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(54) Title: ASCORBIC ACID, QUINONE COMPOUND, AND SODIUM GLUCOSE COTRANSPORTER INHIBITOR FOR TREATING CANCER

(57) Abstract: Provided herein is a method of treating, preventing, or alleviating one or more symptoms of cancer in a subject, comprising administering to the subject a therapeutically effective amount of: (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

ASCORBIC ACID, QUINONE COMPOUND, AND SODIUM GLUCOSE COTRANSPORTER INHIBITOR FOR TREATING CANCER

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to U.S. Provisional Patent Application No. 62/369,637, filed August 1, 2016, the disclosure of which is incorporated herein by reference in its entirety.

FIELD

[0002] Provided herein is a method of treating, preventing, or alleviating one or more symptoms of cancer in a subject, comprising administering to the subject a therapeutically effective amount of: (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

BACKGROUND

[0003] One of the hallmarks of cancer is metabolic deregulation. Warburg *et al.*, *Science* **1956**, *123*, 309-314; Vander Heiden *et al.*, *Science* **2009**, *324*, 1029-1033; Zhao *et al.*, *Cell Death Disease* **2013**, *4*, e532. Cancerous cells reprogram their metabolism in order to satisfy their bioenergetic and biosynthetic requirements. Vander Heiden *et al.*, *Science* **2009**, *324*, 1029-1033; Barger *et al.*, *Endocrine-Related Cancer* **2010**, *17*, R287-R304; Wise *et al.*, *Trends Biochem. Sci.* **2010**, *35*, 427-433. Glucose and glutamine are the two principal nutrients that cancerous cells use to proliferate and survive. Van den Heuvel *et al.*, *Cancer Biol. Ther.* **2012**, *13*, 1185-1194; Venneti *et al.*, *Sch. Transl. Med.* **2015**, *7*, 274ra17.

[0004] Many cancerous cells display increased glucose uptake and breakdown through the process of aerobic glycolysis for growth and proliferation. Warburg *et al.*, *Science* **1956**, *123*, 309-314; Gambhir, *Nat. Rev. Cancer* **2002**, *2*, 683–693. Glucose uptake

in cancerous cells is mediated by two different classes of glucose transporters: the passive glucose transporters (GLUTs) and active sodium glucose cotransporters (SGLTs). Wright *et al.*, *Physiol. Rev.* **2011**, *91*, 733-794; Scafoglio *et al.*, *Proc. Nat'l. Acad. U.S.A.* **2015**. The most studied and well known members of SGLTs are sodium glucose cotransporter type 1 (SGLT1) and type 2 (SGLT2). Wright *et al.*, *Physiol. Rev.* **2011**, *91*, 733-794; Wright, *Mol. Aspects Med.* **2013**, *34*, 183-196. SGLT1 is expressed in colorectal cancer, head and neck cancer, and prostate cancer. Wright *et al.*, *Physiol. Rev.* **2011**, *91*, 733-794; Blessing *et al.*, *J. Cancer Sci. Ther.* **2012**, *40*, 306-312. SGLT2 is expressed in chondrosarcomas, colorectal cancer, gastrointestinal cancer, head and neck cancer, leukemia, lung cancer, pancreatic cancer, prostate cancer, and renal cancer. Wright *et al.*, *Physiol. Rev.* **2011**, *91*, 733-794; Scafoglio *et al.*, *Proc. Nat'l. Acad. U.S.A.* **2015**. Blocking glucose uptake with a SGLT2 inhibitor reduced tumor growth in a xenograft model of pancreatic cancer. *Id.*

[0005] Many cancerous cells exhibit increased dependency on glutamine for growth and proliferation, thus becoming addicted to glutamine. Wise *et al.*, *Trends Biochem. Sci.* **2010**, *35*, 427-433; Van den Heuvel *et al.*, *Cancer Biol. Ther.* **2012**, *13*, 1185-1194. The importance of glutamine as a nutrient in cancer derives from its abilities to donate its nitrogen and carbon into an array of growth-promoting pathways. DeBerardinis *et al.*, *Proc. Natl. Acad. Sci. USA* **2007**, *104*,19345-19350; Lukey *et al.*, *Future Med. Chem.* **2013**, *5*, 1685-1700; Hensley *et al.*, *J. Clin. Invest.* **2013**, *123*, 3678-3684. Essential functions of glutamine include its conversion to glutamate as a metabolic intermediate to be channeled into the TCA cycle. Zhao *et al.*, *Cell Death Disease* **2013**, *4*, e532. The mitochondrial enzyme glutaminase (GLS), a rate-limiting enzyme of glutaminolysis, catalyzes the conversion of glutamine to glutamate. Van den Heuvel *et al.*, *Cancer Biol. Ther.* **2012**, *13*, 1185-1194. Increased expression of glutaminase is often observed in tumor and rapidly dividing cells. Cassago *et al.*, *Proc. Natl. Acad. Sci. USA.* **2012**, *109*, 1092-1097. Suppression of the broadly expressed form of glutaminase with either small-molecule inhibitors or by genetic knockdown has been shown to have antitumor activity across a variety of tumor types, including lymphoma, glioma, breast cancer, pancreatic cancer, non–small cell lung cancer, and renal cancer. Gao *et al.*, *Nature* **2009**, *458*, 762-765; Wang *et al.*, *Cancer Cell*, **2010** *18*, 207-219; Seltzer *et al.*, *Cancer Res.* **2010**, *70*, 8981-8987; *Emadi et al*, *Exp. Hematol.* **2014**, *42*, 247-251; Gross *et al.*, *Mol. Cancer Ther.* **2014**,*13*, 890-891.

[0006] Therefore, there exists a need for an effective cancer therapy by targeting the metabolic pathways utilized by cancer.

SUMMARY OF THE DISCLOSURE

[0007] Provided herein is a method of treating, preventing, or alleviating one or more symptoms of cancer in a subject, comprising administering to the subject a therapeutically effective amount of: (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0008] Also provided herein is a method of inhibiting the growth of cancer in a subject, comprising administering to the subject a therapeutically effective amount of: (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0009] Further provided herein is a method of inhibiting the growth of a cancerous cell, comprising the step of contacting the cell with an effective amount of: (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0010] Additionally, provided herein is a method of killing a cell, comprising the step of contacting the cell with an effective amount of: (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0011] Provided herein is a method of treating, preventing, or alleviating one or more symptoms of cancer in a subject, comprising administering to the subject a therapeutically effective amount of: (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iv) a glutamine inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0012] Provided herein is a method of inhibiting the growth of cancer in a subject, comprising administering to the subject a therapeutically effective amount of: (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iv) a glutamine inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0013] Provided herein is a method of inhibiting the growth of a cancerous cell, comprising the step of contacting the cell with an effective amount of: (i) ascorbic acid, or a

single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iv) a glutamine inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0014] Provided herein is a method of killing a cell, comprising the step of contacting the cell with an effective amount of: (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iv) a glutamine inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

DETAILED DESCRIPTION

[0015] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below.

[0016] Generally, the nomenclature used herein and the laboratory procedures in biochemistry, biology, medicinal chemistry, organic chemistry, pharmaceutical chemistry, pharmacology, and others described herein are those well known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0017] The term “subject” refers to an animal, including, but not limited to, a primate (*e.g.*, human), cow, pig, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms

"subject" and "patient" are used interchangeably herein in reference, for example, to a mammalian subject, such as a human subject, in one embodiment, a human.

[0018] The terms "treat," "treating," and "treatment" are meant to include alleviating or abrogating a disorder, disease, or condition, or one or more of the symptoms associated with the disorder, disease, or condition; or alleviating or eradicating the cause(s) of the disorder, disease, or condition itself.

[0019] The terms "prevent," "preventing," and "prevention" are meant to include a method of delaying and/or precluding the onset of a disorder, disease, or condition, and/or one or more of its attendant symptoms; barring a subject from acquiring a disorder, disease, or condition; or reducing a subject's risk of acquiring a disorder, disease, or condition.

[0020] The terms "alleviate" and "alleviating" is meant to refer to easing or reducing one or more symptoms (*e.g.,* pain) of a disorder, disease, or condition. The terms can also refer to reducing adverse effects associated with an active ingredient. Sometimes, the beneficial effects that a subject derives from a prophylactic or therapeutic agent do not result in a cure of the disorder, disease, or condition.

[0021] The term "contacting" or "contact" is meant to refer to bringing together of a therapeutic agent and cell or tissue such that a physiological and/or chemical effect takes place as a result of such contact. Contacting can take place *in vitro*, *ex vivo*, or *in vivo*. In one embodiment, a therapeutic agent is contacted with a cell in cell culture (*in vitro*) to determine the effect of the therapeutic agent on the cell. In another embodiment, the contacting of a therapeutic agent with a cell or tissue includes the administration of a therapeutic agent to a subject having the cell or tissue to be contacted.

[0022] The terms "therapeutically effective amount" and "effective amount" are meant to include the amount of a compound or a combination of compounds that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disorder, disease, or condition being treated. The term "therapeutically effective amount" or "effective amount" also refers to the amount of a compound or a combination of compounds that is sufficient to elicit the biological or medical response of a biological molecule (*e.g.*, a protein, enzyme, RNA, or DNA), cell, tissue, system, animal, or human, which is being sought by a researcher, veterinarian, medical doctor, or clinician.

[0023] The term "pharmaceutically acceptable carrier," "pharmaceutically acceptable excipient," "physiologically acceptable carrier," or "physiologically acceptable excipient" refers to a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, solvent, or encapsulating material. In one embodiment, each component is "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. *See, Remington: The Science and Practice of Pharmacy*, 22nd ed.; Allen *et al.*, Eds.; The Pharmaceutical Press, 2012; *Handbook of Pharmaceutical Excipients*, 7th ed.; Rowe *et al.*, Eds.; The Pharmaceutical Press: 2012; *Handbook of Pharmaceutical Additives*, 3rd ed.; Ash and Ash Eds.; Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation*, 2nd ed.; Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009.

[0024] The term "about" or "approximately" means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term "about" or "approximately" means within 1, 2, 3, or 4 standard deviations. In certain embodiments, the term "about" or "approximately" means within 50%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range.

[0025] The terms "active ingredient" and "active substance" refer to a compound, which is administered, alone or in combination with one or more pharmaceutically acceptable excipients, to a subject for treating, preventing, or ameliorating one or more symptoms of a disorder, disease, or condition. As used herein, "active ingredient" and "active substance" may be an optically active isomer of a compound described herein.

[0026] The terms "drug," "therapeutic agent," and "chemotherapeutic agent" refer to a compound, or a pharmaceutical composition thereof, which is administered to a subject for treating, preventing, or ameliorating one or more symptoms of a disorder, disease, or condition.

[0027] The term "drug resistance" refers to the condition when a disorder, disease, or condition does not respond to the treatment of a drug or drugs. Drug resistance can be either intrinsic, which means the disorder, disease, or condition has never been responsive to the

drug or drugs, or it can be acquired, which means the disorder, disease, or condition ceases responding to a drug or drugs that the disorder, disease, or condition had previously responded to. In certain embodiments, drug resistance is intrinsic. In certain embodiments, the drug resistance is acquired.

[0028] The term "alkyl" refers to a linear or branched saturated monovalent hydrocarbon radical, wherein the alkyl is optionally be substituted with one or more substituents Q as described herein. For example, C_{1-6} alkyl refers to a linear saturated monovalent hydrocarbon radical of 1 to 6 carbon atoms or a branched saturated monovalent hydrocarbon radical of 3 to 6 carbon atoms. In certain embodiments, the alkyl is a linear saturated monovalent hydrocarbon radical that has 1 to 20 (C_{1-20}), 1 to 15 (C_{1-15}), 1 to 10 (C_{1-10}), or 1 to 6 (C_{1-6}) carbon atoms, or branched saturated monovalent hydrocarbon radical of 3 to 20 (C_{3-20}), 3 to 15 (C_{3-15}), 3 to 10 (C_{3-10}), or 3 to 6 (C_{3-6}) carbon atoms. As used herein, linear C_{1-6} and branched C_{3-6} alkyl groups are also referred as "lower alkyl." Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl (including all isomeric forms, *e.g.*, *n*-propyl and isopropyl), butyl (including all isomeric forms, *e.g.*, *n*-butyl, isobutyl, *sec*-butyl, and *t*-butyl), pentyl (including all isomeric forms), and hexyl (including all isomeric forms).

[0029] The term "alkenyl" refers to a linear or branched monovalent hydrocarbon radical, which contains one or more, in one embodiment, one to five, in another embodiment, one, carbon-carbon double bond(s), wherein the alkenyl is optionally substituted with one or more substituents Q as described herein. The term "alkenyl" embraces radicals having a "*cis*" or "*trans*" configuration or a mixture thereof, or alternatively, a "Z" or "E" configuration or a mixture thereof, as appreciated by those of ordinary skill in the art. For example, C_{2-6} alkenyl refers to a linear unsaturated monovalent hydrocarbon radical of 2 to 6 carbon atoms or a branched unsaturated monovalent hydrocarbon radical of 3 to 6 carbon atoms. In certain embodiments, the alkenyl is a linear monovalent hydrocarbon radical of 2 to 20 (C_{2-20}), 2 to 15 (C_{2-15}), 2 to 10 (C_{2-10}), or 2 to 6 (C_{2-6}) carbon atoms, or a branched monovalent hydrocarbon radical of 3 to 20 (C_{3-20}), 3 to 15 (C_{3-15}), 3 to 10 (C_{3-10}), or 3 to 6 (C_{3-6}) carbon atoms. Examples of alkenyl groups include, but are not limited to, ethenyl, propen-1-yl, propen-2-yl, allyl, butenyl, and 4-methylbutenyl.

[0030] The term "alkynyl" refers to a linear or branched monovalent hydrocarbon radical, which contains one or more, in one embodiment, one to five, in another embodiment,

one, carbon-carbon triple bond(s), wherein the alkynyl is optionally substituted with one or more substituents Q as described herein. For example, C_{2-6} alkynyl refers to a linear unsaturated monovalent hydrocarbon radical of 2 to 6 carbon atoms or a branched unsaturated monovalent hydrocarbon radical of 4 to 6 carbon atoms. In certain embodiments, the alkynyl is a linear monovalent hydrocarbon radical of 2 to 20 (C_{2-20}), 2 to 15 (C_{2-15}), 2 to 10 (C_{2-10}), or 2 to 6 (C_{2-6}) carbon atoms, or a branched monovalent hydrocarbon radical of 4 to 20 (C_{4-20}), 4 to 15 (C_{4-15}), 4 to 10 (C_{4-10}), or 4 to 6 (C_{4-6}) carbon atoms. Examples of alkynyl groups include, but are not limited to, ethynyl (–C≡CH), propynyl (including all isomeric forms, *e.g.*, 1-propynyl (–C≡CCH_3) and propargyl (–CH_2C≡CH)), butynyl (including all isomeric forms, *e.g.*, 1-butyn-1-yl and 2-butyn-1-yl), pentynyl (including all isomeric forms, *e.g.*, 1-pentyn-1-yl and 1-methyl-2-butyn-1-yl), and hexynyl (including all isomeric forms, *e.g.*, 1-hexyn-1-yl).

[0031] The term "cycloalkyl" refers to a cyclic saturated or non-aromatic unsaturated, bridged or non-bridged monovalent hydrocarbon radical, which is optionally substituted with one or more substituents Q as described herein. In certain embodiments, the cycloalkyl is a cyclic saturated bridged or non-bridged monovalent hydrocarbon radical. In certain embodiments, the cycloalkyl has from 3 to 20 (C_{3-20}), from 3 to 15 (C_{3-15}), from 3 to 10 (C_{3-10}), or from 3 to 7 (C_{3-7}) carbon atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, decalinyl, and adamantyl.

[0032] The term "aryl" refers to a monocyclic aromatic group and/or multicyclic monovalent aromatic group that contain at least one aromatic hydrocarbon ring, wherein the aryl is optionally substituted with one or more substituents Q as described herein. In certain embodiments, the aryl has from 6 to 20 (C_{6-20}), from 6 to 15 (C_{6-15}), or from 6 to 10 (C_{6-10}) ring atoms. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, fluorenyl, azulenyl, anthryl, phenanthryl, pyrenyl, biphenyl, and terphenyl. In certain embodiments, the term "aryl" refers to a bicyclic or tricyclic carbon ring, where one of the rings is aromatic and the others of which may be saturated, partially unsaturated, or aromatic, for example, dihydronaphthyl, indenyl, indanyl, or tetrahydronaphthyl (tetralinyl).

[0033] The term "aralkyl" or "arylalkyl" refers to a monovalent alkyl group substituted with one or more aryl groups, wherein the alky and aryl moieties are each independently and optionally substituted with one or more substituents Q as described herein.

In certain embodiments, the aralkyl has from 7 to 30 (C_{7-30}), from 7 to 20 (C_{7-20}), or from 7 to 16 (C_{7-16}) carbon atoms. Examples of aralkyl groups include, but are not limited to, benzyl, 1-phenylethyl, 2-phenylethyl, and 3-phenylpropyl.

[0034] The term "heteroaryl" refers to a monovalent monocyclic aromatic group or monovalent polycyclic aromatic group that contain at least one aromatic ring, wherein at least one aromatic ring contains one or more heteroatoms, each of which is independently selected from O, S, N, and P, in the ring. A heteroaryl group is bonded to the rest of a molecule through its aromatic ring *via* a heteroatom or carbon atom to form a stable compound. Each ring of a heteroaryl group can contain one or two O atoms, one or two S atoms, one to four N atoms, and/or one or two P atoms, provided that the total number of heteroatoms in each ring is four or less and each ring contains at least one carbon atom. In certain embodiments, the heteroaryl has from 5 to 20, from 5 to 15, or from 5 to 10 ring atoms. In certain embodiments, the heteroaryl is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, in which nitrogen or sulfur atoms may be optionally oxidized, nitrogen atoms may be optionally quaternized, and some rings may be partially or fully saturated, or aromatic. Examples of monocyclic heteroaryl groups include, but are not limited to, furanyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl, tetrazolyl, triazinyl, and triazolyl. Examples of bicyclic heteroaryl groups include, but are not limited to, benzofuranyl, benzimidazolyl, benzoisoxazolyl, benzopyranyl, benzothiadiazolyl, benzothiazolyl, benzothienyl, benzotriazolyl, benzoxazolyl, furopyridyl, imidazopyridinyl, imidazothiazolyl, indolizinyl, indolyl, indazolyl, isobenzofuranyl, isobenzothienyl, isoindolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxazolopyridinyl, phthalazinyl, pteridinyl, purinyl, pyridopyridyl, pyrrolopyridyl, quinolinyl, quinoxalinyl, quinazolinyl, thiadiazolopyrimidyl, and thienopyridyl. Examples of tricyclic heteroaryl groups include, but are not limited to, acridinyl, benzindolyl, carbazolyl, dibenzofuranyl, perimidinyl, phenanthrolinyl, phenanthridinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxazinyl, and xanthenyl. In certain embodiments, the heteroaryl is optionally substituted with one or more substituents Q as described herein.

[0035] The term "heterocyclyl" or "heterocyclic" refers to a monovalent monocyclic non-aromatic ring system or monovalent polycyclic ring system that contains at least one non-aromatic ring, wherein one or more of the non-aromatic ring atoms are heteroatoms, each

of which is independently selected from O, S, N, and P; and the remaining ring atoms are carbon atoms. In certain embodiments, the heterocyclyl or heterocyclic group has from 3 to 20, from 3 to 15, from 3 to 10, from 3 to 8, from 4 to 7, or from 5 to 6 ring atoms. A heterocyclyl group is bonded to the rest of a molecule through its non-aromatic ring *via* a heteroatom or carbon atom to form a stable compound. In certain embodiments, the heterocyclyl is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may be spiro, fused, or bridged, and in which nitrogen or sulfur atoms may be optionally oxidized, nitrogen atoms may be optionally quaternized, and some rings may be partially or fully saturated, or aromatic. Examples of heterocyclic groups include, but are not limited to, azepinyl, benzodioxanyl, benzodioxolyl, benzofuranonyl, benzopyranonyl, benzopyranyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, benzothiopyranyl, benzoxazinyl, β-carbolinyl, chromanyl, chromonyl, cinnolinyl, coumarinyl, decahydroisoquinolinyl, dihydrobenzisothiazinyl, dihydrobenzisoxazinyl, dihydrofuryl, dihydroisoindolyl, dihydropyranyl, dihydropyrazolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dioxolanyl, 1,4-dithianyl, furanonyl, imidazolidinyl, imidazolinyl, indolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isochromanyl, isocoumarinyl, isoindolinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, oxazolidinonyl, oxazolidinyl, oxiranyl, piperazinyl, piperidinyl, 4-piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydropyranyl, tetrahydrothienyl, thiamorpholinyl, thiazolidinyl, tetrahydroquinolinyl, and 1,3,5-trithianyl. In certain embodiments, the heterocyclyl is optionally substituted with one or more substituents Q as described herein.

