate, ibandronate, G-CSF, 5-HT3 receptor antagonists, NK1 antagonists, olanzapine, corticosteroids, dopamine antagonists, serotonin antagonists, benzodiazepines, aprepitant, and cannabinoids.

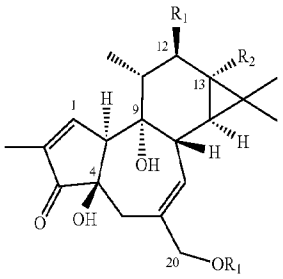
98. The method of claim **91**, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

99. The method of claim **98**, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

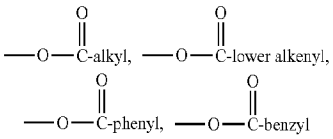
100. The method of claim **91**, wherein the one or more side effects of chemotherapeutic treatment are alopecia, nausea, vomiting, poor appetite, soreness, neutropenia, anemia, thrombocytopenia, dizziness, fatigue, constipation, oral ulcers, itchy skin, peeling, nerve and muscle leprosy, auditory changes, weight loss, diarrhea, immunosuppression, bruising, tendency to bleed easily, heart damage, liver damage, kidney damage, vertigo or encephalopathy.

101. A composition for preventing or treating one or more side effects of chemotherapy in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

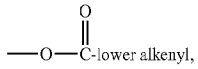
Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,

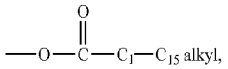


and substituted derivatives thereof, R_3 is hydrogen,

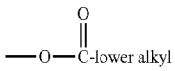


and substituted derivatives thereof.

102. The composition of claim **101**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

103. The composition of claim **101**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenyl

acetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

104. The composition of claim **101**, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

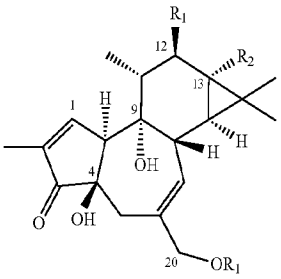
105. The composition of claim **101** further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent a side effect of chemotherapy in said subject.

106. The composition of claim **105**, wherein the at least one secondary or adjunctive therapeutic agent is pegfilgrastim, epoeitn alfa, darbepoetin alfa, alendronate sodium, risedronate, ibandronate, G-CSF, 5-HT3 receptor antagonists, NK1 antagonists, olanzapine, corticosteroids, dopamine antagonists, serotonin antagonists, benzodiazepines, aprepitant, or cannabinoids.

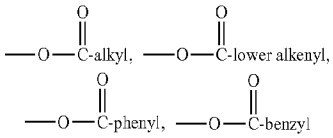
107. The composition of claim **101**, wherein the one or more side effects of chemotherapeutic treatment are alopecia, nausea, vomiting, poor appetite, soreness, neutropenia, anemia, thrombocytopenia, dizziness, fatigue, constipation, oral ulcers, itchy skin, peeling, nerve and muscle leprosy, auditory changes, weight loss, diarrhea, immunosuppression, bruising, tendency to bleed easily, heart damage, liver damage, kidney damage, vertigo or encephalopathy.

108. A method for preventing or treating one or more side effects of radiation therapy in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

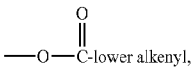
Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,

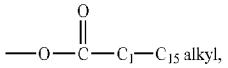


and substituted derivatives thereof, R_3 is hydrogen,

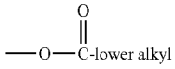


and substituted derivatives thereof.

109. The method of claim **108**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

110. The method of claim **108**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

111. The method of claim **108**, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

112. The method of claim **108**, further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent side effects of radiation therapy to said subject.

113. The method of claim **112**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

114. The method of claim **113**, wherein the at least one secondary or adjunctive therapeutic agent is selected from the group consisting of steroids, amifostine, chlorhexidine, benzydamine, sucralfate, KGF, palifermin, Cu/Zn superoxide dismutase, Interleukin 11, or prostaglandins.

