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(54) **NUTRITIONAL SUPPLEMENT
COMPOSITIONS**

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(57) **ABSTRACT**

Dietary supplement compositions containing one or more compounds such as arginine, selenium, calcium, calcium sources, morphine precursors (e.g., reticuline), morphine, and morphine-6 β -glucuronide are provided.

NUTRITIONAL SUPPLEMENT COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Ser. No. 60/714,769, filed Sep. 6, 2005 and U.S. Provisional Application Ser. No. 60/615,048, filed Oct. 1, 2004, each of which is incorporated by reference in its entirety into this specification.

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

[0002] Funding for the work described herein was provided by the federal government, which may have certain rights in the invention.

BACKGROUND

[0003] 1. Technical Field

[0004] The document relates to nutritional supplement compositions. For example, this document relates to nutritional supplement compositions containing one or more compounds such as arginine, selenium, calcium, calcium sources, morphine precursors (e.g., reticuline), morphine, and morphine-6 β -glucuronide.

[0005] 2. Background Information

[0006] Many people suffer from conditions such as depression, neurodegenerative diseases, pro-inflammatory diseases, autoimmune disorders, and atherosclerosis. In many cases, few, if any, successful treatments are available for these people.

[0007] Analgesic compounds such as morphine are routinely used to reduce pain in humans. For example, surgery patients are typically instructed to take 5 to 10 mg of morphine per person to alleviate pain caused by the surgical procedure. In some cases, patients suffering from extreme pain (e.g., bum victims or cancer patients) are instructed to take higher doses of morphine.

SUMMARY

[0008] This document provides compositions containing one or more compounds such as arginine, selenium, calcium, calcium sources, morphine precursors (e.g., reticuline), morphine, and morphine-6 β -glucuronide. For example, this document provides compositions containing a low dose of morphine (e.g., a dose that is below that which is given to relieve a mammal of pain). The compositions provided herein can be used as nutritional supplement compositions. For example, the compositions provided herein can be used to provide a mammal with a long-term, low level of morphine that can allow the mammal to experience behavioral changes (e.g., a general overall calm feeling). In addition, the compositions provided herein can be used to provide a mammal with a long-term, low level of morphine that can allow the mammal to experience reduced *inflammatory responses and can allow the mammal to maintain an increased, basal level of constitutive nitric oxide release. In some cases, the compositions provided herein can be used to down regulate immune, vascular, neural, and gastrointestinal tissues via nitric oxide produced within a mammal. For example, the compositions provided herein can be used to reduce the excited state of inflamed gastrointestinal tissues

in mammals having Crohn's disease. In some cases, the compositions provided herein can be used to treat (e.g., reduce the severity of symptoms) neural conditions (e.g., schizophrenia, chronic pain, mania, depression, psychosis, paranoia, autism, stress, Alzheimer's disease, or Parkinson's disease), immune conditions (e.g., pro-inflammatory diseases, autoimmune disorders, histolytic medullary reticulosis, lupus, or arthritis), vascular conditions (e.g., atherosclerosis or neuronal vasculopathy), gastrointestinal conditions (e.g., colitis, Crohn's disease, or irritable bowel syndrome), or addiction (e.g., opiate addiction). For example, a nutritional supplement composition containing morphine or a morphine precursor such as reticuline, norlaudanosoline, L-DOPA, or codeine can be used to treat neural conditions such as neurovascular alterations involving hypothalamic hormone secretion (e.g., reproductive and growth hormones).

[0009] In general, the compositions provided herein can include one or more of the following: arginine, selenium, calcium, calcium sources, morphine precursors (e.g., reticuline), morphine, and morphine-6 β -glucuronide. As described herein, a long-term, low level of morphine can be achieved in a mammal by administering a low dose of morphine, by administering a morphine precursor, or by administering a combination of morphine and morphine precursors. In some cases, inhibitors such as dopamine β -hydroxylase inhibitors can be used to inhibit the dopamine to norepinephrine step in adrenaline synthesis, which can result in an endogenous dopamine level increase as well as an endogenous morphine level increase.