[0036] The term "halogen", "halide" or "halo" refers to fluorine, chlorine, bromine, and/or iodine.

[0037] The term "optionally substituted" is intended to mean that a group or substituent, such as an alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, or heterocyclyl group, may be substituted with one or more substituents Q, each of which is independently selected from, *e.g.*, (a) cyano (–CN), halo, nitro ($–NO_2$), and oxo (=O); (b) $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ cycloalkyl, $C_{6–15}$ aryl, $C_{7–15}$ aralkyl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; and (c) $–C(O)R^a$, $–C(O)OR^a$,

$-C(O)NR^bR^c$, $-C(NR^a)NR^bR^c$, $-OR^a$, $-OC(O)R^a$, $-OC(O)OR^a$, $-OC(O)NR^bR^c$, $-OC(=NR^a)NR^bR^c$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-OS(O)NR^bR^c$, $-OS(O)_2NR^bR^c$, $-NR^bR^c$, $-NR^aC(O)R^d$, $-NR^aC(O)OR^d$, $-NR^aC(O)NR^bR^c$, $-NR^aC(=NR^d)NR^bR^c$, $-NR^aS(O)R^d$, $-NR^aS(O)_2R^d$, $-NR^aS(O)NR^bR^c$, $-NR^aS(O)_2NR^bR^c$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^bR^c$, and $-S(O)_2NR^bR^c$, wherein each R^a, R^b, R^c, and R^d is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-15} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; or (iii) R^b and R^c together with the N atom to which they are attached form heteroaryl or heterocyclyl, each optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a. As used herein, all groups that can be substituted are "optionally substituted," unless otherwise specified.

[0038] In one embodiment, each Q^a is independently selected from the group consisting of (a) cyano, halo, nitro, and oxo; and (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-15} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl; and (c) $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^fR^g$, $-C(NR^e)NR^fR^g$, $-OR^e$, $-OC(O)R^e$, $-OC(O)OR^e$, $-OC(O)NR^fR^g$, $-OC(=NR^e)NR^fR^g$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^fR^g$, $-OS(O)_2NR^fR^g$, $-NR^fR^g$, $-NR^eC(O)R^h$, $-NR^eC(O)OR^h$, $-NR^eC(O)NR^fR^g$, $-NR^eC(=NR^h)NR^fR^g$, $-NR^eS(O)R^h$, $-NR^eS(O)_2R^h$, $-NR^eS(O)NR^fR^g$, $-NR^eS(O)_2NR^fR^g$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^fR^g$, and $-S(O)_2NR^fR^g$; wherein each R^e, R^f, R^g, and R^h is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-15} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) R^f and R^g together with the N atom to which they are attached form heteroaryl or heterocyclyl.

[0039] In certain embodiments, "optically active" and "enantiomerically active" refer to a collection of molecules, which has an enantiomeric excess of no less than about 50%, no less than about 70%, no less than about 80%, no less than about 90%, no less than about 91%, no less than about 92%, no less than about 93%, no less than about 94%, no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 99%, no less than about 99.5%, or no less than about 99.8%. In certain embodiments, the compound comprises about 95% or more of one enantiomer and about 5% or less of the other enantiomer based on the total weight of the racemate in question.

[0040] In describing an optically active compound, the prefixes *R* and *S* are used to denote the absolute configuration of the molecule about its chiral center(s). The (+) and (–)

are used to denote the optical rotation of the compound, that is, the direction in which a plane of polarized light is rotated by the optically active compound. The (–) prefix indicates that the compound is levorotatory, that is, the compound rotates the plane of polarized light to the left or counterclockwise. The (+) prefix indicates that the compound is dextrorotatory, that is, the compound rotates the plane of polarized light to the right or clockwise. However, the sign of optical rotation, (+) and (–), is not related to the absolute configuration of the molecule, *R* and *S*.

[0041] The term "solvate" refers to a complex or aggregate formed by one or more molecules of a solute, *e.g.*, a compound provided herein, and one or more molecules of a solvent, which present in stoichiometric or non-stoichiometric amount. Suitable solvents include, but are not limited to, water, methanol, ethanol, *n*-propanol, isopropanol, and acetic acid. In certain embodiments, the solvent is pharmaceutically acceptable. In one embodiment, the complex or aggregate is in a crystalline form. In another embodiment, the complex or aggregate is in a noncrystalline form. Where the solvent is water, the solvate is a hydrate. Examples of hydrates include, but are not limited to, a hemihydrate, monohydrate, dihydrate, trihydrate, tetrahydrate, and pentahydrate.

[0042] The term "chromium-free" refers to a chemical (*e.g.*, a compound or composition) that contains no more than 100 ppm, 50 ppm, 20 ppm, 10 ppm, 5 ppm, 2 ppm, 1 ppm, 0.1 ppm, 10 ppb, or 1 ppb of chromium. In one embodiment, the term "chromium-free" refers to a chemical that contains no more than 10 ppm of chromium. In another embodiment, the term "chromium-free" refers to a chemical that contains no more than 5 ppm of chromium. In yet another embodiment, the term "chromium-free" refers to a chemical that contains no more than 2 ppm of chromium. In still another embodiment, the term "chromium-free" refers to a chemical that contains no more than 1 ppm of chromium. The chromium content can be determined using a conventional technique well known to one of ordinary skill in the art, *e.g.*, inductively coupled plasma (ICP) technique.

Ascorbic Acid Compounds

[0043] In one embodiment, the ascorbic acid compound is L-ascorbic acid or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate or hydrate thereof. L-Ascorbic acid is also known as vitamin C, L-xyloascorbic acid, 3-oxo-L-gulofuranolactone (enol form), L-3-ketothreohexuronic acid lactone, antiscorbutic vitamin,

cevitamic acid, adenex, allercorb, ascorin, ascorteal, ascorvit, cantan, cantaxin, catavin C, cebicure, cebion, cecon, cegiolan, celaskon, celin, cenetone, cereon, cergona, cescorbat, cetamid, cetabe, cetemican, cevalin, cevatine, cevex, cevimin, ce-vi-sol, cevitan, cevitex, cewin, ciamin, cipca, concemin, C-vin, daviamon C, duoscorb, hybrin, laroscorbine, lemascorb, planavit C, proscorbin, redoxon, ribena, scorbacid, scorbu-C, testascorbic, vicelat, vitacee, vitacimin, vitacin, vitascorbol, and xitix.

[0044] In one embodiment, the ascorbic acid compound is L-ascorbic acid. In another embodiment, the ascorbic acid compound is a pharmaceutically acceptable salt of L-ascorbic acid, or a pharmaceutically acceptable solvate or hydrate thereof.

[0045] Suitable bases for forming a pharmaceutically acceptable salt of L-ascorbic acid include, but are not limited to, inorganic bases, such as magnesium hydroxide, calcium hydroxide, potassium hydroxide, zinc hydroxide, and sodium hydroxide; and organic bases, such as primary, secondary, tertiary, and quaternary, aliphatic and aromatic amines, including, but not limited to, L-arginine, benethamine, benzathine, choline, deanol, diethanolamine, diethylamine, dimethylamine, dipropylamine, diisopropylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylamine, ethylenediamine, isopropylamine, *N*-methyl-glucamine, hydrabamine, 1*H*-imidazole, L-lysine, morpholine, 4-(2-hydroxyethyl)-morpholine, methylamine, piperidine, piperazine, propylamine, pyrrolidine, 1-(2-hydroxyethyl)-pyrrolidine, pyridine, quinuclidine, quinoline, isoquinoline, triethanolamine, trimethylamine, triethylamine, *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, and tromethamine.

[0046] In one embodiment, the ascorbic acid compound is an alkali or alkaline earth metal salt of L-ascorbic acid, or a pharmaceutically acceptable solvate or hydrate thereof. In another embodiment, the ascorbic acid compound is sodium, potassium, calcium, or magnesium L-ascorbate, or a pharmaceutically acceptable solvate or hydrate thereof. In yet another embodiment, the ascorbic acid compound is sodium L-ascorbate, or a pharmaceutically acceptable solvate or hydrate thereof. In yet another embodiment, the ascorbic acid compound is sodium L-ascorbate, which is also known as vitamin C sodium, ascorbin, sodascorbate, natrascorb, cenolate, ascorbicin, or cebitate. In yet another embodiment, the ascorbic acid compound is potassium L-ascorbate, or a pharmaceutically acceptable solvate or hydrate thereof. In yet another embodiment, the ascorbic acid compound is calcium L-ascorbate, or a pharmaceutically acceptable solvate or hydrate

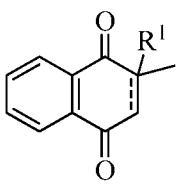
thereof. In yet another embodiment, the ascorbic acid compound is calcium L-ascorbate. In yet another embodiment, the ascorbic acid compound is magnesium L-ascorbate, or a pharmaceutically acceptable solvate or hydrate thereof. In still another embodiment, the ascorbic acid compound is magnesium L-ascorbate.

[0047] In certain embodiments, the the ascorbic acid compound is D-ascorbic acid or a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate or hydrate thereof.

[0048] In certain embodiments, the the ascorbic acid compound is chromium-free. In certain embodiments, the chromium-free ascorbic acid compound contains no more than 100 ppm, 50 ppm, 20 ppm, 10 ppm, 5 ppm, 2 ppm, 1 ppm, 0.1 ppm, 10 ppb, or 1 ppb of chromium. In certain embodiments, the chromium-free ascorbic acid compound contains no greater than 10 ppm of chromium. In certain embodiments, the chromium-free ascorbic acid compound contains no greater than 5 ppm of chromium. In certain embodiments, the chromium-free ascorbic acid compound contains no greater than 2 ppm of chromium. In certain embodiments, the chromium-free ascorbic acid compound contains no greater than 1 ppm of chromium.

Quinone Compounds

[0049] In one embodiment, the quinone compound is vitamin K. In certain embodiments, the vitamin K is a 2-methyl-1,4-naphthoquinone of Formula I, II, or III:



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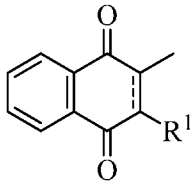
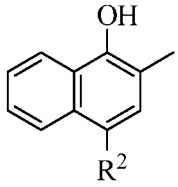


II



III

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; wherein R^1 is C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, or $-SO_3H$; and R^2 is hydroxyl or amino.

[0050] In certain embodiments, the vitamin K is vitamin K_1, vitamin K_2, vitamin K_3, vitamin K_4, vitamin K_5, or a mixture of two or more thereof.

[0051] In one embodiment, the vitamin K is vitamin K_1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof. Vitamin K_1 is also known as phylloquinone, [*R*-[*R**,*R**-(*E*)]]-2-methyl-3-(3,7,11,15-tetramethyl-2-hexadecenyl)-1,4-naphthalenedione, 2-methyl-3-phytyl-1,4-naphthoquinone, 3-phytylmenadione, phytomenadione, phytonadione, aqua-merphyton, konakion, mephyton, mono-day, veda-K_1, and veta-K_1.

[0052] In another embodiment, the vitamin K is vitamin K_2, or a pharmaceutically acceptable salt, solvate, or hydrate thereof. Vitamin K_2 is also known as menaquinones, and 2-methyl-3-*all-trans*-polyprenyl-1,4-naphthoquinones. Some non-limiting examples of vitamin K_2 include menaquinone 4, which is also known as vitamin $K_{2(20)}$; menaquinone 6, which is also known as vitamin $K_{2(30)}$; and menaquinone 7, which is also known as vitamin $K_{2(35)}$.

[0053] In yet another embodiment, the vitamin K is vitamin K_3, or a pharmaceutically acceptable salt, solvate, or hydrate thereof. Vitamin K_3 is also known as menadione, 2-methyl-1,4-naphthalenedione, 2-methyl-1,4-naphthoquinone, menaphthone, vitamin $K_{2(0)}$, kanone, kappaxin, kayklot, kayquinone, klottone, kolklot, thyloquinone, 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonic acid, and sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate. In certain embodiments, the vitamin K is menadione (*i.e.*, 2-methyl-1,4-naphthalenedione).

[0054] In one embodiment, the vitamin K is 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonic acid, or a pharmaceutically acceptable salt, solvate, or hydrate thereof. In another embodiment, the vitamin K is 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate (also known as menadione bisulfite), or a pharmaceutically acceptable solvate or hydrate thereof. Suitable bases for forming a pharmaceutically acceptable salt include, but are not limited to, inorganic bases, such as magnesium hydroxide, calcium hydroxide, potassium hydroxide, zinc hydroxide, and sodium hydroxide; and organic bases, such as primary, secondary, tertiary, and quaternary, aliphatic and aromatic amines, including, but not limited to, L-arginine, benethamine, benzathine, choline, deanol, diethanolamine, diethylamine, dimethylamine, dipropylamine, diisopropylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylamine, ethylenediamine, isopropylamine, *N*-methyl-glucamine, hydrabamine, 1*H*-imidazole, L-lysine, morpholine, 4-(2-hydroxyethyl)-morpholine, methylamine, piperidine, piperazine, propylamine, pyrrolidine, 1-(2-hydroxyethyl)-pyrrolidine, pyridine, quinuclidine, quinoline, isoquinoline, triethanolamine,

trimethylamine, triethylamine, *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, and tromethamine.

[0055] In one embodiment, vitamin K_3 is an alkali or alkaline earth metal salt of 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonic acid, or a pharmaceutically acceptable solvate or hydrate thereof. In another embodiment, vitamin K_3 is sodium, potassium, calcium, or magnesium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate, or a pharmaceutically acceptable solvate or hydrate thereof. In yet another embodiment, vitamin K_3 is sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate, or a pharmaceutically acceptable solvate or hydrate thereof. In yet another embodiment, vitamin K_3 is potassium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate, or a pharmaceutically acceptable solvate or hydrate thereof. In yet another embodiment, vitamin K_3 is magnesium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate, or a pharmaceutically acceptable solvate or hydrate thereof. In yet another embodiment, vitamin K_3 is sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate. In yet another embodiment, vitamin K_3 is anhydrous sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate. In yet another embodiment, vitamin K_3 is sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate hydrate. In still another embodiment, vitamin K_3 is sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate trihydrate.

[0056] In certain embodiments, the vitamin K is vitamin K_4, or a pharmaceutically acceptable salt, solvate, or hydrate thereof. Vitamin K_4 is also known as menadiol, 2-methyl-1,4-naphthalenediol, 2-methyl-1,4-naphthohydroquinone, 2-methyl-1,4-naphthoquinol, and dihydrovitamin K_3.

[0057] In certain embodiments, the vitamin K comprises vitamin K_3 and vitamin K_4, or pharmaceutically acceptable salts, solvates, or hydrates thereof.

[0058] In certain embodiments, the vitamin K is vitamin K_5, or a pharmaceutically acceptable salt, solvate, or hydrate thereof. Vitamin K_5 is also known as 4-amino-2-methyl-1-naphthalenol, 4-amino-2-methyl-1-naphthol, 1-hydroxy-2-methyl-4-aminonaphalene, 2-methyl-4-amino-1-hydroxynaphthalene, 2-methyl-4-amino-1-naphthol, 3-methyl-4-hydroxy-1-naphthylamine, and synkamin.

[0059] In certain embodiments, the vitamin K is chromium-free. In certain embodiments, the chromium-free vitamin K contains no more than 100 ppm, 50 ppm, 20 ppm, 10 ppm, 5 ppm, 2 ppm, 1 ppm, 0.1 ppm, 10 ppb, or 1 ppb of chromium. In certain embodiments, the chromium-free vitamin K contains no greater than 10 ppm of chromium. In certain embodiments, the chromium-free vitamin K contains no greater than 5 ppm of chromium. In certain embodiments, the chromium-free vitamin K contains no greater than 2 ppm of chromium. In certain embodiments, the chromium-free vitamin K contains no greater than 1 ppm of chromium.

[0060] In certain embodiments, the vitamin K is chromium-free vitamin K_3. In certain embodiments, the chromium-free vitamin K_3 contains no more than 100 ppm, 50 ppm, 20 ppm, 10 ppm, 5 ppm, 2 ppm, 1 ppm, 0.1 ppm, 10 ppb, or 1 ppb of chromium. In certain embodiments, the chromium-free vitamin K_3 contains no greater than 10 ppm of chromium. In certain embodiments, the chromium-free vitamin K_3 contains no greater than 5 ppm of chromium. In certain embodiments, the chromium-free vitamin K_3 contains no greater than 2 ppm of chromium. In certain embodiments, the chromium-free vitamin K_3 contains no greater than 1 ppm of chromium.

[0061] In certain embodiments, the vitamin K is chromium-free sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate. In certain embodiments, the chromium-free sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate contains no more than 100 ppm, 50 ppm, 20 ppm, 10 ppm, 5 ppm, 2 ppm, 1 ppm, 0.1 ppm, 10 ppb, or 1 ppb of chromium. In certain embodiments, the chromium-free sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate contains no greater than 10 ppm of chromium. In certain embodiments, the chromium-free sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate contains no greater than 5 ppm of chromium. In certain embodiments, the chromium-free sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate contains no greater than 2 ppm of chromium. In certain embodiments, the chromium-free sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate contains no greater than 1 ppm of chromium.

[0062] In certain embodiments, the chromium-free vitamin K_3 is made *via* a cerium mediator electrochemical technology (CETECH^{TM}) as described in U.S. Pat. No. 6,468,414, the disclosure of which is incorporated by reference herein in its entirety. Alternatively,

chromium-free vitamin K_3 is available from commercial sources, such as PRO-K™ (Lonza Group Ltd, Switzerland).

[0063] In one embodiment, the quinone compound is one that is capable of increasing the production of a reactive oxygen species (*e.g.*, in one embodiment superoxide anon, in another embodiment, hydrogen peroxide) in a cell.

[0064] In another embodiment, the quinone compound is one that is capble of inducing autoschizis. Taper *et al.*, *J. Histochem. Cytochem.* **2001**, *49*, 109-119; Jamison *et al.*, *Biochem. Pharm.* **2002**, *63*, 1773-1783; the disclosure of each of which is incorporated herein by reference in its entirety.

[0065] In certain embodiments, the quinone compound is a naphthalenedione, optionally substituted with one or more substituents Q as defined herein. In certain embodiments, the quinone compound is a naphthalene-1,2-dione, optionally substituted with one or more substituents Q as defined herein. In certain embodiments, the quinone compound is a naphthalene-1,4-dione, optionally substituted with one or more substituents Q as defined herein. In certain embodiments, the quinone compound is a naphthalene-1,4-dione, substituted with one, two, three, or four substituents Q, each of which is independently selected from amino, halo, cyano, nitro, C_{1-6} alkyl, $-OR^a$, $-SR^a$, and $-COR^a$, wherein R^a is (i) hydrogen; or (ii) C_{1-6} alkyl, C_{6-15} aryl, or heteroaryl, each optionally substituted with one or more substituents Q. In certain embodiments, the quinone compound is a naphthalene-1,4-dione, substituted with one, two, three, or four substituents Q, each of which is independently selected from amino, bromo, chloro, cyano, nitro, methyl, $-OR^a$, $-SR^a$, and $-COR^a$, wherein R^a is hydrogen, methyl, phenyl, chlorophenyl, fluorophenyl, *tert*-butylphenyl, methoxyphenyl, trimethoxyphenyl, or (methoxy-2-oxo-2*H*-chromenyl)methyl. In certain embodiments, the quinone compound is a naphthalene-1,4-dione, substituted with one, two, three, or four substituents Q, each of which is independently selected from amino, bromo, chloro, cyano, nitro, methyl, $-OR^a$, $-SR^a$, and $-COR^a$, wherein R^a is hydrogen, methyl, phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-fluorophenyl, 4-*tert*-butylphenyl, 4-methoxyphenyl, 3,4,5-trimethoxyphenyl, or (7-methoxy-2-oxo-2*H*-chromen-4-yl)methyl. Additional quinone compounds include, but are not limited to, those disclosed in U.S. Pat. App. Pub. No. 2013/0219528; and Benites *et al. Invest. New Drugs* **2011**, *29*, 760-767; the disclosure of each of which is incorporated herein by reference in its entirety.