115. The method of claim **108**, wherein the one or more side effects of radiation therapy are moist desquamation, soreness, diarrhea, nausea, vomiting, appetite loss, constipation, itchy skin, peeling, mouth and throat sores, edema, infertility, fibrosis, epilation, or mucosal dryness.

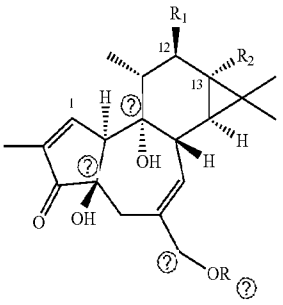
116. The method of claim **108**, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

117. The method of claim **108**, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

118. A composition for preventing or treating one or more side effects of radiation therapy in a mammalian subject comprising an effective amount of a phorbol ester or deriva-

tive compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

Formula I



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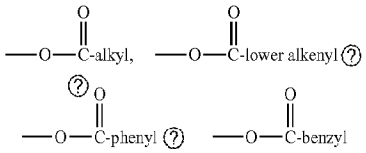
wherein R_1 and R_2 are selected from the group consisting of hydrogen,



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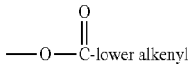
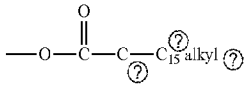
and substituted derivatives thereof, R_3 is hydrogen,



and substituted derivatives thereof.

119. The composition of claim **118**, wherein R_1 or R_2 is



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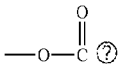
the remaining R_1 or R_2 is



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and R_3 is hydrogen.

120. The composition of claim **118**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 2-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

121. The composition of claim **118**, wherein the phorbol ester is 12-O-tetradecanoyl phorbol-13-acetate.

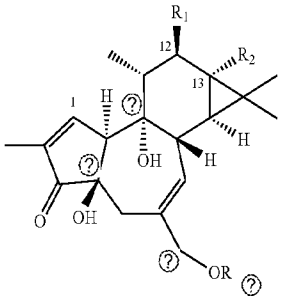
122. The composition of claim **118** further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent a side effect of radiation therapy in said subject.

123. The composition of claim **118**, wherein the one or more secondary or adjunctive therapeutic agents are steroids, amifostine, chlorhexidine, benzydamine, sucralfate, KGF, palifermin, Cu/Zn superoxide dismutase, Interleukin 11, or prostaglandins.

124. The composition of claim **118**, wherein the one or more side effects of radiation therapy are moist desquamation, soreness, diarrhea, nausea, vomiting, appetite loss, constipation, itchy skin, peeling, mouth and throat sores, edema, infertility, fibrosis, epilation, or mucosal dryness.

125. A method for preventing or treating one or more of the effects of stroke in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

Formula I



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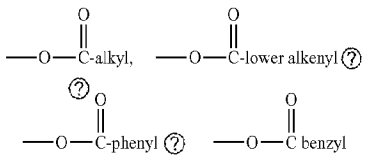
wherein R_1 and R_2 are selected from the group consisting of hydrogen,



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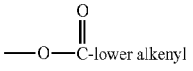
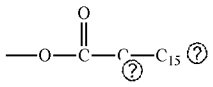
and substituted derivatives thereof, R_3 is hydrogen,



and substituted derivatives thereof.

126. The method of claim **125**, wherein R_1 or R_2 is



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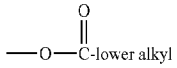
the remaining R_1 or R_2 is



and R_3 is hydrogen.

127. The method of claim **125**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

128. The method of claim **125**, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

129. The method of claim **125**, further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent effects of stroke in said subject.

130. The method of claim **129**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

131. The method of claim **129**, wherein the at least one secondary or adjunctive therapeutic agent is tissue plasminogen activator, an anticoagulant, a statin, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitor, beta-blocker, calcium channel blocker, or diuretic.

132. The method of claim **125**, further comprising surgical intervention in combination with phorbol ester or derivative compound of Formula I to treat or prevent effects of stroke in said subject.

133. The method of claim **132**, wherein the surgical intervention is a carotid endarterectomy, angioplasty, stent placement, craniotomy, endovascular coil emobilization, or patent foramen ovale closure.