[0010] As disclosed herein, prolonged treatment with a low dose of morphine can result the continued positive effects of morphine such as nitric oxide release, without the need to escalate morphine dosages with time to achieve the same beneficial effects. In addition, the use of low doses of morphine can allow mammals to experience the beneficial effects of morphine, while not experiencing possible negative effects of morphine (e.g., addiction or powerful analgesia). Likewise, providing mammals with a morphine precursor such as reticuline can allow mammals to experience the beneficial effects of morphine, while not experiencing possible negative effects of morphine (e.g., addiction or powerful analgesia). For example, using a morphine precursor such as reticuline can allow patients to receive a low dose of morphine indirectly with a reduced risk of overdosing.

[0011] In general, one aspect of this document features a dietary supplement composition comprising, or consisting essentially of, morphine or morphine-6 β -glucuronide in an amount that results in less than 0.05 mg of the morphine or morphine-6 β -glucuronide being administered to a human per kg of body weight of the human. The composition can comprise less than 4.0 mg (e.g., 3.0, 2.0, 1.0, 0.5, 0.1, 0.05 mg) of the morphine or morphine-6 β -glucuronide. The composition can comprise less than 1.0 mg of the morphine or morphine-6 β -glucuronide. The composition can comprise a morphine precursor. The composition can be in the form of a tablet. The composition can comprise selenium. The composition can comprise L-arginine. The composition can comprise a calcium source. The morphine or morphine-6 β -glucuronide can be in an amount that results in less than 0.025 mg of the morphine or morphine-6 β -glucuronide being administered to the human per kg of body weight of

the human. The morphine or morphine-6 β -glucuronide can be in an amount that results in less than 0.01 mg of the morphine or morphine-6 β -glucuronide being administered to the human per kg of body weight of the human. The composition can comprise morphine. The composition can comprise morphine and morphine-6 β -glucuronide. The composition can comprise thebaine, codeine, reticuline, norlaudanoline, salutaridine, dopamine, L-DOPA, tyrosine, tyramine, phenylalanine, 3,4 dihydroxyphenyl pyruvate, dihydroxyphenyl acetaldehyde, or combinations thereof.

[0012] Another aspect of this document features a dietary supplement composition comprising, or consisting essentially of, morphine and a compound selected from the group consisting of selenium and arginine. The composition can comprise between 35 μ g and 700 μ g of morphine. The composition can comprise between 55 μ g and 300 μ g of selenium. The composition can comprise between 1 mg and 500 mg of arginine. The composition can comprise a calcium source. The composition can comprise between 1 g and 1.3 g of the calcium source. The calcium source can be calcium citrate.

[0013] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

[0014] Other features and advantages of the invention will be apparent from the following detailed description, and from the claims.

DETAILED DESCRIPTION

[0015] This document provides methods and materials related to nutritional supplement compositions containing one or more of the following compounds: arginine, selenium, morphine, morphine precursors (e.g., tyrosine, tyramine, phenyl alanine, 3,4 dihydroxyphenyl pyruvate, dihydroxyphenyl acetaldehyde, dopamine, L-DOPA, reticuline, norlaudanoline, salutaridine, thebaine, or codeine), morphine-6 β -glucuronide, inhibitors of morphine synthesis or activity, or inhibitors of dopamine synthesis. Such nutritional supplement compositions can be used to treat diseases, to reduce inflammation, or to restore normal function.

[0016] In one embodiment, this document provides compositions containing morphine, morphine precursors, morphine-6 β -glucuronide, or combinations thereof. Morphine or morphine-6 β -glucuronide can be formulated into compositions designed to deliver a low dose of morphine or morphine-6 β -glucuronide to a mammal. Typically, a low dose of morphine is a dose that is below that which is given to relieve a mammal of pain. For example, a low dose of morphine can be between 0.5 and 10 μ g (e.g., between 1 and 9 μ g, between 1 and 8 μ g, between 1 and 7 μ g, between 1 and 6 μ g, between 1 and 5 μ g, between 2 and 10 μ g, between 3 and 10 μ g, between 4 and 10 μ g, or between 5 and 10 μ g) per

kg of body weight per day. A low level of morphine-6 β -glucuronide can be similar to those of morphine. For example, a low dose of morphine-6 β -glucuronide can be between 1 and 10 μ g (e.g., between 1 and 9 μ g, between 1 and 8 μ g, between 1 and 7 μ g, between 1 and 6 μ g, between 1 and 5 μ g, between 2 and 10 μ g, between 3 and 10 μ g, between 4 and 10 μ g, or between 5 and 10 μ g) per kg of body weight per day. In some cases, morphine or morphine-6 β -glucuronide can be formulated to deliver between 35 and 700 μ g of morphine or morphine-6 β -glucuronide for a 70 kg individual. In some cases, a low dose can be any amount that is high enough to cause cells within the mammal to release nitric oxide yet low enough to not cause the mammal to experience analgesia. Such a dose can be, without limitation, about 5 μ g per kg of body weight per day.