[0066] In certain embodiments, the quinone compound is 2-bromo-1,4-naphthoquinone, 2-methoxy-1,4-naphthoquinone, or 2-methyl-1,4-naphthoquinone; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, the quinone compound is 2-(((7-methoxy-2-oxo-2*H*-chromen-4-yl)methyl)thio)naphthalene-1,4-dione, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. Additional quinone compounds include, but are not limited to, those disclosed in Bana *et al.*, *Mol. Carcinog.* **2013**, DOI: 10.1002/mc.22094, the disclosure of which is incorporated herein by reference in its entirety; or pharmaceutically acceptable salts, solvates, hydrates, and prodrugs thereof.

[0067] In certain embodiments, the quinone compound is 2-amino-3-bromo-1,4-naphthoquinone, 2-amino-3-chloro-1,4-naphthoquinone, or 2-amino-3-methoxy-1,4-naphthoquinone; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, the quinone compound is 2,3-dichloro-1,4-naphthoquinone or 2,3-dimethoxy-1,4-naphthoquinone; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. Additional quinone compounds include, but are not limited to, those disclosed in Graciani and Ximenes, *Braz. J. Med. Biol. Res.* **2012**, *45*, 701-710, the disclosure of which is incorporated herein by reference in its entirety; or pharmaceutically acceptable salts, solvates, hydrates, and prodrugs thereof.

[0068] In certain embodiments, the quinone compound is 2-dibenzoylamino-3-chloro-1,4-naphthoquinone, 2-dibenzoylamino-3-bromo-1,4-naphthoquinone, 2-dibenzoylamino-3-methoxy-1,4-naphthoquinone, 2-bis-(2-chlorobenzoyl)amino-3-chloro-1,4-naphthoquinone, 2-bis-(2-chlorobenzoyl)amino-3-bromo-1,4-naphthoquinone, 2-bis-(2-chlorobenzoyl)amino-3-methoxy-1,4-naphthoquinone, 2-bis-(3-chlorobenzoyl)amino-3-chloro-1,4-naphthoquinone, 2-bis-(3-chlorobenzoyl)amino-3-bromo-1,4-naphthoquinone, 2-bis-(3-chlorobenzoyl)amino-3-methoxy-1,4-naphthoquinone, 2-bis-(4-chlorobenzoyl)amino-3-chloro-1,4-naphthoquinone, 2-bis-(4-chlorobenzoyl)amino-3-bromo-1,4-naphthoquinone, 2-bis-(4-chlorobenzoyl)amino-3-methoxy-1,4-naphthoquinone, 2-bis-(4-fluorobenzoyl)amino-3-chloro-1,4-naphthoquinone, 2-bis-(4-fluorobenzoyl)amino-3-bromo-1,4-naphthoquinone, 2-bis-(4-fluorobenzoyl)amino-3-methoxy-1,4-naphthoquinone, 2-bis-(4-tert-butylbenzoyl)amino-3-chloro-1,4-naphthoquinone, 2-bis-(4-*tert*-butylbenzoyl)amino-3-bromo-1,4-naphthoquinone, 2-bis-(4-*tert*-butylbenzoyl)amino-3-methoxy-1,4-naphthoquinone, 2-bis-(4-methoxybenzoyl)amino-3-chloro-1,4-naphthoquinone, 2-bis-(4-methoxybenzoyl)amino-3-bromo-1,4-naphthoquinone,

2-bis-(3,4,5-trimethoxybenzoyl)-amino-3-chloro-1,4-naphthoquinone, 2-*N*-(4-chlorobenzoyl))-amino-3-chloro-1,4-naphthoquinone, 2-(*N*-benzoyl-*N*-(4-chlorobenzoyl))-amino-3-chloro-1,4-naphthoquinone, 2-*N*-acteylamino-3-chloro-1,4-naphthoquinone, or 2-(*N*-acetyl-*N*-(4-chlorobenzoyl))-amino-3-chloro-1,4-naphthoquinone; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. Additional quinone compounds include, but are not limited to, those disclosed in Brandy *et al.*, *Molecules* **2013**, *18*, 1973-1984, the disclosure of which is incorporated herein by reference in its entirety; or pharmaceutically acceptable salts, solvates, hydrates, and prodrugs thereof.

[0069] In certain embodiments, the quinone compound is plumbagin, also known as 5-hydroxy-2-methyl-naphthalene-1,4-dione. In certain embodiments, the quinone compound is plumbazeylanone. In certain embodiments, the quinone compound is lawsone, also known as 2-hydroxy-1,4-naphthoquinone. In certain embodiments, the quinone compound is juglone, also known as 5-hydroxy-1,4-naphthalenedione. Additional quinone compounds include, but are not limited to, those disclosed in Padhye *et al.*, *Med. Res. Rev.* **2012**, *32*, 1131-1158, the disclosure of which is incorporated herein by reference in its entirety; or pharmaceutically acceptable salts, solvates, hydrates, and prodrugs thereof.

[0070] In certain embodiments, the quinone compound is mitomycin C, also known as [6-amino-8*a*-methoxy-5-methyl-4,7-dioxo-1,1*a*,2,4,7,8,8*a*,8*b*-octahydroazireno[2',3':3,4]-pyrrolo[1,2-*a*]indol-8-yl]methyl carbamate. In certain embodiments, the quinone compound is daunorubicin, also known as (8*S*,10*S*)-8-acetyl-10-[(2*S*,4*S*,5*S*,6*S*)-4-amino-5-hydroxy-6-methyl-oxan-2-yl]oxy-6,8,11-trihydroxy-1-methoxy-9,10-dihydro-7*H*-tetracene-5,12-dione. In certain embodiments, the quinone compound is doxorubicin, also known as (7*S*,9*S*)-7-[(2*R*,4*S*,5*S*,6*S*)-4-amino-5-hydroxy-6-methyloxan-2-yl]oxy-6,9,11-trihydroxy-9-(2-hydroxyacetyl)-4-methoxy-8,10-dihydro-7*H*-tetracene-5,12-dione. In certain embodiments, the quinone compound is mitoxantrone, also known as 1,4-dihydroxy-5,8-bis[2-(2-hydroxyethylamino)ethylamino]-anthracene-9,10-dione.

[0071] In certain embodiments, the quinone compound is chromium-free. In certain embodiments, the chromium-free quinone compound contains no more than 100 ppm, 50 ppm, 20 ppm, 10 ppm, 5 ppm, 2 ppm, 1 ppm, 0.1 ppm, 10 ppb, or 1 ppb of chromium. In certain embodiments, the chromium-free quinone compound contains no greater than 10 ppm of chromium. In certain embodiments, the chromium-free quinone compound contains no greater than 5 ppm of chromium. In certain embodiments, the chromium-free quinone

compound contains no greater than 2 ppm of chromium. In certain embodiments, the chromium-free quinone compound contains no greater than 1 ppm of chromium.

[0072] The quinone compound may also be provided as a prodrug, which is a functional derivative of the quinone compound and is readily convertible into the parent quinone compound *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent compound. They may, for instance, be bioavailable by oral administration whereas the parent compound is not. The prodrug may also have enhanced solubility in pharmaceutical compositions over the parent compound. A prodrug may be converted into the parent drug by various mechanisms, including enzymatic processes and metabolic hydrolysis. See Harper, *Progress in Drug Research* **1962**, *4*, 221-294; Morozowich *et al.* in "Design of Biopharmaceutical Properties through Prodrugs and Analogs," Roche Ed., APHA Acad. Pharm. Sci. 1977; "Bioreversible Carriers in Drug in Drug Design, Theory and Application," Roche Ed., APHA Acad. Pharm. Sci. 1987; "Design of Prodrugs," Bundgaard, Elsevier, 1985; Wang *et al.*, *Curr. Pharm. Design* **1999**, *5*, 265-287; Pauletti *et al.*, *Adv. Drug. Delivery Rev.* **1997**, *27*, 235-256; Mizen *et al.*, *Pharm. Biotech.* **1998**, *11*, 345-365; Gaignault *et al.*, *Pract. Med. Chem.* **1996**, 671-696; Asgharnejad in "Transport Processes in Pharmaceutical Systems," Amidon *et al.*, Ed., Marcell Dekker, 185-218, 2000; Balant *et al.*, *Eur. J. Drug Metab. Pharmacokinet.* **1990**, *15*, 143-53; Balimane and Sinko, *Adv. Drug Delivery Rev.* **1999**, *39*, 183-209; Browne, *Clin. Neuropharmacol.* **1997**, *20*, 1-12; Bundgaard, *Arch. Pharm. Chem.* **1979**, *86*, 1-39; Bundgaard, *Controlled Drug Delivery* **1987**, *17*, 179-96; Bundgaard, *Adv. Drug Delivery Rev.* **1992**, *8*, 1-38; Fleisher *et al.*, *Adv. Drug Delivery Rev.* **1996**, *19*, 115-130; Fleisher *et al.*, *Methods Enzymol.* **1985**, *112*, 360-381; Farquhar *et al.*, *J. Pharm. Sci.* **1983**, *72*, 324-325; Freeman *et al.*, *J. Chem. Soc., Chem. Commun.* **1991**, 875-877; Friis and Bundgaard, *Eur. J. Pharm. Sci.* **1996**, *4*, 49-59; Gangwar *et al.*, *Des. Biopharm. Prop. Prodrugs Analogs*, **1977**, 409-421; Nathwani and Wood, *Drugs* **1993**, *45*, 866-94; Sinhababu and Thakker, *Adv. Drug Delivery Rev.* **1996**, *19*, 241-273; Stella *et al.*, *Drugs* **1985**, *29*, 455-73; Tan *et al.*, *Adv. Drug Delivery Rev.* **1999**, *39*, 117-151; Taylor, *Adv. Drug Delivery Rev.* **1996**, *19*, 131-148; Valentino and Borchardt, *Drug Discovery Today* **1997**, *2*, 148-155; Wiebe and Knaus, *Adv. Drug Delivery Rev.* **1999**, *39*, 63-80; and Waller *et al.*, *Br. J. Clin. Pharmac.* **1989**, *28*, 497-507.

Sodium Glucose Cotransporter Inhibitors

[0073] As used herein, the term "sodium glucose cotransporter inhibitor" or "SGLT inhibitor" refers to a compound that measurably slows, decreases, inactivates, or inhibits the activity of a sodium glucose cotransporter.

[0074] In one embodiment, the SGLT inhibitor is a sodium glucose cotransporter 1 (SGLT1) inhibitor, sodium glucose cotransporter 2 (SGLT2) inhibitor, or a combination thereof. In another embodiment, the SGLT inhibitor is a dual SGLT1 and SGLT2 inhibitor.

[0075] In yet another embodiment, the SGLT inhibitor is a SGLT1 inhibitor. In yet another embodiment, the SGLT inhibitor is a SGLT1-selective inhibitor. In certain embodiments, the SGLT inhibitor has a selectivity for SGLT1 over SGLT2 ranging from about 2 to about 10,000, from about 5 to about 5,000, from about 10 to about 2,000, from about 20 to about 1,000, from about 50 to about 1,000, or from about 100 to about 1,000.

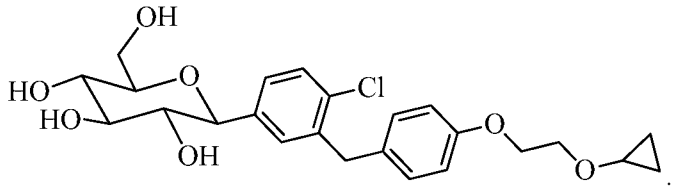
[0076] In yet another embodiment, the SGLT inhibitor is a SGLT2 inhibitor. In yet another embodiment, the SGLT inhibitor is a SGLT2-selective inhibitor. n certain embodiments, the SGLT inhibitor has a selectivity for SGLT2 over SGLT1 ranging from about 2 to about 10,000, from about 5 to about 5,000, from about 10 to about 2,000, from about 20 to about 1,000, from about 50 to about 1,000, or from about 100 to about 1,000.

[0077] In certain embodiments, the SGLT inhibitor is bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, phlorizin, remogliflozin, sergliflozin, sotagliflozin, tofogliflozin, BI 44847, DSP-3235, or T-1095. In certain embodiments, the SGLT inhibitor is canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, or luseogliflozin.

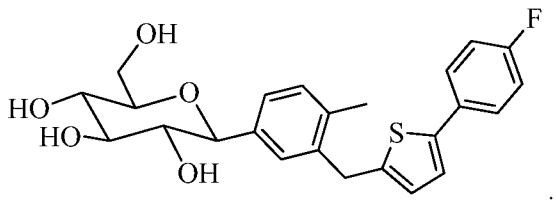
[0078] In certain embodiments, the SGLT1 inhibitor is phlorizin, sotagliflozin, DSP-3235, or T-1095. In certain embodiments, the SGLT1-selective inhibitor is DSP-3235. In certain embodiments, the SGLT1-specific inhibitor is DSP-3235. In certain embodiments, the SGLT2 inhibitor is bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, phlorizin, remogliflozin, sergliflozin, sotagliflozin, or tofogliflozin, BI 44847, DSP-3235, or T-1095. In certain embodiments, the SGLT2-selective inhibitor is bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, remogliflozin, sergliflozin, or tofogliflozin. In certain

embodiments, the SGLT2-specific inhibitor is bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, remogliflozin, sergliflozin, or tofogliflozin. In certain embodiments, the due SGLT1 and SGLT2 inhibitor is sotagliflozin.

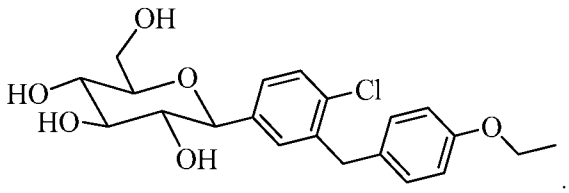
[0079] In certain embodiments, the SGLT inhibitor is bexagliflozin, which is also known as EGT 1442 or (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)-benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol, having the structure of:



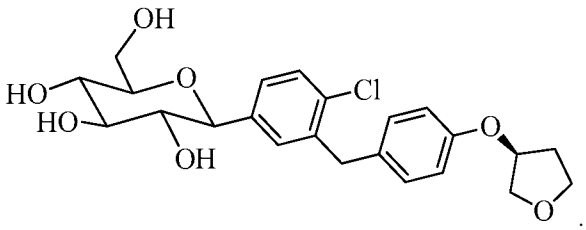
[0080] In certain embodiments, the SGLT inhibitor is canagliflozin, which is also known as TA-7284, JNJ-28431754, or (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-(5-(4-fluorophenyl)-thien-2-ylmethyl)-4-methylphenyl}-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol, having the structure of:



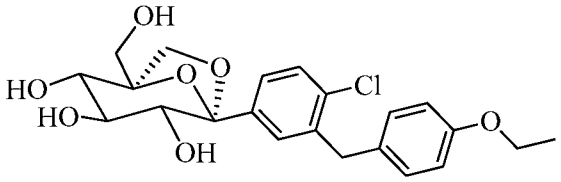
[0081] In certain embodiments, the SGLT inhibitor is dapagliflozin, which is also known as BMS-512148 or (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol, having the structure of:



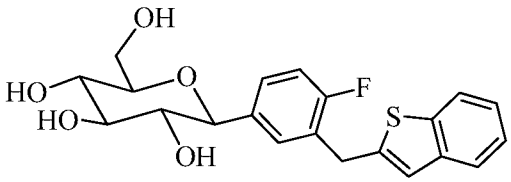
[0082] In certain embodiments, the SGLT inhibitor is empagliflozin, which is also known as BI 10773 or (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-chloro-3-(4-((3*S*)-oxolan-3-yloxy)benzyl)-phenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol, having the structure of:



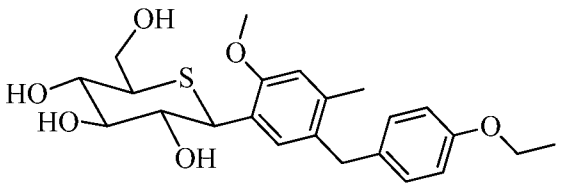
[0083] In certain embodiments, the SGLT inhibitor is ertugliflozin, which is also known as PF-04971729 or (1*S*,2*S*,3*S*,4*R*)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol, having the structure of:



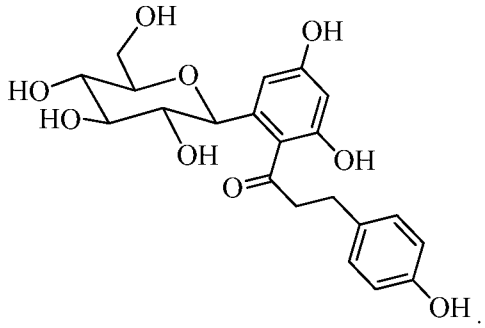
[0084] In certain embodiments, the SGLT inhibitor is ipragliflozin, which is also known as ASP 1941 or (2*S*,3*R*,4R,5*S*,6*R*)-2-(3-(benzo[*b*]thiophen-2-ylmethyl)-4-fluorophenyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol, having the structure of:



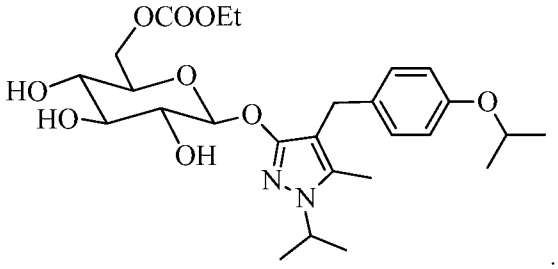
[0085] In certain embodiments, the SGLT inhibitor is luseogliflozin, which is also known as TS-071 or (2*S*,3*R*,4R,5*S*,6*R*)-2-(5-(4-ethoxybenzyl)-2-methoxy-4-methylphenyl)-6-(hydroxymethyl)tetrahydro-2*H*-thiopyran-3,4,5-triol, having the structure of:



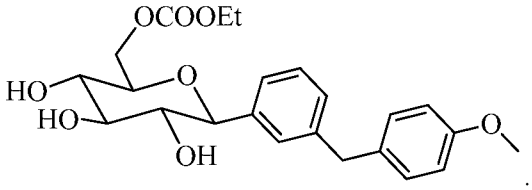
[0086] In certain embodiments, the SGLT inhibitor is phlorizin, which is also known as 1-(2,4-dihydroxy-6-((2*S*,3*R*,4R,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxyphenyl)-3-(4-hydroxyphenyl)propan-1-one, having the structure of:



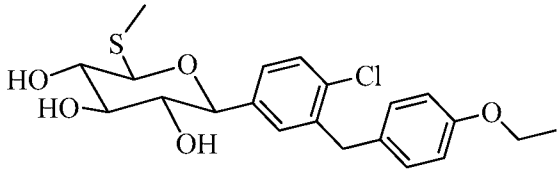
[0087] In certain embodiments, the SGLT inhibitor is remogliflozin, which is also known as 5-methyl-4-(4-(1-methylethoxy)benzyl)-1-(1-methylethyl)-1*H*-pyrazol-3-yl 6-O-(ethoxycarbonyl)-β-D-glucopyranoside, having the structure of:



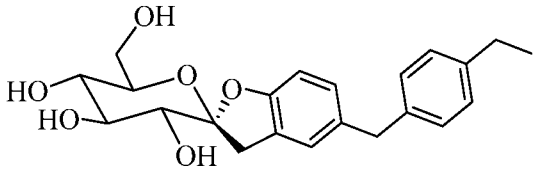
[0088] In certain embodiments, the SGLT inhibitor is sergliflozin, which is also known as GW869682X or 2-(4-methoxybenzyl)phenyl-6-O-(ethoxycarbonyl)-β-D-glucopyranoside, having the structure of:



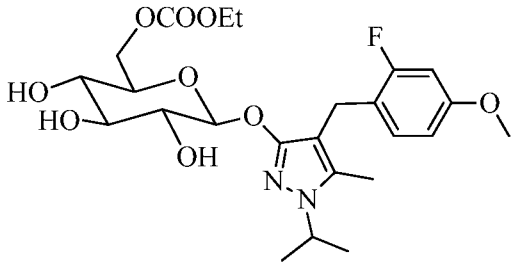
[0089] In certain embodiments, the SGLT inhibitor is sotagliflozin, which is also known as LX 4211 or (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)-tetrahydro-2*H*-pyran-3,4,5-triol, having the structure of:



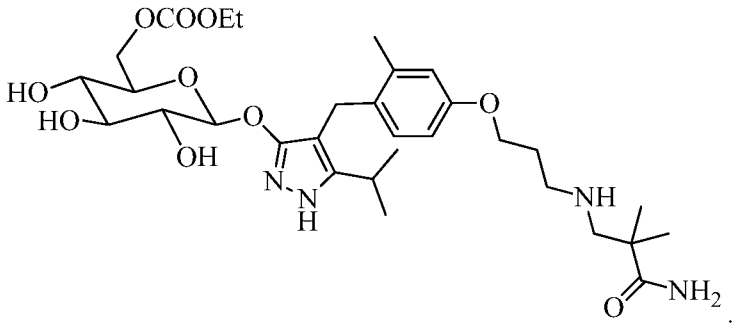
[0090] In certain embodiments, the SGLT inhibitor is tofogliflozin, which is also known as CSG452 or (2*R*,3'*R*,4'*S*,5'*S*,6'*R*)-5-(4-ethylbenzyl)-6'-(hydroxymethyl)-3',4',5',6'-tetrahydro-3*H*-spiro(benzofuran-2,2'-pyran)-3',4',5'-triol, having the structure of:



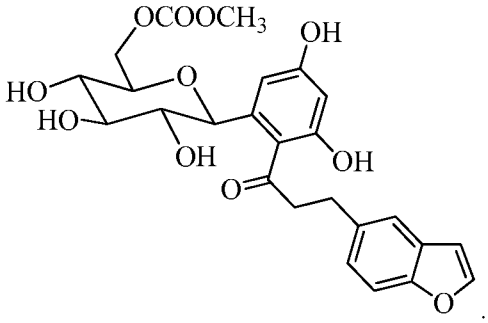
[0091] In certain embodiments, the SGLT inhibitor is BI 44847, which is also known as ethyl (((2*R*,3*S*,4*S*,5*R*,6*S*)-6-((4-(2-fluoro-4-methoxybenzyl)-1-isopropyl-5-methyl-1*H*-pyrazol-3-yl)oxy)-3,4,5-trihydroxytetrahydro-2*H*-pyran-2-yl)methyl) carbonate, having the structure of:



[0092] In certain embodiments, the SGLT inhibitor is DPS-3235, which has the structure of:



[0093] In certain embodiments, the SGLT inhibitor is T-1095, which is also known as ((2*R*,3*S*,4*R*,5*R*,6*S*)-6-(2-(3-(benzofuran-5-yl)propanoyl)-3,5-dihydroxyphenyl)-3,4,5-trihydroxytetrahydro-2*H*-pyran-2-yl)methyl methyl carbonate, having the structure of:



[0094] Additional SGLT inhibitors include, but are not limited to, those disclosed in Handlon, *Expert Opin. Ther. Pat.* **2005**, *15*, 1531-1540; Washburn, *Expert Opin. Ther. Pat.* **2009**, *19*, 1485-1499; Lv *et al.*, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6877-6881; Zhou *et al.*, *ACS Med. Chem. Lett.* **2010**, *1*, 19-23; Nomura, *Curr. Top. Med. Chem.* **2010**, *10*, 411-418; Chao *et al.*, *Nat. Rev. Drug Discov.* **2010**, *9*, 551-559; Robinson *et al.*, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1569-1572; Xu *et al.*, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4422-4432; Song *et al.*, *ACS Med. Chem. Lett.* **2011**, *2*, 182-187; Ohkura, *World J. Diabetes*, **2015**, *6*, 136-144; the disclosure of each of which is incorporated by reference herein in its entirety.

Glutamine inhibitors

[0095] As used herein, the term "glutamine inhibitor" refers to a compound that measurably slows, decreases, inactivates, or inhibits glutamine metabolism, in one embodiment, glutamine catabolism; or measurably decreases, reduces, or depletes the plasma glutamine level.

[0096] In one embodiment, the glutamine inhibitor is 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid (BCH), (2*S*)-amino((5*S*)-3-chloro-4,5-dihydro-1,2-oxazol-5-yl)ethanoic acid (acivicin), (5*S*)-5-amino-1-diazonio-6-hydroxy-6-oxohex-1-en-2-olate (6-diazo-5-oxo-L-norleucine or DON), aminooxyacetic acid (AOA), L-2-amino-4-oxo-5-chloropentoic acid, L-asparaginase, azaserine (O-(2-diazoacetyl)-L-serine), azotomycin, 3,7-bis(dimethylamino)-phenazathionium chloride (methylene blue), bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulfide (BPTES), 5-(3-bromo-4-(dimethylamino)phenyl)-2,2-dimethyl-2,3,5,6-tetrahydrobenzo[*a*]phenanthridin-4(1*H*)-one, bromothymol blue, *O*-carbamoyl-L-serine, *p*-chloromercuriphenylsulfonate (pCMPS), dicoumarol, (-)-epigallocatechin gallate (EGCG), *N*-ethylmaleimide (NEM), γ-L-glutamyl-*p*-nitroanilide (GPNA), metformin, palmitoyl coenzyme A, pegaspargase, perphenazine, phenylbutyrate, phenylacetate, 2-(pyridin-2-yl)-*N*-(5-(4-(6-(2-(3-(trifluoromethoxy)phenyl)acetamido)-pyridazin-3-yl)butyl)-1,3,4-thiadiazol-2-yl)acetamide, or stearoyl coenzyme A. Additional glutamine inhibitors include, but are not limited to, those disclosed in U.S. Pat. No. 7,288,246; the disclosure of which is incorporated herein by reference in its entirety.

[0097] In one embodiment, the glutamine inhibitor is an inhibitor of glutaminolysis.

[0098] In another embodiment, the glutamine inhibitor is a glutamine transporter inhibitor. In certain embodiments, the glutamine transporter inhibitor is an inhibitor of the

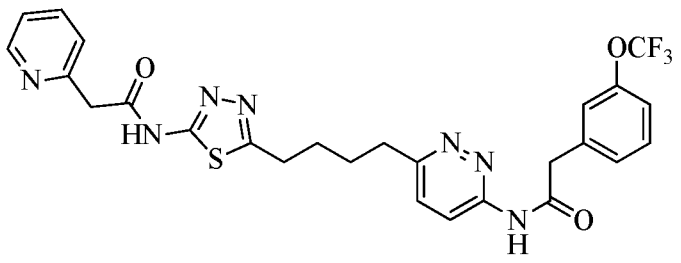
glutamine transporter SLC1A5. In certain embodiments, the glutamine transporter inhibitor is an inhibitor of the ASCT2 neutral amino acid transport. In certain embodiments, the glutamine transporter inhibitor is an inhibitor of a neutral amino acid transporter. In certain embodiments, the glutamine transporter inhibitor is an inhibitor of a neutral amino acid transporter B(0). In certain embodiments, the glutamine transporter inhibitor is γ-L-glutamyl-*p*-nitroanilide (GPNA). In certain embodiments, the glutamine inhibitor is 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid. Additional glutamine transporter inhibitors include, but are not limited to, those disclosed in Esslinger *et al.*, *Bioorg. Med. Chem.* **2005**, *13*, 1111-1118; the disclosure of which is incorporated herein by reference in its entirety.

[0099] In yet another embodiment, the glutamine inhibitor is an inhibitor of glutamine metabolism.

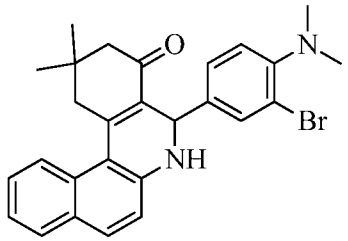
[00100] In yet another embodiment, the glutamine inhibitor is a glutamine amidotransferase inhibitor. In certain embodiments, the glutamine amidotransferase inhibitor is azaserine. In certain embodiments, the glutamine amidotransferase inhibitor is aminooxyacetic acid.

[00101] In yet another embodiment, the glutamine inhibitor is a γ-glutamyl transferase inhibitor. In certain embodiments, the γ-glutamyl transferase inhibitor is acivicin.

[00102] In yet another embodiment, the glutamine inhibitor is a glutaminase inhibitor. In one embodiment, the glutaminase inhibitor is 2-(pyridin-2-yl)-*N*-(5-(4-(6-(2-(3-(trifluoromethoxy)phenyl)acetamido)pyridazin-3-yl)butyl)-1,3,4-thiadiazol-2-yl)acetamide, having the structure of:



[00103] In another embodiment, the glutaminase inhibitor is 5-(3-bromo-4-(dimethylamino)phenyl)-2,2-dimethyl-2,3,5,6-tetrahydrobenzo[*a*]phenanthridin-4(1*H*)-one, having the structure of:



[00104] In yet another embodiment, the glutaminase inhibitor is bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulfide. Additional glutaminase inhibitors include, but are not limited to, those disclosed in U.S. Pat. No. 8,604,016; Wang *et al.*, *Cancer Cell.* **2010**, *18*, 207-219; and Shukla *et al.*, *J. Med. Chem.* **2012**, *55*, 10551-10563; the disclosure of each of which is incorporated herein by reference in its entirety.

[00105] In certain embodiments, the glutamine inhibitor is an inhibitor of a kidney-type glutaminase. In certain embodiments, the glutamine inhibitor is an inhibitor of a liver-type glutaminase. In certain embodiments, the glutamine inhibitor is an inhibitor of a mitochondrial glutaminase. In certain embodiments, the glutamine inhibitor is an inhibitor of glutaminase C. In certain embodiments, the glutamine inhibitor is an inhibitor of human kidney-type glutaminase.

[00106] In still another embodiment, the glutamine inhibitor is a glutamate dehydrogenase inhibitor. In one embodiment, the glutamate dehydrogenase inhibitor is (-)-epigallocatechin gallate. In another embodiment, the glutamate dehydrogenase inhibitor is perphenazine.

Pharmaceutical Compositions

[00107] In one embodiment, a pharmaceutical composition comprises (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; and (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00108] In another embodiment, a pharmaceutical composition comprises (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a

pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00109] In yet another embodiment, a pharmaceutical composition comprises (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iii) a glutamine inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00110] In still another embodiment, a pharmaceutical composition comprises (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iv) a glutamine inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00111] In certain embodiments, the pharmaceutical compositions each independently further comprise a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture of two or more thereof.

[00112] In certain embodiments, the ascorbic acid used in each of the pharmaceutical compositions is independently chromium-free. In certain embodiments, the quinone compound used in each of the pharmaceutical compositions is independently chromium-free.

[00113] In certain embodiments, the pharmaceutical compositions are each independently chromium-free. In certain embodiments, the pharmaceutical compositions each independently contain no more than 100 ppm, 50 ppm, 20 ppm, 10 ppm, 5 ppm, 2 ppm,

1 ppm, 0.1 ppm, 10 ppb, or 1 ppb of chromium. In certain embodiments, the pharmaceutical compositions each independently contain no greater than 10 ppm of chromium. In certain embodiments, the pharmaceutical compositions each independently contain no greater than 5 ppm of chromium. In certain embodiments, the pharmaceutical compositions each independently contain no greater than 2 ppm of chromium. In certain embodiments, the pharmaceutical compositions each independently contain no greater than 1 ppm of chromium.

[00114] In one embodiment, the weight ratio of the ascorbic acid to the quinone compound in each of the pharmaceutical compositions is independently ranging from about 4 to about 500, from about 10 to about 500, from about 50 to about 500, from about 25 to about 250, from about 50 to about 200, from about 50 to about 150, or from about 80 to about 120. In another embodiment, the weight ratio of the ascorbic acid to the quinone compound in each of the pharmaceutical compositions is independently about 10, about 20, about 30, about 40, about 50, about 60, about 70, about 80, about 90, about 100, about 110, about 120, about 130, about 140, about 150, about 160, about 170, about 180, about 190, about 200, about 210, about 220, about 230, about 240, or about 250. In yet another embodiment, the weight ratio of the ascorbic acid to the quinone compound in each of the pharmaceutical compositions is independently about 100. In still another embodiment, the weight ratio of the ascorbic acid to the quinone compound in each of the pharmaceutical compositions is independently about 200.

[00115] In one embodiment, the molar ratio of the ascorbic acid to the quinone compound in each of the pharmaceutical compositions is independently ranging from about 10 to about 500, from about 25 to about 250, from about 50 to about 200, from about 50 to about 150, or from about 80 to about 120. In another embodiment, the molar ratio of the ascorbic acid to the quinone compound in each of the pharmaceutical compositions is independently about 10, about 20, about 30, about 40, about 50, about 60, about 70, about 80, about 90, about 100, about 110, about 120, about 130, about 140, about 150, about 160, about 170, about 180, about 190, about 200, about 210, about 220, about 230, about 240, or about 250. In yet another embodiment, the molar ratio of the ascorbic acid to the quinone compound in each of the pharmaceutical compositions is independently about 100. In still another embodiment, the molar ratio of the ascorbic acid to the quinone compound in each of the pharmaceutical compositions is independently about 200.

[00116] In certain embodiments, the pharmaceutical compositions are each independently formulated in various dosage forms for oral, parenteral, and topical administration. In certain embodiments, the pharmaceutical compositions are each independently formulated as modified release dosage forms, including, but not limited to, delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated-, fast-, targeted-, and programmed-release; and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (S*ee, e.g., Remington: The Science and Practice of Pharmacy*, *supra*; *Modified-Release Drug Delivery Technology*, 2nd ed., Drugs and the Pharmaceutical Sciences; Rathbone *et al.*, Eds.; CRC Press LLC: Boca Raton, FL, 2008).

[00117] In one embodiment, the pharmaceutical compositions are each independently formulated in a dosage form for oral administration. In another embodiment, the pharmaceutical compositions are each independently formulated in a dosage form for parenteral administration. In yet another embodiment, the pharmaceutical compositions are each independently formulated in a dosage form for intravenous administration. In yet another embodiment, the pharmaceutical compositions are each independently formulated in a dosage form for topical administration. In still another embodiment, the pharmaceutical compositions are each independently formulated in a dosage form for local injection.

[00118] In one embodiment, the pharmaceutical compositions are each independently formulated as a capsule. In one embodiment, the capsule comprises (i) from about 10 mg to about 1,000 mg, from about 25 mg to about 900 mg, from about 50 mg to about 800 mg, from about 100 mg to about 700 mg, from about 200 mg to about 600 mg, from about 300 mg to about 600 mg, or from about 400 mg to about 600 mg of ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; and (ii) from about 0.1 mg to about 10 mg, from about 1 mg to about 9 mg, from about 2 mg to about 8 mg, from about 3 mg to about 7 mg, or from about 4 mg to about 6 mg of a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00119] In another embodiment, the capsule comprises (i) from about 400 mg to about 600 mg of ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; and

(ii) from about 4 mg to about 6 mg of a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00120] In yet another embodiment, the capsule comprises (i) about 200 mg, about 300 mg, about 400, about 500, about 600 mg, about 700 mg, about 800 mg, or about 900 mg of ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; and (ii) about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, or about 10 mg of a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00121] In still another embodiment, the capsule comprises (i) about 500 mg of ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; and (ii) about 5 mg of a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00122] In certain embodiments, the capsule consists essentially of (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; and (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00123] In certain embodiments, the capsule contains (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; and (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00124] In one embodiment, the ascorbic acid compound in each of the pharmaceutical compositions is independently L-ascorbic acid or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate or hydrate thereof. In another embodiment, the ascorbic acid compound in each of the pharmaceutical compositions is independently an

alkali or alkaline earth metal salt of L-ascorbic acid, or a pharmaceutically acceptable solvate or hydrate thereof; or a mixture thereof. In yet another embodiment, the ascorbic acid compound in each of the pharmaceutical compositions is independently sodium, potassium, calcium, or magnesium salt of L-ascorbic acid, or a pharmaceutically acceptable solvate or hydrate thereof; or a mixture thereof. In yet another embodiment, the ascorbic acid compound in each of the pharmaceutical compositions is independently sodium L-ascorbate. In yet another embodiment, the ascorbic acid compound in each of the pharmaceutical compositions is independently calcium L-ascorbate. In yet another embodiment, the ascorbic acid compound in each of the pharmaceutical compositions is independently magnesium L-ascorbate. In still another embodiment, the ascorbic acid compound in each of the pharmaceutical compositions is independently a mixture of two or three of sodium L-ascorbate, calcium L-ascorbate, and magnesium L-ascorbate.

[00125] In one embodiment, the quinone compound in each of the pharmaceutical compositions is independently vitamin K, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, or hydrate thereof. In another embodiment, the quinone compound in each of the pharmaceutical compositions is independently vitamin K_3, or a pharmaceutically acceptable salt, solvate, or hydrate thereof. In yet another embodiment, the quinone compound in each of the pharmaceutical compositions is independently 2-methyl-1,4-naphthalenedione, or a pharmaceutically solvate or hydrate thereof. In yet another embodiment, the quinone compound in each of the pharmaceutical compositions is independently 2-methyl-1,4-naphthalenedione. In yet another embodiment, the quinone compound in each of the pharmaceutical compositions is independently 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonic acid, or a pharmaceutically acceptable salt, solvate, or hydrate thereof. In yet another embodiment, the quinone compound in each of the pharmaceutical compositions is independently an alkali or alkaline earth metal salt of 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonic acid, or a pharmaceutically acceptable solvate or hydrate thereof; or a mixture thereof. In yet another embodiment, the quinone compound in each of the pharmaceutical compositions is independently sodium, potassium, calcium, or magnesium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate, or a pharmaceutically acceptable solvate or hydrate thereof; or a mixture thereof. In yet another embodiment, the quinone compound in each of the pharmaceutical compositions is independently sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate, or a

pharmaceutically acceptable solvate or hydrate thereof. In yet another embodiment, the quinone compound in each of the pharmaceutical compositions is independently potassium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate, or a pharmaceutically acceptable solvate or hydrate thereof. In yet another embodiment, the quinone compound in each of the pharmaceutical compositions is independently magnesium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate, or a pharmaceutically acceptable solvate or hydrate thereof. In yet another embodiment, the quinone compound in each of the pharmaceutical compositions is independently sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate. In yet another embodiment, the quinone compound in each of the pharmaceutical compositions is independently anhydrous sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate. In yet another embodiment, the quinone compound in each of the pharmaceutical compositions is independently sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate hydrate. In still another embodiment, the quinone compound in each of the pharmaceutical compositions is independently sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate trihydrate.

[00126] In one embodiment, the capsule contains about 500 mg of sodium L-ascorbate, and about 5 mg of sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate or a hydrate thereof. In another embodiment, the capsule contains about 500 mg of calcium L-ascorbate, and about 5 mg of sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate or a hydrate thereof. In yet another embodiment, the capsule contains about 500 mg of magnesium L-ascorbate, and about 5 mg of sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate or hydrate thereof. In yet another embodiment, the capsule contains about 500 mg of sodium L-ascorbate and about 5 mg of anhydrous sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate. In yet another embodiment, the capsule contains about 500 mg of sodium L-ascorbate and about 5 mg of sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate trihydrate. In yet another embodiment, the capsule contains about 500 mg of calcium L-ascorbate and about 5 mg of anhydrous sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate. In yet another embodiment, the capsule contains about 500 mg of calcium L-ascorbate and about 5 mg of sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate trihydrate. In yet another embodiment, the capsule contains about 500 mg of magnesium L-ascorbate and about 5 mg of anhydrous sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate. In still another embodiment, the capsule contains about 500 mg of

magnesium L-ascorbate and about 5 mg of sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate trihydrate. In another embodiment, the capsule further comprises a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture of two or more thereof.