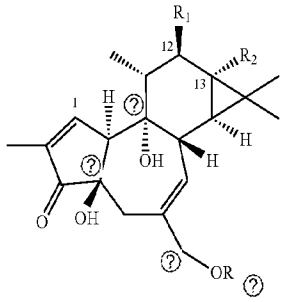
134. The method of claim **125**, wherein the one or more effects of stroke are paralysis, spatial impairment, impaired judgment, left-sided neglect, memory loss, aphasia, coordination and balance problems, nausea, vomiting, cognitive impairment, perception impairment, orientation impairment, homonymous hemianopsia, or impulsivity.

135. The method of claim **125**, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

136. The method of claim **135**, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

137. A composition for the prevention or treatment of one or more effects of stroke in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

Formula I



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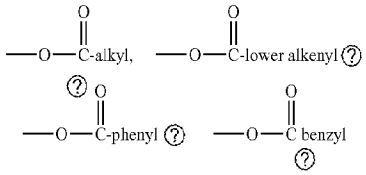
wherein R_1 and R_2 are selected from the group consisting of hydrogen,



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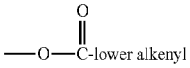
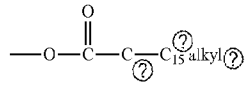
and substituted derivatives thereof, R_3 is hydrogen,



and substituted derivatives thereof.

138. The composition of claim **137**, wherein R_1 or R_2 is



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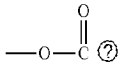
the remaining R_1 or R_2 is



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and R_3 is hydrogen.

139. The composition of claim **138**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate,

phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

140. The composition of claim **138**, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

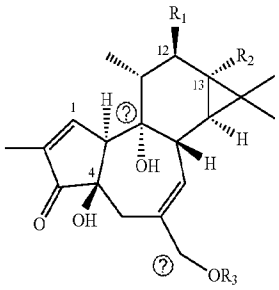
141. The composition of claim **138**, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent an effect of stroke in said subject.

142. The composition of claim **138**, wherein the at least one secondary or adjunctive therapeutic agent is tissue plasminogen activator, an anticoagulant, a statin, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitor, beta-blocker, calcium channel blocker, or diuretic.

143. The composition of claim **138**, wherein the one or more side effects of stroke is paralysis, spatial impairment, impaired judgment, left-sided neglect, memory loss, aphasia, coordination and balance problems, nausea, vomiting, cognitive impairment, perception impairment, orientation impairment, homonymous hemianopsia, or impulsivity.

144. A method for treating or preventing one or more of the symptoms of Parkinson's disease in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

Formula I



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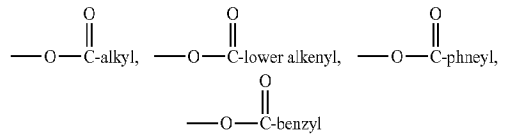
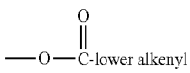
wherein R_1 and R_2 are selected from the group consisting of hydrogen,

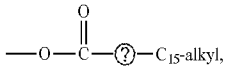


and substituted derivatives thereof, R_3 is hydrogen,



and substituted derivatives thereof.

145. The method of claim **144**, wherein R_1 or R_2 is



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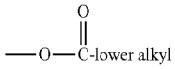
the remaining R_1 or R_2 is



and R_3 is hydrogen.

146. The method of claim **144**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

147. The method of claim **144**, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

148. The method of claim **144**, further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent one or more of the symptoms of Parkinson's disease.

149. The method of claim **148**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

150. The method of claim **148**, wherein the at least one secondary or adjunctive therapeutic agent is levodopa, carbidopa, pyridoxine, seleyiline, rasagiline, tolcapone, dopamine agonist, MAO-B inhibitors, amantidine, or anticholinergics.

151. The method of claim **144**, further comprising surgical intervention in combination with phorbol ester or derivative compound of Formula I to treat or prevent symptoms of Parkinson's disease in said subject.