[0017] When given orally, morphine or morphine-6 β -glucuronide can be formulated into a pill or tablet that contains between 10 and 1000 μ g (e.g., between 10 and 900 μ g, between 10 and 800 μ g, between 10 and 700 μ g, between 10 and 600 μ g, between 10 and 500 μ g, between 30 and 1000 μ g, between 35 and 1000 μ g, between 40 and 1000 μ g, between 50 and 1000 μ g, between 35 to 700 μ g, or between 35 and 500 μ g) of morphine or morphine-6 β -glucuronide. For example, a tablet can be designed to contain 100 μ g of morphine. In these cases, a mammal weighing about 70 kg can be instructed to take between one and three pills or tablets per day. Mammals weighing more or less than 70 kg can be instructed to take the appropriate number of pills or tablets to achieve a similar final concentration. The term "morphine" as used herein includes dihydromorphine, morphine sulfate, morphine hydrochloride, and morphine acetate.

[0018] The compositions provided herein can contain one or more than one (e.g., two, three, four, five, or more) morphine precursors without containing morphine or morphine-6 β -glucuronide. Examples of morphine precursors include, without limitation, tyrosine, tyramine, dopamine, L-DOPA, 3,4 dihydroxyphenyl pyruvate, dihydroxyphenyl acetaldehyde, phenylalanine, reticuline, norlaudanoline, salutaridine, thebaine, and codeine. As described herein, a composition can be designed to contain tyrosine, tyramine, dopamine, L-DOPA, 3,4 dihydroxyphenyl pyruvate, dihydroxyphenyl acetaldehyde, phenylalanine, reticuline, norlaudanoline, salutaridine, thebaine, codeine, or combinations thereof. Such compositions can contain any amount of the morphine precursors such as an amount between 1 and 10 mg per person weighing about 70 kg. For example, a composition can contain between 1 and 10 mg of reticuline.

[0019] The compositions provided herein can contain one or more (e.g., two, three, four, five, or more) morphine precursors in addition to morphine or morphine-6 β -glucuronide or in addition to a combination of morphine and morphine-6 β -glucuronide. In some cases, a composition can contain morphine and reticuline. Compositions containing morphine and a morphine precursor as well as compositions containing morphine-6 β -glucuronide and a morphine precursor can contain any amount of the morphine precursor such as between 0.1 and 100 mg (e.g., between 0.1 and 90 mg, between 0.1 and 75 mg, between 0.1 and 50 mg, between 0.1 and 25 mg, between 0.1 and 10 mg, between 0.5 and 100 mg, between 1 and 100 mg, between 1 and 50 mg, or between 1 and 10 mg) of the morphine precursor. For example, a composition can contain between 10 and 100 μ g

of morphine, between 10 and 100 μg of morphine-6 β -glucuronide, and between 1 and 10 mg of reticuline.

[0020] A composition (e.g., pill or tablet) designed to deliver a low dose of morphine, designed to deliver a low dose of morphine-6 β -glucuronide, designed to contain one or more morphine precursors, or designed to contain any combination thereof (e.g., both morphine and one or more morphine precursors) can be formulated to contain additional components such as L-arginine, selenium, and Ca^{++} . L-arginine can be included to promote a cell's ability to release nitric oxide in response to morphine via nitric oxide synthesis from L-arginine metabolism. Selenium can be added to enhance μ_3 opiate receptor gene expression. Calcium sources such as calcium citrate or CaCO_3 can be added to help facilitate the metabolism of L-arginine into nitric oxide via a calcium-dependent constitutive nitric oxide synthase. To reduce acid reflux problems in oral applications, CaCO_3 can be used as a calcium source. In some cases, a pill or tablet designed to deliver a low dose of morphine can be formulated to contain 35 to 700 μg morphine (e.g., 0.1 mg morphine), 1 mg to 500 mg L-arginine (e.g., 300 mg L-arginine), 55 μg to 200 μg selenium (e.g., 100 μg selenium), and 1000 to 1300 mg Ca^{++} (e.g., 1000 mg Ca^{++}). In some cases, a pill or tablet can be formulated to contain 1 to 10 mg reticuline (e.g., 5 mg reticuline), 1 mg to 500 mg L-arginine (e.g., 300 mg L-arginine), 55 μg to 200 μg selenium (e.g., 100 μg selenium), and 1000 to 1300 mg Ca^{++} (e.g., 1000 mg Ca^{++}). Other components that can be included in a composition provided herein include, without limitation, pharmaceutically acceptable aqueous vehicles, pharmaceutically acceptable solid vehicles, steroids, antibacterial agents, anti-inflammatory agents, immunosuppressants, dilators, vaso-constrictors, anti-cholinergics, anti-histamines, antioxidant, and combinations thereof.