[00127] In one embodiment, the capsule contains about 500 mg of sodium L-ascorbate and about 5 mg of 2-methyl-1,4-naphthalenedione. In another embodiment, the capsule contains about 1,000 mg of sodium L-ascorbate and about 10 mg of 2-methyl-1,4-naphthalenedione. In yet another embodiment, the capsule contains about 925 mg of sodium L-ascorbate and about 9 mg (*e.g.*, 9.25 mg) of 2-methyl-1,4-naphthalenedione.

[00128] In one embodiment, the capsule contains about 500 mg of calcium L-ascorbate and about 5 mg of 2-methyl-1,4-naphthalenedione. In another embodiment, the capsule contains about 1,000 mg of calcium L-ascorbate and about 10 mg of 2-methyl-1,4-naphthalenedione. In yet another embodiment, the capsule contains about 925 mg of calcium L-ascorbate and about 9 mg (*e.g.*, 9.25 mg) of 2-methyl-1,4-naphthalenedione.

[00129] In one embodiment, the capsule contains about 500 mg of magnesium L-ascorbate and about 5 mg of 2-methyl-1,4-naphthalenedione. In another embodiment, the capsule contains about 1,000 mg of magnesium L-ascorbate and about 10 mg of 2-methyl-1,4-naphthalenedione. In yet another embodiment, the capsule contains about 925 mg of magnesium L-ascorbate and about 9 mg (*e.g.*, 9.25 mg) of 2-methyl-1,4-naphthalenedione.

[00130] In one embodiment, the capsule consists essentially of ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; and vitamin K, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, or hydrate thereof. In another embodiment, the capsule consists essentially of ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; and vitamin K_3, or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

[00131] In one embodiment, the capsule consists essentially of sodium L-ascorbate and 2-methyl-1,4-naphthalenedione. In another embodiment, the capsule consists essentially of

calcium L-ascorbate and 2-methyl-1,4-naphthalenedione. In yet another embodiment, the capsule consists essentially of magnesium L-ascorbate and 2-methyl-1,4-naphthalenedione.

[00132] In one embodiment, the capsule consists essentially of sodium L-ascorbate, and sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate or a hydrate thereof. In another embodiment, the capsule consists essentially of calcium L-ascorbate, and sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate or hydrate thereof. In yet another embodiment, the capsule consists essentially of magnesium L-ascorbate, and sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate or hydrate thereof.

[00133] In one embodiment, the capsule consists essentially of sodium L-ascorbate and anhydrous sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate. In another embodiment, the capsule consists essentially of sodium L-ascorbate and sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate trihydrate. In yet another embodiment, the capsule consists essentially of calcium L-ascorbate and anhydrous sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate. In yet another embodiment, the capsule consists essentially of calcium L-ascorbate and sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate trihydrate. In yet another embodiment, the capsule consists essentially of magnesium L-ascorbate and anhydrous sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate. In still another embodiment, the capsule consists essentially of magnesium L-ascorbate and sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate trihydrate.

[00134] The pharmaceutical compositions can also be formulated as known to those skilled in the art. Some examples of pharmaceutical compositions that contain an ascorbic acid compound and a quinone compound are described in U.S. Pat. Nos. 7,091,241 and 8,507,555; and U.S. Pat. App. Pub. Nos. US 2012/184609, US 2013/178522, and US 2014/0200270; each of which is incorporated herein by reference in its entirety.

[00135] In certain embodiments, the pharmaceutical compositions are each independently provided in a unit-dosage or multiple-dosage form. A unit-dosage form, as used herein, refers to a physically discrete unit suitable for administration to a subject, *e.g.*, a human and animal subject, and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of one or more active ingredient(s) sufficient to produce the desired therapeutic effect, optionally in association with one or more pharmaceutical

vehicle(s), carrier(s), diluent(s), or excipient(s). Examples of a unit-dosage form include an ampoule, syringe, and individually packaged tablet and capsule. A unit-dosage form may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage form. Examples of a multiple-dosage form include a vial, bottle of tablets or capsules, or bottle of pints or gallons.

[00136] The pharmaceutical compositions may be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

A. Oral Administration

[00137] The pharmaceutical compositions for oral administration can be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, fastmelts, chewable tablets, capsules, pills, strips, troches, lozenges, pastilles, cachets, pellets, medicated chewing gums, bulk powders, effervescent or non-effervescent powders or granules, oral mists, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions can contain one or more pharmaceutically acceptable carrier(s) or excipient(s), including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, flavoring agents, emulsifying agents, suspending and dispersing agents, preservatives, solvents, non-aqueous liquids, organic acids, and sources of carbon dioxide.

[00138] Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (*e.g.*, STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose;

natural and synthetic gums, such as acacia, alginic acid, alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), and hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, and AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); pectin; cyclodextrin; and mixtures of two or more thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures of two or more thereof. The amount of a binder or filler in the pharmaceutical compositions varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The binder or filler may be present from about 50% to about 99% by weight in the pharmaceutical compositions.

[00139] Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets. The amount of a diluent in the pharmaceutical compositions varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

[00140] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; pectin; and mixtures of two or more thereof. The amount of a disintegrant in the pharmaceutical compositions varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The

pharmaceutical compositions may contain from about 0.5% to about 15% or from about 1% to about 5% by weight of a disintegrant.

[00141] Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, such as peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures of two or more thereof. The amount of a lubricant in the pharmaceutical compositions varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions may contain from about 0.1% to about 5% by weight of a lubricant.

[00142] Suitable glidants include, but are not limited to, colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Suitable coloring agents include, but are not limited to, any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes, and mixtures of two or more thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Suitable flavoring agents include, but are not limited to, natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Suitable sweetening agents include, but are not limited to, sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include, but are not limited to, gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suitable suspending and dispersing agents include, but are not limited to, sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable preservatives include, but are not limited to, glycerin, methyl and propylparaben, benzoic acid, sodium benzoate, and alcohol. Suitable wetting agents include, but are not limited to, propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene

lauryl ether. Suitable solvents include, but are not limited to, glycerin, sorbitol, ethyl alcohol, and syrup. Suitable non-aqueous liquids utilized in emulsions include, but are not limited to, mineral oil and cottonseed oil. Suitable organic acids include, but are not limited to, citric and tartaric acid. Suitable sources of carbon dioxide include, but are not limited to, sodium bicarbonate and sodium carbonate. The amounts of a glidant, coloring agent, flavoring agent, sweetening agent, emulsifying agent, suspending and dispersing agent, preservative, wetting agent, solvent, non-aqueous liquid, organic acid, and carbon dioxide source in the pharmaceutical compositions, if present, each vary upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

[00143] It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

[00144] The pharmaceutical compositions for oral administration can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, enteric-coated tablets, or sugar-coated or film-coated tablets. In one embodiment, enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors, or in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of, *e.g.*, a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. In one embodiment, film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[00145] The tablet dosage forms can be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carrier(s) or excipient(s) described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are useful in the formation of chewable tablets and lozenges.

[00146] The pharmaceutical compositions for oral administration can be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including, but not limited to, methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545, the disclosure of each of which is incorporated by reference herein in its entirety. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[00147] The pharmaceutical compositions for oral administration can be provided in liquid and semisolid dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. An emulsion is a two-phase system, in which one liquid is dispersed in the form of small globules throughout another liquid, which can be oil-in-water or water-in-oil. Emulsions may include a pharmaceutically acceptable non-aqueous liquid or solvent, emulsifying agent, and preservative. Suspensions may include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions may include a pharmaceutically acceptable acetal, such as a di(lower alkyl) acetal of a lower alkyl aldehyde, *e.g.*, acetaldehyde diethyl acetal; and a water-miscible solvent having one or more hydroxyl groups, such as propylene glycol and ethanol. Elixirs are clear, sweetened, and hydroalcoholic solutions. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may also contain a preservative. For a liquid dosage form, for example, a solution in a polyethylene glycol may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be measured conveniently for administration.

[00148] Other useful liquid and semisolid dosage forms include, but are not limited to, those containing the active ingredient(s), and a dialkylated mono- or poly-alkylene glycol,

e.g., 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether, wherein 350, 550, and 750 refer to the approximate average molecular weight of the polyethylene glycol. These formulations can further comprise one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, bisulfite, sodium metabisulfite, thiodipropionic acid and its esters, and dithiocarbamates.

[00149] The pharmaceutical compositions for oral administration can also be provided in the forms of liposomes, micelles, microspheres, or nanosystems. Micellar dosage forms can be prepared as described in U.S. Pat. No. 6,350,458, the disclosure of which is incorporated by reference herein in its entirety.

[00150] The pharmaceutical compositions for oral administration can be provided as non-effervescent or effervescent, granules or powders, to be reconstituted into a liquid dosage form. Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders may include diluents, sweeteners, and wetting agents. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders may include organic acids and a source of carbon dioxide.

[00151] The pharmaceutical compositions for oral administration can be formulated to include a coloring agent and/or flavoring agent.

[00152] The pharmaceutical compositions for oral administration can be formulated as immediate- or modified-release dosage forms, including delayed-, sustained-, pulsed-, controlled-, targeted-, and programmed-release forms.

B. Parenteral Administration

[00153] The pharmaceutical compositions can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, intravesical, and subcutaneous administration.

[00154] The pharmaceutical compositions for parenteral administration can be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science. *See, e.g., Remington: The Science and Practice of Pharmacy*, supra.

[00155] The pharmaceutical compositions intended for parenteral administration can include one or more pharmaceutically acceptable carrier(s) and excipient(s), including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives to prevent the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

[00156] Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Suitable non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Suitable water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (*e.g.*, polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*-methyl-2-pyrrolidone, *N,N*-dimethylacetamide, and dimethyl sulfoxide.

[00157] Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl *p*-hydroxybenzoates, thimerosal, benzalkonium chloride (*e.g.*, benzethonium chloride), methyl- and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as

described herein, including, but not limited to, sodium carboxymethylcelluose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents are those described herein, including, but not limited to, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to, EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and sulfobutylether 7-β-cyclodextrin (CAPTISOL®, CyDex, Lenexa, KS).

[00158] When the pharmaceutical compositions are formulated for multiple dosage administration, the multiple dosage parenteral formulations can contain an antimicrobial agent at bacteriostatic or fungistatic concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

[00159] In one embodiment, the pharmaceutical compositions for parenteral administration are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including, *e.g.*, lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

[00160] The pharmaceutical compositions for parenteral administration can be formulated as immediate- or modified-release dosage forms, including, *e.g.*, delayed-, sustained-, pulsed-, controlled-, targeted-, and programmed-release forms.

[00161] The pharmaceutical compositions for parenteral administration can be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

[00162] Suitable inner matrixes include, but are not limited to, polymethylmethacrylate, polybutyl-methacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

[00163] Suitable outer polymeric membranes include, but are not limited to, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinyl acetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubbers, epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

C. Topical Administration

[00164] The pharmaceutical compositions can be administered topically to the skin, orifices, or mucosa. The topical administration, as used herein, includes (intra)dermal, conjunctival, intracorneal, intraocular, ophthalmic, auricular, transdermal, nasal, vaginal, urethral, respiratory, and rectal administration.

[00165] The pharmaceutical compositions can be formulated in any dosage forms that are suitable for topical administration for local or systemic effect, including, *e.g.*, emulsions, solutions, suspensions, creams, gels, hydrogels, ointments, dusting powders, dressings, elixirs, lotions, suspensions, tinctures, pastes, foams, films, aerosols, irrigations, sprays, suppositories, bandages, and dermal patches. The topical formulation of the pharmaceutical compositions can also comprise liposomes, micelles, microspheres, nanosystems, and mixtures of two or more thereof.

[00166] Pharmaceutically acceptable carriers and excipients suitable for use in the topical formulations include, but are not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives to prevent the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying

agents, complexing agents, sequestering or chelating agents, penetration enhancers, cryoprotectants, lyoprotectants, thickening agents, and inert gases.

[00167] The pharmaceutical compositions can also be administered topically by electroporation, iontophoresis, phonophoresis, sonophoresis, or microneedle or needle-free injection, such as POWDERJECT™ (Chiron Corp., Emeryville, CA), and BIOJECT™ (Bioject Medical Technologies Inc., Tualatin, OR).

[00168] The pharmaceutical compositions can be provided in the forms of ointments, creams, and gels. Suitable ointment vehicles include, *e.g.*, oleaginous or hydrocarbon vehicles, such as lard, benzoinated lard, olive oil, cottonseed oil, and other oils; white petrolatum; emulsifiable or absorption vehicles, such as hydrophilic petrolatum, hydroxystearin sulfate, and anhydrous lanolin; water-removable vehicles, such as hydrophilic ointment; water-soluble ointment vehicles, such as polyethylene glycols of varying molecular weight; and emulsion vehicles, either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, such cetyl alcohol, glyceryl monostearate, lanolin, and stearic acid (*see*, *e.g.*, *Remington: The Science and Practice of Pharmacy*, supra). These vehicles are emollient but generally require addition of antioxidants and preservatives.

[00169] Suitable cream base can be oil-in-water or water-in-oil. Suitable cream vehicles may be water-washable, and contain an oil phase, an emulsifier, and an aqueous phase. The oil phase is also called the "internal" phase, which is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. The aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation may be a nonionic, anionic, cationic, or amphoteric surfactant.

[00170] Gels are semisolid, suspension-type systems. Single-phase gels contain organic macromolecules distributed substantially uniformly throughout the liquid carrier. Suitable gelling agents include, but are not limited to, crosslinked acrylic acid polymers, such as carbomers, carboxypolyalkylenes, and CARBOPOL®; hydrophilic polymers, such as polyethylene oxides, polyoxyethylene-polyoxypropylene copolymers, and polyvinylalcohol; cellulosic polymers, such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and methylcellulose; gums, such as tragacanth and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform

gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing, and/or stirring.

[00171] The pharmaceutical compositions can be administered rectally, urethrally, vaginally, or perivaginally in the forms of suppositories, pessaries, bougies, poultices or cataplasm, pastes, powders, dressings, creams, plasters, contraceptives, ointments, solutions, emulsions, suspensions, tampons, gels, foams, sprays, or enemas. These dosage forms can be manufactured using conventional processes as described in, *e.g.*, *Remington: The Science and Practice of Pharmacy*, supra.

[00172] Rectal, urethral, and vaginal suppositories are solid bodies for insertion into body orifices, which are solid at ordinary temperatures but melt or soften at body temperature to release the active ingredient(s) inside the orifices. Pharmaceutically acceptable carriers utilized in rectal and vaginal suppositories include bases or vehicles, such as stiffening agents, which produce a melting point in the proximity of body temperature, when formulated with the active ingredient(s); and antioxidants as described herein, including, *e.g.*, bisulfite and sodium metabisulfite. Suitable vehicles include, but are not limited to, cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol), spermaceti, paraffin, white and yellow wax, appropriate mixtures of mono-, di- and tri-glycerides of fatty acids, and hydrogels, such as polyvinyl alcohol, hydroxyethyl methacrylate, and polyacrylic acid. Combinations of the various vehicles can also be used. Rectal and vaginal suppositories may be prepared by compressing or molding. The typical weight of a rectal and vaginal suppository is about 2 g to about 3 g.

[00173] The pharmaceutical compositions can be administered ophthalmically in the forms of solutions, suspensions, ointments, emulsions, gel-forming solutions, powders for solutions, gels, ocular inserts, and implants.

[00174] The pharmaceutical compositions can be administered intranasally or by inhalation to the respiratory tract. The pharmaceutical compositions can be provided in the form of an aerosol or solution for delivery using a pressurized container, pump, spray, atomizer, such as an atomizer using electrohydrodynamics to produce a fine mist, or nebulizer, alone or in combination with a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. The pharmaceutical compositions can also be provided as a dry powder for insufflation, alone or in combination with an inert

carrier such as lactose or phospholipids; and nasal drops. For intranasal use, the powder can comprise a bioadhesive agent, including, *e.g.*, chitosan or cyclodextrin.

[00175] Solutions or suspensions for use in a pressurized container, pump, spray, atomizer, or nebulizer can be formulated to contain ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the active ingredient(s); a propellant as solvent; and/or a surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

[00176] The pharmaceutical compositions can be micronized to a size suitable for delivery by inhalation, such as about 50 micrometers or less, or about 10 micrometers or less. Particles of such sizes can be prepared using a comminuting method known to those skilled in the art, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization, or spray drying.

[00177] Capsules, blisters, and cartridges for use in an inhaler or insufflator can be formulated to contain a powder mix of the pharmaceutical compositions; a suitable powder base, such as lactose or starch; and a performance modifier, such as *L*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of a monohydrate. Other suitable excipients or carriers include, but are not limited to, dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose, and trehalose. The pharmaceutical compositions for inhaled/intranasal administration can further comprise a suitable flavor, such as menthol and/or levomenthol; and/or sweeteners, such as saccharin and/or saccharin sodium.

[00178] The pharmaceutical compositions for topical administration can be formulated to be immediate-release or modified-release, including delayed-, sustained-, pulsed-, controlled-, targeted-, and programmed-release.

D. Modified Release

[00179] The pharmaceutical compositions can be formulated as a modified release dosage form. As used herein, the term "modified release" refers to a dosage form in which the rate or place of release of the active ingredient(s) is different from that of an immediate-release dosage form when administered by the same route. Modified release dosage forms include, but are not limited to, delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- or fast-, targeted-, and programmed-release, and gastric retention

dosage forms. The pharmaceutical compositions in modified release dosage forms can be prepared using a variety of modified release devices and methods known to those skilled in the art, including, but not limited to, matrix controlled release devices, osmotic controlled release devices, multiparticulate controlled release devices, ion-exchange resins, enteric coatings, multilayered coatings, microspheres, liposomes, and combinations thereof. The release rate of the active ingredient(s) can also be modified by varying the particle sizes and/or polymorphism of the active ingredient(s).

[00180] Examples of modified release include, but are not limited to, those described in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; and 6,699,500; the disclosure of each of which is incorporated by reference herein in its entirety.

1. Matrix Controlled Release Devices

[00181] The pharmaceutical compositions in a modified release dosage form can be fabricated using a matrix controlled release device known to those skilled in the art. *See*, *e.g.*, Takada *et al.* in "Encyclopedia of Controlled Drug Delivery," Vol. 2, Mathiowitz Ed., Wiley, 1999.

[00182] In certain embodiments, the pharmaceutical compositions in a modified release dosage form are formulated using an erodible matrix device, which is a water-swellable, erodible, or soluble polymer, including, but not limited to, a synthetic polymer, and naturally occurring polymer and derivatives, such as a polysaccharide and protein.

[00183] Materials useful in forming an erodible matrix include, but are not limited to, chitin, chitosan, dextran, pullulan, gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti, guar gum, xanthan gum, scleroglucan, starches (*e.g.*, dextrin and maltodextrin), hydrophilic colloids (*e.g.*, pectin), phosphatides (*e.g.*, lecithin), alginates, propylene glycol alginate, gelatin, collagen, cellulosics (*e.g.*, ethyl cellulose (EC), methylethyl cellulose (MEC), carboxymethyl cellulose (CMC), CMEC, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), CAP, CAT, hydroxypropyl

methyl cellulose (HPMC), HPMCP, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), and ethyl hydroxyethyl cellulose (EHEC)), polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, glycerol fatty acid esters, polyacrylamide, polyacrylic acid, copolymers of ethacrylic acid or methacrylic acid (EUDRAGIT®, Rohm America, Inc., Piscataway, NJ), poly(2-hydroxyethyl-methacrylate), polylactides, copolymers of L-glutamic acid and ethyl-L-glutamate, degradable lactic acid-glycolic acid copolymers, poly-D-(-)-3-hydroxybutyric acid, and other acrylic acid derivatives (*e.g.*, homopolymers and copolymers of butylmethacrylate, methyl methacrylate, ethyl methacrylate, ethylacrylate, (2-dimethylaminoethyl)methacrylate, and (trimethylaminoethyl)methacrylate chloride).