152. The method of claim **151**, wherein the surgical intervention is deep brain stimulation or lesion formation.

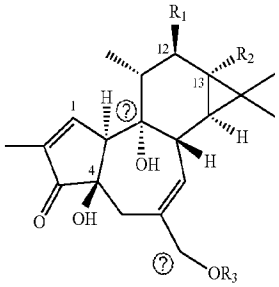
153. The method of claim **144**, wherein the one or more symptoms of Parkinson's disease is tremor at rest, stiffness, bradykinesia, rigidity, speech impairment, cognitive impairment, dementia, mood impairment, drowsiness, insomnia and postural instability.

154. The method of claim **144**, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

155. The method of claim **144**, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

156. A composition for the prevention or treatment of one or more symptoms of Parkinson's disease in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

Formula I



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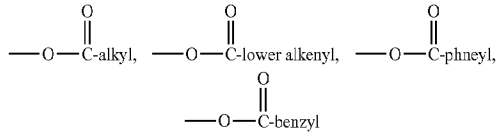
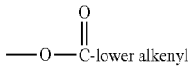
wherein R_1 and R_2 are selected from the group consisting of hydrogen,

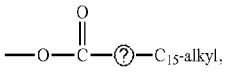


and substituted derivatives thereof, R_3 is hydrogen,



and substituted derivatives thereof.

157. The composition of claim **156**, wherein R_1 or R_2 is



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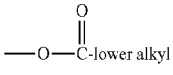
the remaining R_1 or R_2 is



and R_3 is hydrogen.

158. The composition of claim **156**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 3-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

159. The composition of claim **156**, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

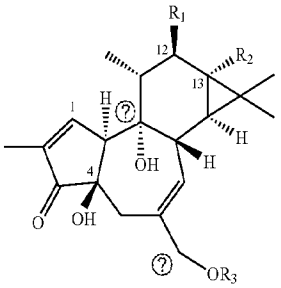
160. The composition of claim **156**, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent an effect of stroke in said subject.

161. The composition of claim **160**, wherein the at least one secondary or adjunctive therapeutic agent is levodopa, carbidopa, pyridoxine, seleyiline, rasagiline, tolcapone, dopamine agonist, MAO-B inhibitors, amantidine, or anticholinergics.

162. The composition of claim **156**, wherein the one or more symptoms of Parkinson's disease is tremor at rest, stiffness, bradykinesia, rigidity, speech impairment, cognitive impairment, dementia, mood impairment, drowsiness, insomnia or postural instability.

163. A method for treating or preventing one or more of the symptoms of prostate hypertrophy in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

Formula I



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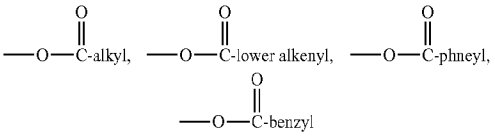
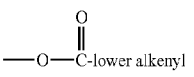
wherein R_1 and R_2 are selected from the group consisting of hydrogen,

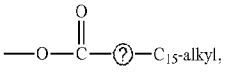


and substituted derivatives thereof, R_3 is hydrogen,



and substituted derivatives thereof.

164. The method of claim **163**, wherein R_1 or R_2 is



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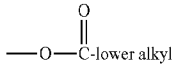
the remaining R_1 or R_2 is



and R_3 is hydrogen.

165. The method of claim **163**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

166. The method of claim **163**, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

167. The method of claim **163**, further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent one or more of the symptoms of prostate hypertrophy.

168. The method of claim **167**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

169. The method of claim **167**, wherein the at least one secondary or adjunctive therapeutic agent is finasteride, dutasteride, terazosin, doxazosin, tamsulosin or an alpha blocker.

170. The method of claim **163**, further comprising surgical intervention in combination with phorbol ester or derivative compound of Formula I to treat or prevent symptoms of prostate hypertrophy disease in said subject.

171. The method of claim **170**, wherein the surgical intervention is transurethral resection of the prostate, transurethral incision of the prostate, laser surgery, or prostatectomy.