[0021] In some cases, a composition (e.g., pill or tablet) designed to deliver a low dose of morphine, designed to deliver a low dose of morphine-6 β -glucuronide, designed to contain one or more morphine precursors, or designed to contain any combination thereof (e.g., both morphine and one or more morphine precursors) can be formulated to contain one or more inhibitors of morphine synthesis (e.g., a CYP2D6 or CYP2D7 inhibitor) or activity (e.g., naloxone), one or more inhibitors of dopamine synthesis or activity, or combinations thereof. Examples of CYP2D6 inhibitors include, without limitation, amiodarone, chloroquine, cimetidine, clomipramine, diphenhydramine, duloxetine, fluoxetine, hydroxychloroquin, paroxetine, propafenone, propoxyphene, and quinidine, terbinafine.

[0022] A pharmaceutically acceptable aqueous vehicle can be, for example, any liquid solution that is capable of dissolving morphine or a morphine precursor (e.g., reticuline) and is not toxic to the particular individual receiving the composition. Examples of pharmaceutically acceptable aqueous vehicles include, without limitation, saline, water, and acetic acid. Typically, pharmaceutically acceptable aqueous vehicles are sterile. A pharmaceutically acceptable solid vehicle can be formulated such that morphine or a morphine precursor is suitable for oral administration. For example, capsules or tablets can contain reticuline in enteric form. The dose supplied by each capsule or tablet can vary since an effective amount can be reached by administering either one or multiple capsules or tablets. Any well known pharmaceutically acceptable material such as gelatin and

cellulose derivatives can be used as a pharmaceutically acceptable solid vehicle. In addition, a pharmaceutically acceptable solid vehicle can be a solid carrier including, without limitation, starch, sugar, or bentonite. Further, a tablet or pill formulation of morphine or a morphine precursor can follow conventional procedures that employ solid carriers, lubricants, and the like.

[0023] Steroids can be any compound containing a hydrocyclopentanophenanthrene ring structure. Examples of steroids include, without limitation, prednisone, dexamethasone, and hydrocortisone. An antibacterial agent can be any compound that is active against bacteria, such as penicillin, erythromycin, neomycin, gentamicin, and clindamycin. An anti-inflammatory agent can be any compound that counteracts inflammation, such as ibuprofen and salicylic acid. An immunosuppressant can be any compound that suppresses or interferes with normal immune function, such as cyclosporine. A dilator can be any compound that causes the expansion of an orifice, such as albuterol. A vaso-constrictor can be any compound that constricts or narrows blood vessels, such as phenylephrine hydrochloride, cocaine, and epinephrine. An anti-cholinergic can be any compound that blocks parasympathetic nerve impulses, such as ipratropium bromide. An anti-histamine can be any compound that opposes the action of histamine or its release from cells (e.g., mast cells), such as terfenadine and astemizole.

[0024] Any method can be used to obtain morphine, morphine-6 β -glucuronide, morphine precursors, or any additional component of a composition provided herein. In some cases, the components of the compositions provided herein can be obtained using common chemical extraction, isolation, or synthesis techniques. For example, reticuline can be obtained as described elsewhere (Brochmann-Hansen and Nielsen, *Tetrahedron Lett.*, 18:1271-4 (1965) and U.S. Pat. No. 3,894,027). In some cases, the components of the compositions provided herein can be obtained from commercial vendors. For example, morphine, morphine-6 β -glucuronide, codeine, norlaudanoline, and salutaridine can be ordered from Sigma, Inc.