[00184] In certain embodiments, the pharmaceutical compositions are formulated with a non-erodible matrix device. The active ingredient(s) is dissolved or dispersed in an inert matrix and is released primarily by diffusion through the inert matrix once administered. Materials suitable for use as a non-erodible matrix device include, but are not limited to, insoluble plastics, such as polyethylene, polypropylene, polyisoprene, polyisobutylene, polybutadiene, polymethylmethacrylate, polybutylmethacrylate, chlorinated polyethylene, polyvinylchloride, methyl acrylate-methyl methacrylate copolymers, ethylene-vinyl acetate copolymers, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubbers, epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, ethylene/vinyloxyethanol copolymer, polyvinyl chloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, silicone rubbers, polydimethylsiloxanes, and silicone carbonate copolymers; hydrophilic polymers, such as ethyl cellulose, cellulose acetate, crospovidone, and cross-linked partially hydrolyzed polyvinyl acetate; and fatty compounds, such as carnauba wax, microcrystalline wax, and triglycerides.

[00185] In a matrix controlled release system, the desired release kinetics can be controlled, for example, *via* the polymer type employed, the polymer viscosity, the particle sizes of the polymer and/or the active ingredient(s), the ratio of the active ingredient(s) *versus* the polymer, and other excipients or carriers in the pharmaceutical compositions.

[00186] The pharmaceutical compositions in a modified release dosage form can be prepared by methods known to those skilled in the art, including direct compression, dry or wet granulation followed by compression, and melt-granulation followed by compression.

2. Osmotic Controlled Release Devices

[00187] The pharmaceutical compositions in a modified release dosage form can be fabricated using an osmotic controlled release device, including, but not limited to, one-chamber system, two-chamber system, asymmetric membrane technology (AMT), and extruding core system (ECS). In general, such devices have at least two components: (a) a core which contains an active ingredient; and (b) a semipermeable membrane with at least one delivery port, which encapsulates the core. The semipermeable membrane controls the influx of water to the core from an aqueous environment of use so as to cause drug release by extrusion through the delivery port(s).

[00188] In addition to the active ingredient(s), the core of the osmotic device optionally includes an osmotic agent, which creates a driving force for transport of water from the environment of use into the core of the device. One class of osmotic agents is water-swellable hydrophilic polymers, which are also referred to as "osmopolymers" and "hydrogels." Suitable water-swellable hydrophilic polymers as osmotic agents include, but are not limited to, hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol (PEG), polypropylene glycol (PPG), poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinylpyrrolidone (PVP), crosslinked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers, PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate and vinyl acetate, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl, cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum, and sodium starch glycolate.

[00189] The other class of osmotic agents is osmogens, which are capable of imbibing water to affect an osmotic pressure gradient across the barrier of the surrounding coating. Suitable osmogens include, but are not limited to, inorganic salts, such as magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium phosphates, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, and sodium sulfate; sugars, such as dextrose, fructose, glucose, inositol, lactose, maltose, mannitol, raffinose, sorbitol, sucrose, trehalose, and xylitol; organic acids, such as ascorbic acid, benzoic acid, fumaric acid, citric acid, maleic acid, sebacic acid, sorbic acid, adipic acid,

edetic acid, glutamic acid, *p*-toluenesulfonic acid, succinic acid, and tartaric acid; urea; and mixtures of two or more thereof.

[00190] Osmotic agents of different dissolution rates can be employed to influence how rapidly the active ingredient(s) is initially delivered from the dosage form. For example, amorphous sugars, such as MANNOGEM™ EZ (SPI Pharma, Lewes, DE) can be used to provide faster delivery during the first couple of hours to promptly produce the desired therapeutic effect, and gradually and continually release of the remaining amount to maintain the desired level of therapeutic or prophylactic effect over an extended period of time. In this case, the active ingredient(s) is released at such a rate to replace the amount of the active ingredient metabolized and excreted.

[00191] The core can also include a wide variety of other excipients and carriers as described herein to enhance the performance of the dosage form or to promote stability or processing.

[00192] Materials useful in forming the semipermeable membrane include various grades of acrylics, vinyls, ethers, polyamides, polyesters, and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs, or are susceptible to being rendered water-insoluble by chemical alteration, such as crosslinking. Examples of suitable polymers useful in forming the coating, include plasticized, unplasticized, and reinforced cellulose acetate (CA), cellulose diacetate, cellulose triacetate, CA propionate, cellulose nitrate, cellulose acetate butyrate (CAB), CA ethyl carbamate, CAP, CA methyl carbamate, CA succinate, cellulose acetate trimellitate (CAT), CA dimethylaminoacetate, CA ethyl carbonate, CA chloroacetate, CA ethyl oxalate, CA methyl sulfonate, CA butyl sulfonate, CA *p*-toluene sulfonate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, triacetate of locust bean gum, hydroxylated ethylene-vinylacetate, EC, PEG, PPG, PEG/PPG copolymers, PVP, HEC, HPC, CMC, CMEC, HPMC, HPMCP, HPMCAS, HPMCAT, poly(acrylic) acids and esters and poly-(methacrylic) acids and esters and copolymers thereof, starch, dextran, dextrin, chitosan, collagen, gelatin, polyalkenes, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00193] Semipermeable membrane can also be a hydrophobic microporous membrane, wherein the pores are substantially filled with a gas and are not wetted by the aqueous

medium but are permeable to water vapor, as disclosed in U.S. Pat. No. 5,798,119, the disclosure of which is incorporated by reference herein in its entirety. Such hydrophobic but water-vapor permeable membrane are typically composed of hydrophobic polymers such as polyalkenes, polyethylene, polypropylene, polytetrafluoroethylene, polyacrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinylidene fluoride, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00194] The delivery port(s) on the semipermeable membrane can be formed post-coating by mechanical or laser drilling. Delivery port(s) can also be formed *in situ* by erosion of a plug of water-soluble material or by rupture of a thinner portion of the membrane over an indentation in the core. In addition, delivery ports can be formed during coating process, as in the case of asymmetric membrane coatings of the type disclosed in U.S. Pat. Nos. 5,612,059 and 5,698,220, the disclosure of each of which is incorporated by reference herein in its entirety.

[00195] The total amount of the active ingredient(s) released and the release rate can substantially be modulated via the thickness and porosity of the semipermeable membrane, the composition of the core, and the number, size, and position of the delivery ports.

[00196] The pharmaceutical compositions in an osmotic controlled-release dosage form can further comprise additional conventional excipient(s) or carrier(s) as described herein to promote performance or processing of the formulation.

[00197] The osmotic controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art. *See, e.g., Remington: The Science and Practice of Pharmacy*, supra; Santus and Baker, *J. Controlled Release* 1995, *35*, 1–21; Verma et al., *Drug Development and Industrial Pharmacy* 2000, *26*, 695–708; Verma et al., *J. Controlled Release* 2002, *79*, 7–27.

[00198] In certain embodiments, the pharmaceutical compositions are formulated as AMT controlled-release dosage form, which comprises an asymmetric osmotic membrane that coats a core comprising the active ingredient(s) and other pharmaceutically acceptable excipient(s) or carrier(s). *See, e.g.*, U.S. Pat. No. 5,612,059 and WO 2002/17918, the disclosure of each of which is incorporated by reference herein in its entirety. The AMT controlled-release dosage forms can be prepared according to conventional methods and

techniques known to those skilled in the art, including, *e.g.*, direct compression, dry granulation, wet granulation, and a dip-coating method.

[00199] In certain embodiments, the pharmaceutical compositions are formulated as ESC controlled-release dosage form, which comprises an osmotic membrane that coats a core comprising the active ingredient(s), a hydroxylethyl cellulose, and other pharmaceutically acceptable excipient(s) or carrier(s).

3. Multiparticulate Controlled Release Devices

[00200] The pharmaceutical compositions in a modified release dosage form can be fabricated as a multiparticulate controlled release device, which comprises a multiplicity of particles, granules, or pellets, ranging from about 10 μm to about 3 mm, from about 50 μm to about 2.5 mm, or from about 100 μm to about 1 mm in diameter. Such multiparticulates can be made by the processes known to those skilled in the art, including, *e.g.*, wet-and dry-granulation, extrusion/spheronization, roller-compaction, and melt-congealing, and by spray-coating seed cores. *See, e.g.*, *Multiparticulate Oral Drug Delivery*; Marcel Dekker: 1994; and *Pharmaceutical Pelletization Technology*; Marcel Dekker: 1989.

[00201] Other excipients or carriers as described herein can be blended with the pharmaceutical compositions to aid in processing and forming the multiparticulates. The resulting particles can themselves constitute the multiparticulate device or can be coated by various film-forming materials, such as, enteric polymers, water-swellable, and water-soluble polymers. The multiparticulates can be further processed as a capsule or a tablet.

4. Targeted Delivery

[00202] The pharmaceutical compositions can also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated, including, *e.g.*, liposome-, resealed erythrocyte-, and antibody-based delivery systems. Examples include, but are not limited to, those disclosed in U.S. Pat. Nos. 6,316,652; 6,274,552; 6,271,359; 6,253,872; 6,139,865; 6,131,570; 6,120,751; 6,071,495; 6,060,082; 6,048,736; 6,039,975; 6,004,534; 5,985,307; 5,972,366; 5,900,252; 5,840,674; 5,759,542; and 5,709,874, the disclosure of each of which is incorporated by reference herein in its entirety.

Methods of Use

[00203] In one embodiment, provided herein is a method of treating, preventing, or alleviating one or more symptoms of cancer in a subject, comprising administering to the subject in need of such a treatment: (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; and (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00204] In another embodiment, provided herein is a method of inhibiting the growth of cancer in a subject, comprising administering to the subject in need of such a treatment: (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; and (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00205] In certain embodiments, the cancer is bladder cancer, breast cancer, cervical cancer, colon cancer (*e.g.*, colorectal cancer), esophageal cancer, glioma, glioblastoma multiforme, head and neck cancer, leukemia (*e.g.*, acute myelogenous leukemia), liver cancer, lung cancer (*e.g.*, small cell and non-small cell lung cancer), lymphoma, melanoma, myeloma, neuroblastoma, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, salivary gland cancer, sarcoma (*e.g.*, osteosarcoma), skin cancer (*e.g.*, squamous cell carcinoma), stomach cancer, testicular cancer, thyroid cancer, or uterine cancer. In certain embodiments, the cancer is pancreatic cancer or prostate cancer.

[00206] In certain embodiments, the cancer is bladder cancer. In certain embodiments, the cancer is breast cancer. In certain embodiments, the cancer is cervical cancer. In certain embodiments, the cancer is colon cancer. In certain embodiments, the cancer is colorectal cancer. In certain embodiments, the cancer is esophageal cancer. In certain embodiments,

the cancer is glioma. In certain embodiments, the cancer is glioblastoma multiforme. In certain embodiments, the cancer is head and neck cancer. In certain embodiments, the cancer is leukemia. In certain embodiments, the cancer is acute myelogenous leukemia. In certain embodiments, the cancer is lymphoma. In certain embodiments, the cancer is liver cancer. In certain embodiments, the cancer is lung cancer. In certain embodiments, the cancer is small cell lung cancer. In certain embodiments, the cancer is non-small cell lung cancer. In certain embodiments, the cancer is melanoma. In certain embodiments, the cancer is myeloma. In certain embodiments, the cancer is neuroblastoma. In certain embodiments, the cancer is ovarian cancer. In certain embodiments, the cancer is pancreatic cancer. In certain embodiments, the cancer is prostate cancer. In certain embodiments, the cancer is renal cancer. In certain embodiments, the cancer is salivary gland cancer. In certain embodiments, the cancer is sarcoma. In certain embodiments, the cancer is osteosarcoma. In certain embodiments, the cancer is skin cancer. In certain embodiments, the cancer is squamous cell carcinoma. In certain embodiments, the cancer is stomach cancer. In certain embodiments, the cancer is testicular cancer. In certain embodiments, the cancer is thyroid cancer. In certain embodiments, the cancer is uterine cancer.

[00207] In certain embodiments, the cancer is metastatic. In certain embodiments, the cancer is refractory. In certain embodiments, the cancer is relapsed. In certain embodiments, the cancer is drug-resistant.

[00208] In certain embodiments, the method provided further comprises a diagnostic step for determining glucose update in the subject having cancer or suspected to have cancer. In certain embodiments, the diagnostic step is performing a PET scan in the subject with a glucose tracer for determining glucose uptake. In certain embodiments, the diagnostic step is performing a PET scan in the subject with a glucose tracer selected from 2-deoxy-2-[^{18}F]fluoro-D-glucose (2FDC) and α-methyl-4-deoxy-4-[^{18}F]fluoro-D-glucopyranoside (Me4FDC). *See e.g.*, Scafoglio *et al.*, *Proc. Nat'l. Acad. U.S.A.* **2015**; the disclosure of which is incorporated by reference herein in its entirety. In certain embodiments, the diagnostic step is performing a PET scan in the subject with a GLUT-specific tracer. In certain embodiments, the GLUT-specific tracer is 2FDC. In certain embodiments, the diagnostic step is performing a PET scan in the subject with a SGLT-specific tracer. In certain embodiments, the SGLT-specific tracer is Me4FDC.

[00209] In certain embodiments, the method provided further comprises administering

a glutamine inhibitor to the subject.

[00210] Thus, in one embodiment, provided herein is a method of treating, preventing, or alleviating one or more symptoms of cancer in a subject, comprising administering to the subject in need of such a treatment a therapeutically effective amount of: (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iv) a glutamine inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00211] In another embodiment, provided herein is a method of inhibiting the growth of cancer in a subject, comprising administering to the subject in need of such a treatment a therapeutically effective amount of: (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iv) a glutamine inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00212] In certain embodiments, the method provided further comprises a diagnostic step for determining glutamine-dependency in the cancer cells of the subject.

[00213] In one embodiment, the diagnostic step is performing a glutamine PET scan in the subject. Liebeman *et al.*, *J. Nucl. Med.* **2011**, *52*, 1947-1955; Shi *et al.*, *Mol. Imaging*, **2014**, *13*, 1-10; Venneti *et al.*, *Sch. Transl. Med.* **2015**, *7*, 274ra17; the disclosure of each of which is incorporated by reference herein in its entirety.

[00214] In another embodiment, the diagnostic step comprises determining the molar ratio of glutamate to glutamine in cancer cells of the subject. In one embodiment, the molar ratio of glutamate to glutamine is no less than about 1.5. In another embodiment, the molar ratio of glutamate to glutamine is no less than about 2.

[00215] In yet another embodiment, the diagnostic step comprises determining the molar ratio of glutaminase to glutamine synthetase in cancer cells of the subject.

[00216] In one embodiment, the molar ratio of glutaminase to glutamine synthetase is no less than about 0.05. In another embodiment, the molar ratio of glutaminase to glutamine synthetase is no less than about 1. In certain embodiments, the molar ratio of glutaminase to glutamine synthetase is determined by measuring the molar ratio of the mRNA level of glutaminase to the mRNA level of glutamine synthetase in the cancer cells. In certain embodiments, the molar ratio of glutaminase to glutamine synthetase is determined by measuring the molar ratio of the protein level of glutaminase to the protein level of glutamine synthetase in the cancer cells. In certain embodiments, the glutaminase is a kidney-type glutaminase. In certain embodiments, the glutaminase is a liver-type glutaminase. In certain embodiments, the glutaminase is a mitochondrial glutaminase. In certain embodiments, the glutaminase is glutaminase C. In certain embodiments, the glutaminase is human kidney-type glutaminase.

[00217] In certain embodiments, the subject to be treated with one of the methods provided herein has not been treated with an anticancer therapy for the cancer before. In certain embodiments, the subject to be treated with one of the methods provided herein has been treated with an anticancer therapy for the cancer before.

[00218] In certain embodiments, the subject to be treated with one of the methods provided herein has been treated with cisplatin, erlotinib, everolimus, fluorouracil, folinic acid, gemcitabine, irinotecan, mitomycin C, oxaliplatin, paclitaxel, sunitinib, or a combination thereof; or others known or approved therapeutic agents for treating the cancer. In certain embodiments, the subject to be treated with one of the methods provided herein has developed drug resistance to cisplatin, erlotinib, everolimus, fluorouracil, folinic acid, gemcitabine, irinotecan, mitomycin C, oxaliplatin, paclitaxel, or sunitinib.

[00219] In certain embodiments, the subject to be treated with one of the methods provided herein has undergone surgery to remove the cancer. In certain embodiments, the

subject to be treated with one of the methods provided herein has not undergone surgery to remove the cancer. In certain embodiments, the subject to be treated with one of the methods provided herein has undergone radiation therapy for treating the cancer. In certain embodiments, the subject to be treated with one of the methods provided herein has not undergone radiation therapy for treating the cancer. In certain embodiments, the subject to be treated with one of the methods provided herein has undergone an ablation (*e.g.*, radiofrequency ablation (RFA), microwave thermotherapy, or cryosurgery or cryoablation) or embolization (*e.g.*, arterial embolization, chemoembolization, or radioembolization) treatment for the cancer. In certain embodiments, the subject to be treated with one of the methods provided herein has not undergone an ablation or embolization treatment for the cancer.

[00220] Because the subjects with the cancer have heterogeneous clinical manifestations and varying clinical outcomes, the treatment given to a particular subject may vary, depending on his/her prognosis. The skilled clinician will be able to readily determine without undue experimentation, specific secondary agents, types of surgery, and types of non-drug based standard therapy that can be effectively used to treat an individual subject with the cancer.

[00221] In certain embodiments, the methods provided herein encompass treating a subject regardless of patient's age, although the cancer may be more common in certain age groups. In certain embodiments, the subject is a male. In certain embodiments, the subject is a female. In certain embodiments, the subject is an elderly.

[00222] In certain embodiments, the ascorbic acid compound, the quinone compound, and the SGLT inhibitor provided herein act synergistically in treating, preventing, or alleviating one or more symptoms of the cancer when compared to the administration of the ascorbic acid compound, the quinone compound, or the SGLT inhibitor alone. In certain embodiments, the ascorbic acid compound, the quinone compound, the SGLT inhibitor, and the glutamine inhibitor provided herein act synergistically in treating, preventing, or alleviating one or more symptoms of the cancer when compared to the administration of the ascorbic acid compound, the quinone compound, the SGLT inhibitor, or the glutamine inhibitor alone.

[00223] Without being limited by any theory, a synergistic effect of the combination of the active ingredients provided herein permits the use of lower dosages of at least one of the active ingredients, and/or less frequent administration of the combination to a subject for treating the cancer. The ability to utilize lower dosages of certain active ingredients in the combination (*e.g.*, a prophylactic or therapeutic agent) and/or to administer the combination less frequently reduces the toxicity associated with the administration of the combination to a subject without reducing the efficacy of the combination in the prevention or treatment of the cancer. In addition, a synergistic effect can result in improved efficacy of the active ingredients in the prevention or treatment of the cancer. Furthermore, a synergistic effect of the combination may avoid or reduce adverse or unwanted side effects associated with the use of at least one of the active ingredients.

[00224] In certain embodiments, the ascorbic acid compound and the quinone compound as used in the methods provided herein are delivered as a single dose such as, *e.g.*, as a single bolus injection, or as a single oral tablet or pill. In certain embodiments, the ascorbic acid compound and the quinone compound as used in the methods provided herein are administered over time, such as, *e.g.*, continuous infusion over time or divided bolus doses over time.

[00225] In certain embodiments, the weight ratio of ascorbic acid to the quinone compound as used in the methods provided herein is ranging from about 1 to about 500, from about 4 to about 500, from about 10 to about 500, from about 50 to about 500, from about 25 to about 250, or from about 50 to about 200, from about 50 to about 150, or from about 80 to about 120. In certain embodiments, the weight ratio of ascorbic acid to the quinone compound as used in the methods provided herein is about 1, about 2, about 4, about 10, about 20, about 30, about 40, about 50, about 60, about 70, about 80, about 90, about 100, about 110, about 120, about 130, about 140, about 150, about 160, about 170, about 180, about 190, about 200, about 210, about 220, about 230, about 240, or about 250. In certain embodiments, the weight ratio of ascorbic acid to the quinone compound as used in the methods provided herein is about 100. In certain embodiments, the weight ratio of ascorbic acid to the quinone compound as used in the methods provided herein is about 200.