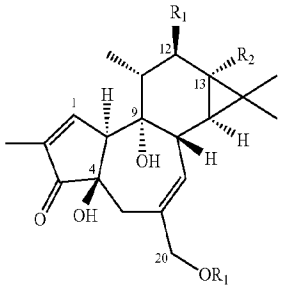
172. The method of claim **163**, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

173. The method of claim **163**, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

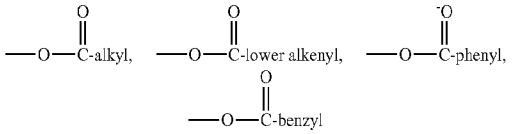
174. The method of claim **163**, wherein the one or more symptoms of prostate hypertrophy are dribbling at the end of urination, urinary retention, incomplete emptying of the bladder, incontinence, urinary frequency, pain with urination, bloody urine, slowed or delayed urination, stopping and starting of urine stream, straining to urinate, weak urine stream, or strong and sudden urge to urinate.

175. A composition for the prevention or treatment of one or more symptoms of prostate hypertrophy in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

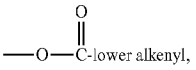
Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,

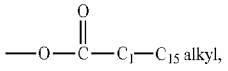


and substituted derivatives thereof, R_3 is hydrogen,

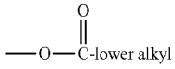


and substituted derivatives thereof.

176. The composition of claim **175**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

177. The composition of claim **175**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,1 diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate,

phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 3-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

178. The composition of claim **175**, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

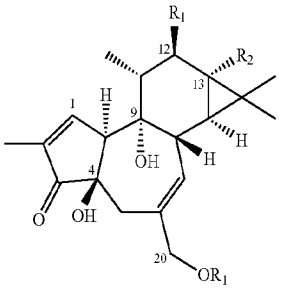
179. The composition of claim **175**, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent a symptom of prostate hypertrophy.

180. The composition of claim **179**, wherein the at least one secondary or adjunctive therapeutic agent is finasteride, dutasteride, terazosin, doxazosin, tamsulosin or an alpha blocker.

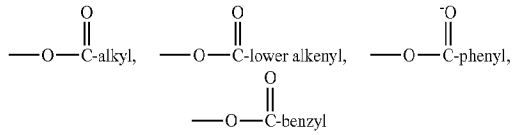
181. The composition of claim **179**, wherein the one or more symptoms of prostate hypertrophy are dribbling at the end of urination, urinary retention, incomplete emptying of the bladder, incontinence, urinary frequency, pain with urination, bloody urine, slowed or delayed urination, stopping and starting of urine stream, straining to urinate, weak urine stream, or strong and sudden urge to urinate.

182. A method for treating or preventing one or more of the symptoms of rheumatoid arthritis in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

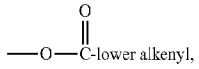
Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,

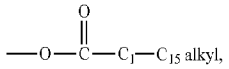


and substituted derivatives thereof, R_3 is hydrogen,

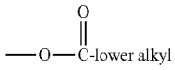


and substituted derivatives thereof.

183. The method of claim **182**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

184. The method of claim **182**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

185. The method of claim **182**, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

186. The method of claim **182**, further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent one or more of the symptoms of rheumatoid arthritis.

187. The method of claim **186**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

188. The method of claim **187**, wherein the at least one secondary or adjunctive therapeutic agent is a non-steroidal anti-inflammatory agent, steroid, disease-modifying anti-rheumatic drug, an immunosuppressant, TNF-α inhibitor, adalimumab, azathioprine, chloroquine, hydroxychloroquine, ciclosporin, D-penicillamine, etanercept, golimumab, gold salts, infliximab, leflunomide, methotrexate, minocycline, sulfasalazine anakinra, abatacept, rituximab, or tocilizumab.

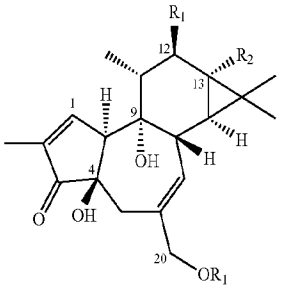
189. The method of claim **182**, wherein the one or more symptoms of rheumatoid arthritis are sore joints, morning stiffness, firm bumps of tissue under the skin of the arms, fatigue, loss of energy, lack of appetite, low-grade fever, or muscle and joint aches.