[0025] Any method can be used to formulate a composition provided herein. For example, common formulation mixing and preparation techniques can be used to make a composition having the components described herein. In addition, the compositions provided herein can be in any form. For example, a composition provided herein can be in the form of a solid, liquid, and/or aerosol including, without limitation, powders, crystalline substances, gels, pastes, ointments, salves, creams, solutions, suspensions, partial liquids, sprays, nebulae, mists, atomized vapors, tinctures, pills, capsules, tablets, and gelcaps. In some cases, the composition can be a dietary supplement. In some embodiments, a composition containing morphine, one or more morphine precursors, or a combination thereof can be prepared for oral administration by mixing the components with one or more of the following: a filler, a binder, a disintegrator, a lubricant, and a coloring agent. Lactose, corn starch, sucrose, glucose, sorbitol, crystalline cellulose, silicon dioxide, or the like can be used as the filler. Polyvinyl alcohol, polyvinyl ether, ethyl cellulose, methyl cellulose, acacia, tragacanth, gelatin, shellac, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, calcium citrate, dextrin, or pectin can be used as the binder. Magnesium stearate, talc, polyethylene glycol, silica, or hardened plant oil can be used

as the lubricant. A pharmaceutically acceptable coloring agent can be used as the coloring agent. Cocoa powder, mentha water, aromatic acid, mentha oil, borneol, or powdered cinnamon bark also can be added. In some cases, a composition containing morphine, one or more morphine precursors, or a combination thereof can be prepared for injection by mixing the components with one or more of the following: a pH adjusting agent, a buffer, a stabilizer, and a solubilizing agent.

[0026] The compositions provided herein can be administered to any mammal (e.g., rat, mouse, dog, cat, horse, cow, goat, pig, monkey, or human). In addition, any route of administration (e.g., oral or parenteral administration) can be used to administer a composition provided herein to a mammal. For example, a composition containing morphine or reticuline can be administered orally or parenterally (e.g., a subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intrastemal, or intravenous injection).

[0027] While not being limited to any particular mode of action, the compositions provided herein can be used to increase or maintain a basal level of nitric oxide release by cells (e.g., cells expressing μ_3 opiate receptors). The administration of morphine precursors such as reticuline to a mammal can lead to the conversion of the morphine precursor into morphine. The morphine produced from the morphine precursor or the morphine provided directly by a composition containing morphine or the morphine-6 β -glucuronide provided directly by a composition containing morphine-6 β -glucuronide can activate μ_3 opiate receptors, which are coupled to nitric oxide release, and can down regulate the activated state of tissues within the mammal making them less excitable. For example, administering morphine or reticuline can limit undesired excitation and restore basal activity levels within a mammal. In addition, certain mammals may not produce enough endogenous morphine to fulfill the needs of processes normally using this material to down regulate their excitatory state (e.g., a run-away pro-inflammatory state, mental disorders, vascular disorders). Administering a morphine precursor such as reticuline can provide mammals with the morphine needed to down regulate excitatory states without administering a controlled substance. Administering morphine or morphine-6 β -glucuronide directly at a low dose can provide mammals with the morphine needed to down regulate excitatory states without triggering tolerance to the administered morphine or morphine-6 β -glucuronide. For example, as described herein, morphine can be administered chronically (e.g., a long duration) at a low dose without observing a reduction of morphine's effects (e.g., nitric oxide release) over time. In addition, administering morphine-6 β -glucuronide can provide mammals with nitric oxide release in the periphery as opposed to the brain since morphine-6 β -glucuronide exhibits a limited ability to cross the blood brain barrier.

[0028] The compositions provided herein can be administered to a mammal in any amount, at any frequency, and for any duration. Typically, a composition provided herein can be administered to a mammal in an amount, at a frequency, and for a duration effective to induce nitric oxide release in the mammal. In some cases, a composition provided herein can be administered to a mammal in an amount, at a frequency, and for a duration effective to reduce the severity of a symptom of a disease or condition (e.g., schizophrenia, mania, depression, psychosis, chronic pain,

paranoia, autism, stress, Alzheimer's disease, Parkinson's disease, pro-inflammatory diseases, autoimmune disorders, histolytic medullary reticulosis, lupus, arthritis, atherosclerosis, neuronal vasculopathy, or addiction).