[00226] In certain embodiments, the ascorbic acid compound and the quinone compound as used in the methods provided herein are administered once daily (QD), or divided into multiple daily doses such as twice daily (BID), three times daily (TID), four

times daily (QID), five times daily, six times daily, seven times daily, eight times daily, nine times daily, or ten times daily. In certain embodiments, the ascorbic acid compound as used in the methods provided herein is administered QD, or divided into multiple daily doses such as BID, TID, QID, five times daily, six times daily, seven times daily, eight times daily, nine times daily, or ten times daily. In certain embodiments, the quinone compound as used in the methods provided herein is administered QD, or divided into multiple daily doses such as BID, TID, QID, five times daily, six times daily, seven times daily, eight times daily, nine times daily, or ten times daily.

[00227] In certain embodiments, the SGLT inhibitor as used in the methods provided herein is administered QD, or divided into multiple daily doses such as BID, TID, or QID.

[00228] In certain embodiments, the glutamine inhibitor as used in the methods provided herein is administered QD, or divided into multiple daily doses such as BID, TID, or fQID.

[00229] In certain embodiments, the ascorbic acid compound and/or the quinone compound as used in the methods provided herein are administered from about 1 to about 20 times a day, from about 1 to about 15 times a day, from about 1 to about 10 times a day, or from about 1 to about 5 times a day. In certain embodiments, the ascorbic acid compound and/or the quinone compound as used in the methods provided herein are administered every 1 to 10 hour(s), every 2 to 8 hours, every 3 to 7 hours, every 4 to 6 hours, or every 5 to 6 hours. In certain embodiments, the ascorbic acid compound and/or the quinone compound as used in the methods provided herein are administered every hour, every 2 hours, every 3 hours, every 4 hours, every 5 hours, every 6 hours, every 7 hours, every 8 hours, every 9 hours, or every 10 hours. In certain embodiments, the ascorbic acid compound and/or the quinone compound as used in the methods provided herein are administered once a day. In certain embodiments, the ascorbic acid compound and/or the quinone compound as used in the methods provided herein are administered 5 times a day. In certain embodiments, the ascorbic acid compound and/or the quinone compound as used in the methods provided herein are administered 10 times a day. In certain embodiments, the ascorbic acid compound and/or the quinone compound as used in the methods provided herein are administered every 4, 5, or 6 hours. In certain embodiments, the ascorbic acid compound and the quinone compound as used in the methods provided herein are administered daily.

[00230] In certain embodiments, the ascorbic acid compound as used in the methods provided herein is administered to the subject in an amount ranging from about 1 to about 1,000 mg/kg/day, from about 5 to about 500 mg/kg/day, or from about 10 to about 100 mg/kg/day. In certain embodiments, the ascorbic acid compound as used in the methods provided herein is administered to the subject in an amount of about 10 mg/kg/day, about 20 mg/kg/day, about 30 mg/kg/day, about 40 mg/kg/day, about 50 mg/kg/day, about 60 mg/kg/day, about 70 mg/kg/day, about 80 mg/kg/day, about 90 mg/kg/day, about 100 mg/kg/day, about 200 mg/kg/day, about 300 mg/kg/day, about 400 mg/kg/day, or about 500 mg/kg/day.

[00231] In certain embodiments, the quinone compound as used in the methods provided herein is administered to the subject in an amount ranging from about 0.01 to about 50 mg/kg/day, from about 0.015 to about 50 mg/kg/day, from about 0.05 to about 40 mg/kg/day, from about 0.2 to about 30 mg/kg/day, or from about 10 to about 30 mg/kg/day. In certain embodiments, the quinone compound as used in the methods provided herein is administered to the subject in an amount of about 0.015 mg/kg/day, about 5 mg/kg/day, about 25 mg/kg/day, or about 30 mg/kg/day.

[00232] In certain embodiments, the SGLT inhibitor as used in the methods provided herein is administered to the subject in an amount ranging from about 1 μg/kg/day to about 100 mg/kg/day, from about 10 μg/kg/day to about 50 mg/kg/day, about 20 μg/kg/day to about 25 mg/kg/day, or about 20 μg/kg/day to about 10 mg/kg/day.

[00233] In certain embodiments, the glutamine inhibitor as used in the methods provided herein is administered to the subject in an amount ranging from about 1 μg/kg/day to about 1,000 mg/kg/day, from about 5 μg/kg/day to about 500 mg/kg/day, or from about 10 μg/kg/day to about 100 mg/kg/day.

[00234] The administered doses of the ascorbic acid compound, the quinone compound, the SGLT inhibitor, and the glutamine inhibitor can also each independently be expressed in units other than the unit "mg/kg/day" or "g/kg/day." For example, doses for parenteral administration can be expressed as $mg/m^2/day$. One of ordinary skill in the art would readily know how to convert doses from mg/kg/day to $mg/m^2/day$, given either the height or weight of a subject or both. For example, a dose of 1 mg/kg/day for a 65 kg human is approximately equal to 38 $mg/m^2/day$.

[00235] In certain embodiments, the ascorbic acid compound as used in the methods provided herein is administered to the subject in an amount ranging from about 0.1 g to about 3 g every four hours. In certain embodiments, the quinone compound as used in the methods provided herein is administered to the subject in an amount ranging from about 0.2 mg to about 300 mg every four hours.

[00236] In certain embodiments, the ascorbic acid compound as used in the methods provided herein is administered to the subject in an amount ranging from about 500 mg to about 3,000 mg a day. In certain embodiments, the quinone compound as used in the methods provided herein is administered to the subject in an amount ranging from about 3 mg to about 30 mg a day. In certain embodiments, the ascorbic acid compound as used in the methods provided herein is administered to the subject in an amount ranging from about 500 mg to about 10,000 mg a day. In certain embodiments, the quinone compound as used in the methods provided herein is administered to the subject in an amount ranging from about 3 mg to about 100 mg a day. In certain embodiments, the ascorbic acid compound as used in the methods provided herein is administered to the subject in an amount of greater than about 500 mg a day. In certain embodiments, the quinone compound as used in the methods provided herein is administered to the subject in an amount of greater than about 3 mg a day. In certain embodiments, the ascorbic acid compound as used in the methods provided herein is administered to the subject in an amount up to about 10,000 mg a day. In certain embodiments, the quinone compound as used in the methods provided herein is administered to the subject in an amount up to about 100 mg a day. In certain embodiments, the ascorbic acid compound as used in the methods provided herein is administered to the subject in an amount up to about 20,000 mg a day. In certain embodiments, the quinone compound as used in the methods provided herein is administered to the subject in an amount up to about 200 mg a day. In certain embodiments, the ascorbic acid compound as used in the methods provided herein is administered to the subject in an amount up to about 30,000 mg a day. In certain embodiments, the quinone compound as used in the methods provided herein is administered to the subject in an amount up to about 300 mg a day. In certain embodiments, the ascorbic acid compound as used in the methods provided herein is administered to the subject in an amount up to about 40,000 mg a day. In certain embodiments, the quinone compound as used in the methods provided herein is administered to the subject in an amount up to about 400 mg a day. In certain embodiments, the ascorbic acid compound as used in the methods provided herein is administered to the subject in an amount up to about 50,000

mg a day. In certain embodiments, the quinone compound as used in the methods provided herein is administered to the subject in an amount up to about 500 mg a day. In certain embodiments, the ascorbic acid compound as used in the methods provided herein is administered to the subject in an amount up to about 60,000 mg a day. In certain embodiments, the quinone compound as used in the methods provided herein is administered to the subject in an amount up to about 600 mg a day. In certain embodiments, the ascorbic acid compound as used in the methods provided herein is administered to the subject in an amount up to about 70,000 mg a day. In certain embodiments, the quinone compound as used in the methods provided herein is administered to the subject in an amount up to about 700 mg a day. In certain embodiments, the ascorbic acid compound as used in the methods provided herein is administered to the subject in an amount up to about 80,000 mg a day. In certain embodiments, the quinone compound as used in the methods provided herein is administered to the subject in an amount up to about 800 mg a day. In certain embodiments, the ascorbic acid compound as used in the methods provided herein is administered to the subject in an amount up to about 90,000 mg a day. In certain embodiments, the quinone compound as used in the methods provided herein is administered to the subject in an amount up to about 900 mg a day. In certain embodiments, the ascorbic acid compound as used in the methods provided herein is administered to the subject in an amount up to about 100,000 mg a day. In certain embodiments, the quinone compound as used in the methods provided herein is administered to the subject in an amount up to about 1,000 mg a day. In certain embodiments, the ascorbic acid compound as used in the methods provided herein is administered to the subject in an amount up to about 200,000 mg a day. In certain embodiments, the quinone compound as used in the methods provided herein is administered to the subject in an amount up to about 2,000 mg a day.

[00237] In certain embodiments, as used in the methods provided herein, the ascorbic acid compound is administered to the subject in an amount ranging from about 2,000 mg to about 3,000 mg a day; and the quinone compound is administered to the subject in an amount ranging from about 12 mg to about 19 mg a day. In certain embodiments, as used in the methods provided herein, the ascorbic acid compound is administered to the subject in an amount ranging from about 2,000 mg to about 3,000 mg a day; and the quinone compound is administered to the subject in an amount ranging from about 20 mg to about 30 mg a day.

[00238] In certain embodiments, as used in the methods provided herein, the ascorbic acid compound is administered to the subject in an amount of about 2,000 mg a day; and the quinone compound is administered to the subject in an amount of about 12 mg a day. In certain embodiments, as used in the methods provided herein, the ascorbic acid compound is administered to the subject in an amount of about 3,000 mg a day; and the quinone compound is administered to the subject in an amount of about 19 mg a day.

[00239] In certain embodiments, as used in the methods provided herein, the ascorbic acid compound is administered to the subject in an amount of about 2,000 mg a day; and the quinone compound is administered to the subject in an amount of about 20 mg a day. In certain embodiments, as used in the methods provided herein, the ascorbic acid compound is administered to the subject in an amount of about 3,000 mg a day; and the quinone compound is administered to the subject in an amount of about 30 mg a day.

[00240] In certain embodiments, as used in the methods provided herein, the ascorbic acid compound and the quinone compound are administered as one or more capsules, each comprising about 500 mg of sodium L-ascorbate and about 3 mg of sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate. In certain embodiments, as used in the methods provided herein, the ascorbic acid compound and the quinone compound are administered as one or more capsules, each comprising about 500 mg of sodium L-ascorbate and about 5 mg of sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate.

[00241] In certain embodiments, as used in the methods provided herein, the ascorbic acid compound and the quinone compound are administered as one or more capsules, each comprising about 1,000 mg of calcium L-ascorbate and about 10 mg of 2-methyl-1,4-naphthalenedione. In certain embodiments, as used in the methods provided herein, the ascorbic acid compound and the quinone compound are administered as one or more capsules, each comprising about 925 mg of calcium L-ascorbate and about 9 mg (*e.g.*, 9.25 mg) of 2-methyl-1,4-naphthalenedione.

[00242] Depending on the condition of the cancer to be treated and the subject's condition, the ascorbic acid compound, the quinone compound, the SGLT inhibitor, and the glutamine inhibitor used in the methods provided herein can be administered by oral, parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous, CIV, intracistemal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or

topical (*e.g.*, transdermal or local) route of administration. In certain embodiments, the ascorbic acid compound, the quinone compound, the SGLT inhibitor, and the glutamine inhibitor used in the methods provided herein are administered by oral, parenteral, intravenous, or topical route of administration. The ascorbic acid compound, the quinone compound, the SGLT inhibitor, and the glutamine inhibitor used in the methods provided herein may be formulated, alone or together, in suitable dosage unit with one or more pharmaceutically acceptable excipients appropriate for each route of administration.

[00243] In one embodiment, the ascorbic acid compound is administered orally. In another embodiment, the ascorbic acid compound is administered parenterally. In yet another embodiment, the ascorbic acid compound is administered intravenously. In still another embodiment, the ascorbic acid compound is administered topically.

[00244] In one embodiment, the quinone compound is administered orally. In another embodiment, the quinone compound is administered parenterally. In yet another embodiment, the quinone compound is administered intravenously. In still another embodiment, the quinone compound is administered topically.

[00245] In one embodiment, the SGLT inhibitor is administered orally. In another embodiment, the SGLT inhibitor is administered parenterally. In yet another embodiment, the SGLT inhibitor is administered intravenously. In still another embodiment, the SGLT inhibitor is administered topically.

[00246] In one embodiment, the glutamine inhibitor is administered orally. In another embodiment, the glutamine inhibitor is administered parenterally. In yet another embodiment, the glutamine inhibitor is administered intravenously. In still another embodiment, the glutamine inhibitor is administered topically.

[00247] The routes of administration of the ascorbic acid compound, the quinone compound, the SGLT inhibitor, and the glutamine inhibitor can be the same or different. In certain embodiments, the ascorbic acid compound, the quinone compound, the SGLT inhibitor, and the glutamine inhibitor are all administered orally.

[00248] In one embodiment, the ascorbic acid compound is administered concurrently with the quinone compound. In another embodiment, the ascorbic acid compound is administered separately with the quinone compound. In yet another embodiment, the

ascorbic acid compound is administered sequentially with the quinone compound. In yet another embodiment, the ascorbic acid compound is administered before the quinone compound. In yet another embodiment, the ascorbic acid compound is administered after the quinone compound.

[00249] In certain embodiments, the ascorbic acid compound and the quinone compound are administered together in a single composition comprising ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; and a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00250] In certain embodiments, the ascorbic acid compound and the quinone compound are administered to the subject after mealtime. In certain embodiments, the ascorbic acid compound and the quinone compound are administered to the subject with a meal.

[00251] In certain embodiments, the SGLT inhibitor as used in the methods provided herein is administered to the subject in an amount ranging from about 0.1 mg to about 1,000 mg per day, from about 0.5 mg to about 500 mg per day, or from about 1 mg to about 500 mg per day.

[00252] In certain embodiments, the ascorbic acid compound, the quinone compound, and the SGLT inhibitor are administered repetitively if necessary, for example, until the subject experiences stable disease or regression, or until the subject experiences disease progression or unacceptable toxicity. In certain embodiments, the ascorbic acid compound, the quinone compound, the SGLT inhibitor, and the glutamine inhibitor compound are administered repetitively if necessary, for example, until the subject experiences stable disease or regression, or until the subject experiences disease progression or unacceptable toxicity. Stable disease or lack thereof is determined by methods known in the art such as evaluation of subject's symptoms, physical examination, or diagnostic testing.

[00253] In certain embodiments, the ascorbic acid compound, the quinone compound, and the SGLT inhibitor are administered to the subject over an extended period of time, ranging from about 1 day to about 50 years, from about 10 days to about 25 years, from about 1 month to about 10 years, or from about 6 months to about 5 years. In certain embodiments,

the ascorbic acid compound, the quinone compound, the SGLT inhibitor, and the glutamine inhibitor are administered to the subject over an extended period of time, ranging from about 1 day to about 50 years, from about 10 days to about 25 years, from about 1 month to about 10 years, or from about 6 months to about 5 years.

[00254] In certain embodiments, the ascorbic acid compound, the quinone compound, and the SGLT inhibitor as used in the methods provided herein are cyclically administered. In certain embodiments, the ascorbic acid compound, the quinone compound, the SGLT inhibitor, and the glutamine inhibitor as used in the methods provided herein are cyclically administered. Cycling therapy involves the administration of an active agent for a period of time, followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

[00255] Consequently, in one embodiment, the ascorbic acid compound, the quinone compound, and the SGLT inhibitor as used in the methods provided herein are administered daily in a single or divided doses for one week, two weeks, three weeks, four weeks, five weeks, six weeks, eight weeks, ten weeks, fifteen weeks, or twenty weeks, followed by a rest period of about 1 day to about ten weeks. In another embodiment, the ascorbic acid compound, the quinone compound, the SGLT inhibitor, and the glutamine inhibitor as used in the methods provided herein are administered daily in a single or divided doses for one week, two weeks, three weeks, four weeks, five weeks, six weeks, eight weeks, ten weeks, fifteen weeks, or twenty weeks, followed by a rest period of about 1 day to about ten weeks. For example, the methods contemplate using cycling of one week, two weeks, three weeks, four weeks, five weeks, six weeks, eight weeks, ten weeks, fifteen weeks, or twenty weeks. In yet another embodiment, the ascorbic acid compound, the quinone compound, and the SGLT inhibitor as used in the methods provided herein are administered daily in a single or divided doses for one week, two weeks, three weeks, four weeks, five weeks, or six weeks with a rest period of 1, 3, 5, 7, 9, 12, 14, 16, 18, 20, 22, 24, 26, 28, 29, or 30 days. In still another embodiment, the ascorbic acid compound, the quinone compound, the SGLT inhibitor, and the glutamine inhibitor as used in the methods provided herein are administered daily in a single or divided doses for one week, two weeks, three weeks, four weeks, five weeks, or six weeks with a rest period of 1, 3, 5, 7, 9, 12, 14, 16, 18, 20, 22, 24, 26, 28, 29, or 30 days. In

certain embodiments, the rest period is 14 days. In certain embodiments, the rest period is 28 days. In certain embodiments, the rest period is a period that is sufficient for bone marrow recovery. The frequency, number and length of dosing cycles can be increased or decreased.

[00256] In certain embodiments, the subject is a mammal. In certain embodiments, the mammal is a human.

[00257] In one embodiment, provided herein is a method of inhibiting the growth of a cancerous cell, comprising the step of contacting the cell with (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00258] In another embodiment, provided herein is a method of killing a cancerous cell, comprising the step of contacting the cell with (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00259] In yet another embodiment, provided herein is a method of inhibiting the growth of a cancerous cell, comprising the step of contacting the cell with an effective amount of: (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iv) a glutamine inhibitor, or a single enantiomer, a

mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00260] In still another embodiment, provided herein is a method of killing a cell, comprising the step of contacting the cell with an effective amount of: (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iv) a glutamine inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00261] In certain embodiments, the cancerous cell is a human cell.

[00262] In certain embodiments, the methods provided herein further comprise administering an additional therapeutic agent or therapy that is useful in treating, preventing, or ameliorating one or more symptoms of the cancer. Effective dosages of the additional therapeutic agent can be administered together with, alternatively to, or sequentially to the administration of the active ingredients provided herein. The dosages given will depend on absorption, inactivation, and excretion rates of the therapeutic agents as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.