190. The method of claim **182**, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

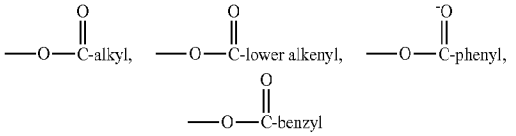
191. The method of claim **182**, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

192. A composition for the prevention or treatment of one or more symptoms of rheumatoid arthritis in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

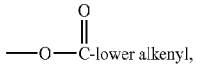
Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,

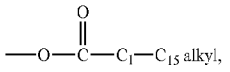


and substituted derivatives thereof, R_3 is hydrogen,

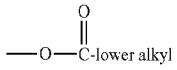


and substituted derivatives thereof.

193. The composition of claim **192**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

194. The composition of claim **192**, wherein the phorbol ester is phorbol 13-butyrate, phorbol 12-decanoate, phorbol 13-decanoate, phorbol 12,13-diacetate, phorbol 13,20-diacetate, phorbol 12,13-dibenzoate, phorbol 12,13-dibutyrate, phorbol 12,13-didecanoate, phorbol 12,13-dihexanoate, phorbol 12,13-dipropionate, phorbol 12-myristate, phorbol 13-myristate, phorbol 12,13,20-triacetate, 12-deoxyphorbol 13-angelate, 12-deoxyphorbol 13-angelate 20-acetate, 12-deoxyphorbol 13-isobutyrate, 12-deoxyphorbol 13-isobutyrate-20-acetate, 12-deoxyphorbol 13-phenylacetate, 12-deoxyphorbol 13-phenylacetate 20-acetate, 12-deoxyphorbol 13-tetradecanoate, phorbol 12-tigliate 13-decanoate, 12-deoxyphorbol 13-acetate, phorbol 12-acetate, or phorbol 13-acetate.

195. The composition of claim **192**, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

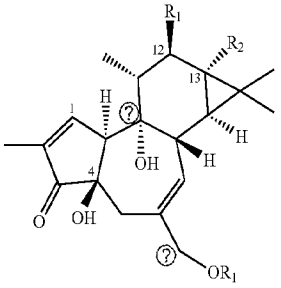
196. The composition of claim **192**, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent a symptom of rheumatoid arthritis.

197. The composition of claim **196**, wherein the at least one secondary or adjunctive therapeutic agent is a non-steroidal anti-inflammatory agent, steroid, disease-modifying anti-rheumatic drug, an immunosuppressant, TNF-α inhibitor, anakinra, abatacept, adalimumab, azathioprine, chloroquine, hydroxychloroquine, ciclosporin, D-penicillamine, etanercept, golimumab, gold salts, infliximab, leflunomide, methotrexate, minocycline, sulfasalazine, rituximab, or tocilizumab.

198. The composition of claim **192**, wherein the one or more symptoms of rheumatoid arthritis are sore joints, morning stiffness, firm bumps of tissue under the skin of the arms, fatigue, loss of energy, lack of appetite, low-grade fever, or muscle and joint aches.

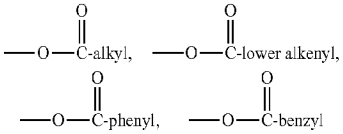
199. A method for treating or preventing one or more of the symptoms of myasthenia gravis in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

Formula I

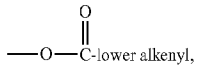


(?) indicates text missing or illegible when filed

wherein R_1 and R_2 are selected from the group consisting of hydrogen,

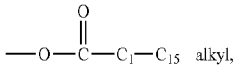


and substituted derivatives thereof, R_3 is hydrogen,

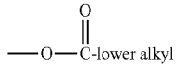


and substituted derivatives thereof.

200. The method of claim **199**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

201. The method of claim **199**, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

202. The method of claim **199** further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent one or more of the symptoms of myasthenia gravis.