[0029] An effective amount of a composition provided herein or of morphine or of a morphine precursor (e.g., reticuline) can be any amount that induces cells to release nitric oxide without producing significant toxicity to the mammal. In some cases, an effective amount of a composition provided herein or of morphine or of a morphine precursor (e.g., reticuline) can be any amount that reduces, prevents, or eliminates a symptom of a disease or condition upon administration to a mammal without producing significant toxicity to the mammal. In some cases involving morphine precursors, an effective amount can be any amount that results in the production of detectable amounts of morphine within a tissue sample.

[0030] Again, a composition provided herein can be administered to a mammal in any amount. In some embodiments, the amount of a composition provided herein or of morphine or of a morphine precursor (e.g., reticuline) can be greater than 0.01 mg/kg of body weight. In some cases, the amount of a composition provided herein or of morphine or of a morphine precursor (e.g., reticuline) can be between about 0.01 and about 50 mg/kg (e.g., between about 0.01 and about 45 mg/kg; between about 0.1 and about 25 mg/kg; or between about 1 and about 5 mg/kg) of body weight. The effective amount can vary depending upon the disease to be treated (if any), the site of administration, and the mammal to be treated. Such effective amounts can be determined using the methods and materials provided herein. For example, the level of morphine production can be assessed using routine experimentation in vitro or in vivo. For example, a patient having a particular condition can receive 5 mg/kg body weight of reticuline. If the patient fails to respond or produce morphine, then the amount can be increased by, for example, ten fold. After receiving this higher concentration, the patient can be monitored for both responsiveness to the treatment and toxicity symptoms, and adjustments made accordingly.

[0031] Various factors can influence the actual amount used for a particular application. For example, the frequency of administration, duration of treatment, combination of other agents, site of administration, stage of disease (if present), and the anatomical configuration of the treated area may require an increase or decrease in the actual amount administered.

[0032] The frequency of administration of a composition provided herein can be any frequency. For example, the frequency of administration can be from about four times a day to about once a month, or more specifically, from about twice a day to about once a week. In addition, the frequency of administration can remain constant or can be variable during the duration of treatment. As with the amount administered, various factors can influence the actual frequency of administration used for a particular application. For example, the amount, duration of treatment, combination of agents, site of administration, stage of disease (if present), and the anatomical configuration of the treated area may require an increase or decrease in administration frequency. In one embodiment, a composition containing reticuline can be administered daily at a dose of about 1 to about 5 mg of reticuline per kg of body weight.

[0033] The duration of administration of a composition provided herein can be any duration. For example, a duration of administration of a composition provided herein can be longer than a week, month, three months, six months, nine months, a year, two years, or three years. In some cases, an effective duration can be any duration that reduces, prevents, or eliminates a symptom of a disease upon administration to a mammal without producing significant toxicity to the mammal. Such an effective duration can vary from several days to several weeks, months, or years. In general, an effective duration for the treatment of an acute disease can range in duration from several days to several months. Once administration of the composition is stopped, however, disease symptoms may return. In such cases, an effective duration for the prevention of certain conditions can last for as long as the individual is alive.

[0034] Multiple factors can influence the actual duration used for a particular treatment or prevention regimen. For example, an effective duration can vary with the frequency of administration, the amount administered, combination of multiple agents, site of administration, state of disease (if present), and anatomical configuration of the treated area.

[0035] If the administration of a composition provided herein (e.g., a composition containing reticuline) is toxic, the mammal can be treated with a combination of L-DOPA and dopamine to inhibit the production of morphine that results from the administered composition. For example, a combination of L-DOPA and dopamine can be used to reduce that amount of morphine produced from a composition containing a morphine precursor such that only 95, 90, 80, 70, 60, 50, 40, 30, 20, 10, or less percent of the morphine normally produced following administration of the composition is actually produced.

[0036] This document also provides methods for inducing nitric oxide release from cells. Such cells can be in vitro or in vivo. In addition, the cells can be any type of cell including, without limitation, neuronal, vascular, respiratory, immune, or digestive cells. To induce nitric oxide release from cells, the compositions provided herein can be administered as described herein. For example, a composition containing morphine can be administered to a mammal in an amount and at a frequency such that the mammal receives between 0.5 μ g and 10 μ g of morphine per kg of body weight per day for a duration of more than one month (e.g., more than two, three, four, five, six, seven, eight, nine, or more months).