[00263] Examples of the additional therapeutic agent include, include, but are not limited to, (1) alpha-adrenergic agents; (2) antiarrhythmic agents; (3) anti-atherosclerotic agents, such as ACAT inhibitors; (4) antibiotics, such as anthracyclines, bleomycins, mitomycin, dactinomycin, and plicamycin; (5) anticancer agents and cytotoxic agents, *e.g.*, alkylating agents, such as nitrogen mustards, alkyl sulfonates, nitrosoureas, ethylenimines, and triazenes; (6) anticoagulants, such as acenocoumarol, argatroban, bivalirudin, lepirudin,

fondaparinux, heparin, phenindione, warfarin, and ximelagatran; (7) anti-diabetic agents, such as biguanides (*e.g.*, metformin), glucosidase inhibitors (*e.g.*, acarbose), insulins, meglitinides (*e.g.*, repaglinide), sulfonylureas (*e.g.*, glimepiride, glyburide, and glipizide), thiozolidinediones (*e.g.*, troglitazone, rosiglitazone, and pioglitazone), and PPAR-gamma agonists; (8) antifungal agents, such as amorolfine, amphotericin B, anidulafungin, bifonazole, butenafine, butoconazole, caspofungin, ciclopirox, clotrimazole, econazole, fenticonazole, filipin, fluconazole, isoconazole, itraconazole, ketoconazole, micafungin, miconazole, naftifine, natamycin, nystatin, oxyconazole, ravuconazole, posaconazole, rimocidin, sertaconazole, sulconazole, terbinafine, terconazole, tioconazole, and voriconazole; (9) antiinflammatories, *e.g.*, non-steroidal anti-inflammatory agents, such as aceclofenac, acemetacin, amoxiprin, aspirin, azapropazone, benorilate, bromfenac, carprofen, celecoxib, choline magnesium salicylate, diclofenac, diflunisal, etodolac, etoricoxib, faislamine, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, ketorolac, lornoxicam, loxoprofen, lumiracoxib, meclofenamic acid, mefenamic acid, meloxicam, metamizole, methyl salicylate, magnesium salicylate, nabumetone, naproxen, nimesulide, oxyphenbutazone, parecoxib, phenylbutazone, piroxicam, salicyl salicylate, sulindac, sulfinpyrazone, suprofen, tenoxicam, tiaprofenic acid, and tolmetin; (10) antimetabolites, such as folate antagonists, purine analogues, and pyrimidine analogues; (11) anti-platelet agents, such as GPIIb/IIIa blockers (*e.g.*, abciximab, eptifibatide, and tirofiban), P2Y(AC) antagonists (*e.g.*, clopidogrel, ticlopidine and CS-747), cilostazol, dipyridamole, and aspirin; (12) antiproliferatives, such as methotrexate, FK506 (tacrolimus), and mycophenolate mofetil; (13) anti-TNF antibodies or soluble TNF receptor, such as etanercept, rapamycin, and leflunimide; (14) aP2 inhibitors; (15) beta-adrenergic agents, such as carvedilol and metoprolol; (16) bile acid sequestrants, such as questran; (17) calcium channel blockers, such as amlodipine besylate; (18) chemotherapeutic agents; (19) cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib and rofecoxib; (20) cyclosporins; (21) cytotoxic drugs, such as azathioprine and cyclophosphamide; (22) diuretics, such as chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzothiazide, ethacrynic acid, ticrynafen, chlorthalidone, furosenide, muzolimine, bumetanide, triamterene, amiloride, and spironolactone; (23) endothelin converting enzyme (ECE) inhibitors, such as phosphoramidon; (24) enzymes, such as L-asparaginase; (25) Factor VIIa Inhibitors and Factor Xa Inhibitors; (26) farnesyl-protein transferase inhibitors; (27) fibrates; (28) growth factor inhibitors, such as modulators of PDGF activity; (29) growth hormone secretagogues;

(30) HMG CoA reductase inhibitors, such as pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 (a.k.a. itavastatin, nisvastatin, or nisbastatin), and ZD-4522 (also known as rosuvastatin, atavastatin, or visastatin); neutral endopeptidase (NEP) inhibitors; (31) hormonal agents, such as glucocorticoids (*e.g.*, cortisone), estrogens/antiestrogens, androgens/antiandrogens, progestins, and luteinizing hormone-releasing hormone antagonists, and octreotide acetate; (32) immunosuppressants; (33) mineralocorticoid receptor antagonists, such as spironolactone and eplerenone; (34) microtubule-disruptor agents, such as ecteinascidins; (35) microtubule-stabilizing agents, such as pacitaxel, docetaxel, and epothilones A-F; (36) MTP Inhibitors; (37) niacin; (38) phosphodiesterase inhibitors, such as PDE III inhibitors (*e.g.*, cilostazol) and PDE V inhibitors (*e.g.*, sildenafil, tadalafil, and vardenafil); (39) plant-derived products, such as vinca alkaloids, epipodophyllotoxins, and taxanes; (40) platelet activating factor (PAF) antagonists; (41) platinum coordination complexes, such as cisplatin, satraplatin, and carboplatin; (42) potassium channel openers; (43) prenyl-protein transferase inhibitors; (44) protein tyrosine kinase inhibitors; (45) renin inhibitors; (46) squalene synthetase inhibitors; (47) steroids, such as aldosterone, beclometasone, betamethasone, deoxycorticosterone acetate, fludrocortisone, hydrocortisone (cortisol), prednisolone, prednisone, methylprednisolone, dexamethasone, and triamcinolone; (48) TNF-alpha inhibitors, such as tenidap; (49) thrombin inhibitors, such as hirudin; (50) thrombolytic agents, such as anistreplase, reteplase, tenecteplase, tissue plasminogen activator (tPA), recombinant tPA, streptokinase, urokinase, prourokinase, and anisoylated plasminogen streptokinase activator complex (APSAC); (51) thromboxane receptor antagonists, such as ifetroban; (52) topoisomerase inhibitors; (53) vasopeptidase inhibitors (dual NEP-ACE inhibitors), such as omapatrilat and gemopatrilat; and (54) other miscellaneous agents, such as, hydroxyurea, procarbazine, mitotane, hexamethylmelamine, and gold compounds; (55) glutaminase inhibitors.

[00264] In certain embodiments, the additional therapy that is used in combination with the methods herein include, but are not limited to, surgery, endocrine therapy, biologic response modifiers (*e.g.*, interferons, interleukins, and tumor necrosis factor (TNF)), hyperthermia and cryotherapy, and agents to attenuate any adverse effects (*e.g.*, antiemetics).

[00265] In certain embodiments, the additional therapeutic agents that are in combination with the methods provided herein include, but are not limited to, alkylating drugs (mechlorethamine, chlorambucil, cyclophosphamide, melphalan, and ifosfamide),

antimetabolites (cytarabine (also known as cytosine arabinoside or Ara-C), HDAC (high dose cytarabine), and methotrexate), purine antagonists and pyrimidine antagonists (6-mercaptopurine, 5-fluorouracil, cytarbine, and gemcitabine), spindle poisons (vinblastine, vincristine, and vinorelbine), podophyllotoxins (etoposide, irinotecan, and topotecan), antibiotics (daunorubicin, doxorubicin, bleomycin, and mitomycin), nitrosoureas (carmustine and lomustine), enzymes (asparaginase), and hormones (tamoxifen, leuprolide, flutamide, and megestrol), imatinib, adriamycin, dexamethasone, and cyclophosphamide. For a more comprehensive discussion of updated cancer therapies; *See*, http://www.nci.nih.gov/, a list of the FDA approved oncology drugs at http://www.fda.gov/cder/cancer/druglistframe.htm, and The Merck Manual, Seventeenth Ed. 1999, the entire contents of which are hereby incorporated by reference.

[00266] In certain embodiments, the method provided herein further comprises administering one or more chemotherapeutic agents and/or therapies selected from: alkylation agents (*e.g.*, cisplatin, carboplatin); antimetabolites (*e.g.*, methotrexate and 5-FU); antitumour antibiotics (*e.g.*, adriamymycin and bleomycin); antitumour vegetable alkaloids (*e.g.*, taxol and etoposide); antitumor hormones (*e.g.*, dexamethasone and tamoxifen); antitumour immunological agents (*e.g.*, interferon α, β, and γ); radiation therapy; and surgery.

[00267] Such additional therapeutic agents, or drugs, can be administered, by a route and in an amount commonly used therefor, simultaneously or sequentially with the active ingredients provided herein.

[00268] In certain embodiments, the additional therapeutic agent is capecitabine, cisplatin, dacarbazine (DTIC), docetaxel, doxorubicin, erlotinib, everolimus, 5-fluorouracil (5-FU), gemcitabine, irinotecan, leucovorin, mitomycin C, oxaliplatin, paclitaxel, somatostatin, streptozocin, sunitinib, or temozolomide. In certain embodiments, the additional therapeutic agent is capecitabine, 5-fluorouracil (5-FU), everolimus, gemcitabine, somatostatin, or sunitinib.

[00269] In certain embodiments, provided herein are kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of active ingredients to a subject. In certain embodiments, the kit provided herein includes containers and dosage forms of the active ingredients provided herein.

[00270] Kits provided herein can further include devices that are used to administer the

active ingredients. Examples of such devices include, but are not limited to, syringes, needle-less injectors drip bags, patches, and inhalers. The kits provided herein can also include condoms for administration of the active ingredients.

[00271] Kits provided herein can further include pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: aqueous vehicles, including, but not limited to, Water for Injection USP, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles, including, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles, including, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

[00272] The disclosure will be further understood by the following non-limiting examples.

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[00273] The examples set forth above are provided to give those of ordinary skill in the art with a complete disclosure and description of how to make and use the claimed embodiments, and are not intended to limit the scope of what is disclosed herein. Modifications that are obvious to persons of skill in the art are intended to be within the scope of the following claims. All publications, patents, and patent applications cited in this specification are incorporated herein by reference as if each such publication, patent or patent application were specifically and individually indicated to be incorporated herein by reference.

What is claimed is:

1. A method of treating, preventing, or alleviating one or more symptoms of cancer in a subject, comprising administering to the subject in need of such a treatment a therapeutically effective amount of: (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

2. A method of inhibiting the growth of cancer in a subject, comprising administering to the subject in need of such a treatment a therapeutically effective amount of: (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

3. The method of claim 1 or 2, wherein the cancer is bladder cancer, breast cancer, cervical cancer, colon cancer, colorectal cancer, esophageal cancer, glioma, glioblastoma multiforme, head and neck cancer, leukemia, acute myelogenous leukemia, liver cancer, lung cancer, small cell lung cancer, non-small cell lung cancer, melanoma, myeloma, neuroblastoma, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, salivary gland cancer, sarcoma, osteosarcoma, skin cancer, squamous cell carcinoma, stomach cancer, testicular cancer, thyroid cancer, or uterine cancer.

4. The method of any one of claims 1 to 3, wherein the cancer is pancreatic cancer or prostate cancer.

5. The method of any one of claims 1 to 4, wherein the cancer is metastatic.

6. The method of any one of claims 1 to 5, wherein the cancer is refractory.

7. The method of any one of claims 1 to 6, wherein the cancer is relapsed.

8. The method of any one of claims 1 to 7, wherein the cancer is drug-resistant.

9. The method of any one of claims 1 to 8, wherein the subject is a human.

10. The method of any one of claims 1 to 9, wherein the ascorbic acid is administered orally.

11. The method of any one of claims 1 to 10, wherein the quinone compound is administered orally.

12. The method of any one of claims 1 to 11, wherein the ascorbic acid and the quinone compound are administered together in a single composition comprising ascorbic acid, , or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; and a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

13. The method of any one of claims 1 to 12, wherein the ascorbic acid and the quinone compound are formulated together in a single oral dosage form.

14. The method of claim 13, wherein the single oral dosage form is a tablet.

15. The method of claim 13, wherein the single oral dosage form is a capsule.

16. The method of claim 15, wherein the capsule comprises about 500 mg of ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; and about 5 mg of a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

17. The method of claim 15 or 16, wherein the capsule consists essentially of ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; and a quinone

compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

18. The method of any one of claims 1 to 17, wherein the ascorbic acid is L-ascorbic acid or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate or hydrate thereof.

19. The method of claim 18, wherein the ascorbic acid is an alkali or alkaline earth metal salt of L-ascorbic acid, or a pharmaceutically acceptable solvate or hydrate thereof.

20. The method of claim 19, wherein the ascorbic acid is sodium L-ascorbate, potassium L-ascorbate, calcium L-ascorbate, or magnesium L-ascorbate, or a pharmaceutically acceptable solvate or hydrate thereof; or a mixture thereof.

21. The method of claim 19, wherein the ascorbic acid is sodium L-ascorbate, or a pharmaceutically acceptable solvate or hydrate thereof.

22. The method of claim 19, wherein the ascorbic acid is potassium L-ascorbate, or a pharmaceutically acceptable solvate or hydrate thereof.

23. The method of claim 19, wherein the ascorbic acid is calcium L-ascorbate, or a pharmaceutically acceptable solvate or hydrate thereof.

24. The method of claim 19, wherein the ascorbic acid is magnesium L-ascorbate, or a pharmaceutically acceptable solvate or hydrate thereof.

25. The method of any one of claims 1 to 24, wherein the quinone compound is vitamin K.

26. The method of claim 25, wherein the quinone compound is vitamin K_3.

27. The method of claim 26, wherein vitamin K_3 is 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonic acid or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate or hydrate thereof.

28. The method of claim 26 or 27, wherein vitamin K_3 is an alkali or alkaline earth metal salt of 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonic acid, or a pharmaceutically acceptable solvate or hydrate thereof.

29. The method of any one of claims 26 to 28, wherein vitamin K_3 is sodium or magnesium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate, or a pharmaceutically acceptable solvate or hydrate thereof.

30. The method of any one of claims 26 to 29, wherein vitamin K_3 is anhydrous sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate.

31. The method of claim 26, wherein vitamin K_3 is 2-methyl-1,4-naphthalenedione; or a pharmaceutically acceptable solvate or hydrate thereof.

32. The method of any one of claims 1 to 31, wherein the molar ratio of the ascorbic acid to the quinone compound is ranging from about 50 to about 500.

33. The method of any one of claims 1 to 32, wherein the molar ratio of the ascorbic acid to the quinone compound is about 100.

34. The method of any one of claims 1 to 33, wherein the ascorbic acid is administered once, twice, three times, four times, five times, or six times a day.

35. The method of any one of claims 1 to 34, wherein the ascorbic acid is administered every 4 to 6 hours a day.

36. The method of any one of claims 1 to 35, wherein the quinone compound is administered once, twice, three times, four times, five times, or six times a day.

37. The method of any one of claims 1 to 36, wherein the quinone compound is administered every 4 to 6 hours a day.

38. The method of any one of claims 1 to 37, wherein the ascorbic acid is administered in an amount ranging from about 500 mg to about 10,000 mg per day, and the quinone compound is administered in an amount ranging from about 3 mg to about 100 mg per day.

39. The method of any one of claims 1 to 13, 15 to 21, 25 to 30, and 32 to 38, wherein the ascorbic acid and the quinone compound are administered as one or more capsules, each comprising about 500 mg of sodium L-ascorbate and about 3 mg of sodium 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate.

40. The method of any one of claims 1 to 13, 15 to 20, 22, 25, 26, and 31 to 38, wherein the ascorbic acid and the quinone compound are administered as one or more capsules, each comprising about 1,000 mg of calcium L-ascorbate and about 10 mg of 2-methyl-1,4-naphthalenedione.

41. The method of any one of claims 1 to 40, wherein the sodium glucose cotransporter inhibitor is a sodium glucose cotransporter type 1-selective inhibitor.

42. The method of any one of claims 1 to 40, wherein the sodium glucose cotransporter inhibitor is a sodium glucose cotransporter type 2-selective inhibitor.

43. The method of any one of claims 1 to 40, wherein the sodium glucose cotransporter inhibitor is a sodium glucose cotransporter types 1 and 2 dual inhibitor.

44. The method of any one of claims 1 to 40, wherein the sodium glucose cotransporter inhibitor is bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, phlorizin, remogliflozin, sergliflozin, sotagliflozin, tofogliflozin, BI 44847, DSP-3235, or T-1095.

45. The method of claim 44, wherein the sodium glucose cotransporter inhibitor is canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, or luseogliflozin.

46. The method of any one of claims 1 to 45, wherein the sodium glucose cotransporter inhibitor is administered in an amount ranging from about 1 μg/kg/day to about 100 mg/kg/day.

47. The method of any one of claims 1 to 46, further comprising a diagnostic step for determining glucose uptake in the subject using a glucose tracer.

48. The method of claim 47, wherein the glucose tracer is GLUT-specific.

49. The method of claim 47 or 48, wherein the glucose tracer is 2-deoxy-2-[^{18}F]fluoro-D-glucose.

50. The method of claim 47, wherein the glucose tracer is SGLT-specific.

51. The method of claim 47 or 50, wherein the glucose tracer is α-methyl-4-deoxy-4-[^{18}F]fluoro-D-glucopyranoside.

52. The method of any one of claims 1 to 51, further comprising administering a glutamine inhibitor to the subject.

53. The method of claim 52, wherein the glutamine inhibitor is 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid, (2*S*)-amino((5*S*)-3-chloro-4,5-dihydro-1,2-oxazol-5-yl)ethanoic acid, (5*S*)-5-amino-1-diazonio-6-hydroxy-6-oxohex-1-en-2-olate, aminooxyacetic acid, L-2-amino-4-oxo-5-chloropentoic acid, L-asparaginase, azaserine, azotomycin, 3,7-bis(dimethylamino)-phenazathionium chloride, bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulfide, 5-(3-bromo-4-(dimethylamino)phenyl)-2,2-dimethyl-2,3,5,6-tetrahydrobenzo[*a*]phenanthridin-4(1*H*)-one, bromothymol blue, *O*-carbamoyl-L-serine, *p*-chloromercuriphenylsulfonate, dicoumarol, *N*-ethylmaleimide, γ-L-glutamyl-*p*-nitroanilide, metformin, palmitoyl coenzyme A, pegaspargase, perphenazine, phenylbutyrate, phenylacetate, 2-(pyridin-2-yl)-*N*-(5-(4-(6-(2-(3-(trifluoromethoxy)phenyl)acetamido)-pyridazin-3-yl)butyl)-1,3,4-thiadiazol-2-yl)acetamide, or stearoyl coenzyme A.

54. The method of claim 52, wherein the glutamine inhibitor is an inhibitor of glutaminolysis.

55. The method of claim 52, wherein the glutamine inhibitor is a glutamine transporter inhibitor.

56. The method of claim 52, wherein the glutamine inhibitor is a glutamine amidotransferase inhibitor.

57. The method of claim 52, wherein the glutamine inhibitor is a γ-glutamyl transferase inhibitor.

58. The method of claim 52, wherein the glutamine inhibitor is a glutaminase inhibitor

59. The method of claim 58, wherein the glutaminase inhibitor is 2-(pyridin-2-yl)-*N*-(5-(4-(6-(2-(3-(trifluoromethoxy)phenyl)acetamido)pyridazin-3-yl)butyl)-1,3,4-thiadiazol-2-yl)acetamide.

60. The method of any one of claims 1 to 59, further comprising a diagnostic step for determining the glutamine-dependency in cancer cells of the subject.

61. The method of claim 60, wherein the diagnostic step is performing a glutamine PET scan.

62. The method of claim 60, wherein the diagnostic step comprises determining the molar ratio of glutamate to glutamine in the cancer cells of the subject.

63. The method of claim 62, wherein the molar ratio of glutamate to glutamine is no less than about 1.5.

64. The method of claim 62 or 63, wherein the molar ratio of glutamate to glutamine is no less than about 2.

65. The method of claim 61, wherein the diagnostic step comprises determining the molar ratio of glutaminase enzyme to glutamine synthetase in cancer cells of the subject.

66. The method of claim 65, wherein the molar ratio of glutaminase enzyme to glutamine synthetase is no less than about 0.05.

67. The method of claim 65 or 66, wherein the molar ratio of glutaminase enzyme to glutamine synthetase is no less than about 1.

68. The method of any one of claims 65 to 67, wherein the molar ratio of glutaminase enzyme to glutamine synthetase is determined by measuring the molar ratio of the mRNA level of glutaminase enzyme to the mRNA level of glutamine synthetase in the cancer cells.

69. The method of any one of claims 65 to 67, wherein the molar ratio of glutaminase enzyme to glutamine synthetase is determined by measuring the molar ratio of the protein level of glutaminase enzyme to the protein level of glutamine synthetase in the cancer cells.

70. The method of any one of claims 65 to 69, wherein the glutaminase enzyme is glutaminase C.

71. The method of any one of claims 65 to 69, wherein the glutaminase enzyme is human kidney-type glutaminase.

72. A method of inhibiting the growth of a cancerous cell, comprising the step of contacting the cell with an effective amount of: (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

73. A method of killing a cancerous cell, comprising the step of contacting the cell with an effective amount of: (i) ascorbic acid, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; (ii) a quinone compound, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and (iii) a sodium glucose cotransporter inhibitor, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

74. The method of claim 72 or 73, wherein the cancerous cell is a mammalian cancerous cell.

75. The method of claim 74, wherein the mammalian cancerous cell is a human cancerous cell.

76. The method of any one of claims 72 to 75, further comprising contacting the cell with a glutamine inhibitor.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/44574

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/122; 31/375; 31/7056; A61P 35/00 (2017.01)
CPC - A61K31/122; A61K31/7056; A61K31/375

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 8,450,286 B2 (Maldonado et al.); 28 May 2013 (28.05.2013); col 2, ln 55-61; col 4, ln 21-24; col 19, ln 22-24, ln 28-34, ln 50-53	1-3, 72-75
Y	US 5,639,787 A (Riordan et al.) 17 June 1997 (17.06.1997); col 1, ln 7-10, ln 40-42	1-3, 72-75
A	Scafoglioa et al., Functional expression of sodium-glucose transporters in cancer, PNAS, 2015, Vol. 112, No. 30, pages E4111-E4119; abstract	2, 72
A	US 4,684,627 A (LeVeen et al.) 4 August 1987 (04.08.1987); entire document	1-3, 72-75
A	US 2014/0336129 A1 (The University of Houston System) 13 November 2014 (13.11.2014); entire document	1-3, 72-75
A	US 2013/0281386 A1 (Anthony et al.) 24 October 2013 (24.10.2013); entire document	1-3, 72-75

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 September 2017 (18.09.2017)	18 OCT 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/44574

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-71 and 76
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.