203. The method of claim **202**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

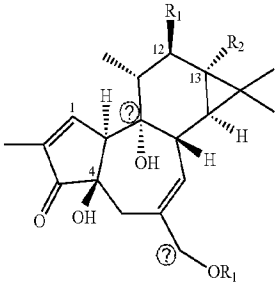
204. The method of claim **202**, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinesterase, corticosteroid, or immunosuppressive agent.

205. The method of claim **199**, wherein the one or more symptoms of myasthemia gravis are ptosis, diplopia, speech impairment, fatigability, muscle weakness, dysphagia, or dysarthria.

206. The method of claim **199**, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

207. The method of claim **199**, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

208. A composition for the prevention or treatment of one or more symptoms of myasthenia gravis in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof



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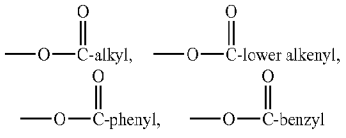
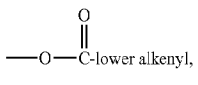
wherein R_1 and R_2 are selected from the group consisting of hydrogen,

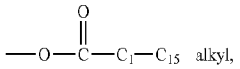


and substituted derivatives thereof, R_3 is hydrogen,

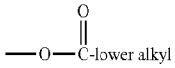


and substituted derivatives thereof.

209. The composition of claim **208**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

210. The composition of claim **208**, wherein the phorbol ester is 12-O-tetradecanoylphorbol 13-acetate.

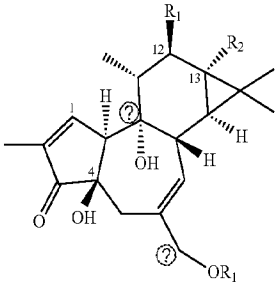
211. The composition of claim **208**, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent a symptom of myasthenia gravis.

212. The composition of claim **211**, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinesterase, corticosteroid, or immunosuppressive agent.

213. The composition of claim **208**, wherein the one or more symptoms of myasthemia gravis are ptosis, diplopia, speech impairment, fatigability, muscle weakness, dysphagia, or dysarthria.

214. A method for treating or preventing symptoms of kidney disease in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

Formula I



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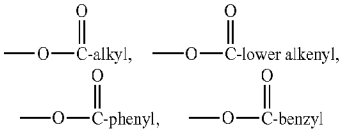
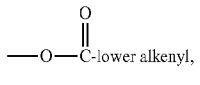
wherein R_1 and R_2 are selected from the group consisting of hydrogen,

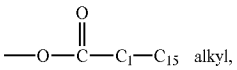


and substituted derivatives thereof, R_3 is hydrogen,

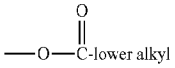


and substituted derivatives thereof.

215. The method of claim **214**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

216. The method of claim **214**, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

217. The method of claim **214**, further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent symptoms of kidney disease.

218. The method of claim **217**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

219. The method of claim **217**, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinergic, topical estrogen, imipramine or duloxetine.

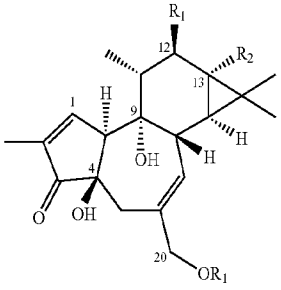
220. The method of claim **214**, wherein the symptom of kidney disease is urinary incontinence, increased excretion of urine, uremia, or oliguria.

221. The method of claim **214**, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

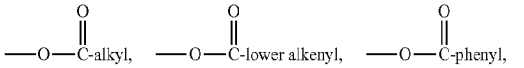
222. The method of claim **214**, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

223. A composition for the prevention or treatment of kidney disease in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,



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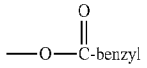
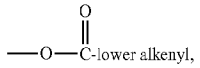
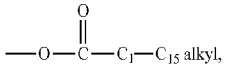


and substituted derivatives thereof, R_3 is hydrogen,

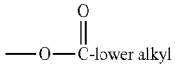


and substituted derivatives thereof.