[0037] In addition, this document provides methods for treating a mammal having a disease or condition using a composition provided herein. Examples of diseases or conditions that can be treated using the compositions provided herein include, without limitation, rheumatoid arthritis, systemic lupus erythematosus, systemic scleroderma, Behcet disease, periarteritis, ulcerative colitis, Crohn's disease, active chronic hepatitis, glomerular nephritis, autoimmune diseases, osteoarthritis, gout, atherosclerosis, psoriasis, atopic dermatitis, pulmonary diseases with granuloma, encephalitis, endotoxin shock, sepsis, inflammatory colitis, diabetes, acute myelocytic leukemia, pneumonia, heart transplantation, encephalomyelitis, anorexia, acute hepatitis, chronic hepatitis, drug-induced hepatic injury, alcoholic hepatitis, viral hepatitis, jaundice, hepatic cirrhosis, hepatic insufficiency, atrial myxoma, Castleman syndrome, multiple

myeloma, Rennert T lymphomatosis, mesangial nephritis, renal cell carcinoma, cytomegaloviral hepatitis, cytomegaloviral retinopathy, adenoviral cold syndrome, adenoviral pharyngoconjunctival fever, adenoviral ophthalmia, AIDS, atherosclerosis, arteriosclerosis, vasculopathy associated with diabetes, mania, depression, chronic pain, schizophrenia, psychosis, and paranoia. To treat a mammal having such a disease or condition, the compositions provided herein can be administered as described herein. For example, a composition containing morphine can be administered to a mammal in an amount and at a frequency such that the mammal receives between 0.5 μ g and 10 μ g of morphine per kg of body weight per day for a duration of more than one month (e.g., more than two, three, four, five, six, seven, eight, nine, or more months). In some cases, the compositions provided herein can be used to reduce the severity of a symptom of the disease or condition, or to prevent the development or onset of the disease or condition.

Other Embodiments

[0038] It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. A dietary supplement composition comprising morphine or morphine-6 β -glucuronide in an amount that results in less than 0.05 mg of said morphine or morphine-6 β -glucuronide being administered to a human per kg of body weight of said human.
2. The composition of claim 1, wherein said composition comprises less than 4.0 mg of said morphine or morphine-6 β -glucuronide.
3. The composition of claim 1, wherein said composition comprises less than 1.0 mg of said morphine or morphine-6 β -glucuronide.
4. The composition of claim 1, wherein said composition comprises a morphine precursor.
5. The composition of claim 1, wherein said composition is in the form of a tablet.
6. The composition of claim 1, wherein said composition comprises selenium.
7. The composition of claim 1, wherein said composition comprises L-arginine.
8. The composition of claim 1, wherein said composition comprises a calcium source.
9. The composition of claim 1, wherein said morphine or morphine-6 β -glucuronide is in an amount that results in less than 0.025 mg of said morphine or morphine-6 β -glucuronide being administered to said human per kg of body weight of said human.
10. The composition of claim 1, wherein said morphine or morphine-6 β -glucuronide is in an amount that results in less than 0.01 mg of said morphine or morphine-6 β -glucuronide being administered to said human per kg of body weight of said human.
11. The composition of claim 1, wherein said composition comprises morphine.
12. The composition of claim 1, wherein said composition comprises morphine and morphine-6 β -glucuronide.

13. The composition of claim 1, wherein said composition comprises thebaine, codeine, reticuline, norlaudanoline, salutaridine, dopamine, L-DOPA, tyrosine, tyramine, phenylalanine, 3,4 dihydroxyphenyl pyruvate, or dihydroxyphenyl acetaldehyde.

14. A dietary supplement composition comprising morphine and a compound selected from the group consisting of selenium and arginine.

1515. The composition of claim 14, wherein said composition comprises between 35 μ g and 700 μ g of morphine.

16. The composition of claim 14, wherein said composition comprises between 55 μ g and 300 μ g of selenium.

17. The composition of claim 14, wherein said composition comprises between 1 mg and 500 mg of arginine.

18. The composition of claim 14, wherein said composition comprises a calcium source.

19. The composition of claim 18, wherein said composition comprises between 1 g and 1.3 g of said calcium source.

20. The composition of claim 18, wherein said calcium source is calcium citrate.

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