224. The composition of claim **223**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

225. The composition of claim **223**, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

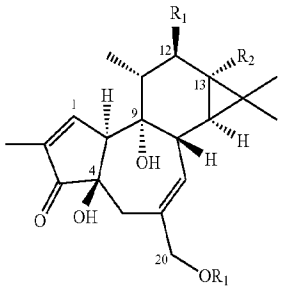
226. The composition of claim **223**, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent a symptom of kidney disease.

227. The composition of claim **226**, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinergic, topical estrogen, imipramine or duloxetine.

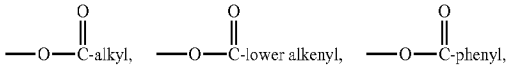
228. The composition of claim **223**, wherein the symptom of kidney disease is urinary incontinence, increased excretion of urine, uremia, or oliguria.

229. A method for treating or preventing urinary incontinence in a mammalian subject comprising administering an effective amount of phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof to said subject

Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,



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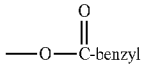
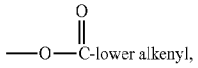
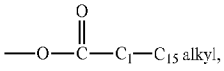


and substituted derivatives thereof, R_3 is hydrogen,

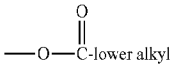


and substituted derivatives thereof.

230. The method of claim **229**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

231. The method of claim **229**, wherein the phorbol ester is 12-O-tetradecanoylphobol-13-acetate.

232. The method of claim **229**, further comprising administering at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation or coordinate treatment regimen with said phorbol ester or derivative compound of Formula I to treat or prevent symptoms of urinary incontinence.

233. The method of claim **232**, wherein the at least one secondary or adjunctive therapeutic agent is administered to said subject in a coordinate administration protocol, simultaneously with, prior to, or after, administration of said phorbol ester to said subject.

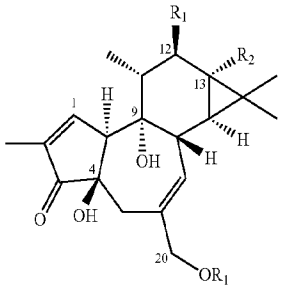
234. The method of claim **232**, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinergic, topical estrogen, imipramine or duloxetine.

235. The method of claim **229**, wherein said effective amount comprises between about 10 μg and about 1500 μg of said phorbol ester or derivative compound of Formula I every day.

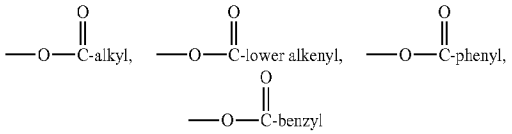
236. The method of claim **229**, wherein said effective amount comprises between about 125 μg to about 500 μg of said phorbol ester or derivative compound of Formula I every day.

237. A composition for the prevention or treatment of urinary incontinence in a mammalian subject comprising an effective amount of a phorbol ester or derivative compound of Formula I, or a pharmaceutically-acceptable salt, isomer, enantiomer, solvate, hydrate, polymorph or prodrug thereof

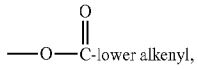
Formula I



wherein R_1 and R_2 are selected from the group consisting of hydrogen,

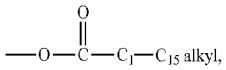


and substituted derivatives thereof, R_3 is hydrogen,

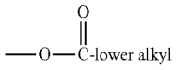


and substituted derivatives thereof.

238. The composition of claim **237**, wherein R_1 or R_2 is



the remaining R_1 or R_2 is



and R_3 is hydrogen.

239. The composition of claim **237**, wherein the phorbol ester is 12-O-tetradecanoylphorbol-13-acetate.

240. The composition of claim **237**, further comprising at least one secondary or adjunctive therapeutic agent that is effective in a combinatorial formulation with said phorbol ester or derivative compound of Formula I to treat or prevent urinary incontinence.

241. The composition of claim **240**, wherein the at least one secondary or adjunctive therapeutic agent is an anticholinergic, topical estrogen, imipramine or duloxetine.

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