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(54) **Title**: TREATING ALZHEIMER'S DISEASE AND OSTEOPOROSIS AND REDUCING AGING

(57) **Abstract**: Use of a composition for treating Alzheimer's disease, osteoporosis, sleep apnea, erectile dysfunction, McArdle disease, or a carbohydrate metabolism disorder, or for reducing aging or fatigue. The composition includes a first agent selected from the group consisting of an oxidative phosphorylation inhibitor, an ionophore, and an adenosine 5'- monophosphate-activated protein kinase activator; a second agent that possesses anti-inflammatory activity; and a third agent that possesses serotonin activity.

# Treating Alzheimer's Disease and Osteoporosis and Reducing Aging

## CROSS REFERENCE TO RELATED APPLICATION

Pursuant to 35 U.S.C. § 119(e), this application claims priority to U.S. Provisional Application Serial No. 61/160,533, filed March 16, 2009, the contents of which are hereby incorporated by reference.

## BACKGROUND

Alzheimer's disease is an age-related neurological disease characterized by memory loss and dementia. Osteoporosis, also an age-related disease, results in low bone mass and loss of bone tissue. There is a need to develop a new approach to treat these two age-related diseases or otherwise reduce aging.

## SUMMARY

In one aspect, the present invention features a method for treating Alzheimer's disease or osteoporosis by administering to a subject in need of the treatment a composition that includes (1) a first agent that can be an oxidative phosphorylation inhibitor, an ionophore, or an adenosine 5'-monophosphate-activated protein kinase (AMPK) activator, (2) a second agent that possesses anti-inflammatory activity, and (3) a third agent that possesses or maintains serotonin activity. The term "oxidative phosphorylation inhibitor" refers to a suitable agent that inhibits oxidative phosphorylation, such as oxidative phosphorylation uncouplers. An ionophore is a lipid-soluble molecule capable of transporting an ion across the lipid bilayer of cell membranes. An AMPK activator is an agent that activates AMPK to phosphorylate its substrates, e.g., acetyl-CoA carboxylase and malonyl-CoA decarboxylase. Examples of the first agent include metformin (e.g., metformin chloride), phenformin, buformin, ephedrine, thyroxine, salicylanilide, and salicylic acid. The second agent can be a suitable anti-inflammatory compound (e.g., non-steroidal anti-inflammatory compound). Examples include aspirin, diclofenac (e.g., diclofenac potassium or diclofenac sodium),

ibuprofen (e.g., dexibuprofen or dexibuprofen lysine), indomethacin, acetaminophen, nimesulide, and a COX-2 inhibitor (e.g., a nitric oxide-based COX-2 inhibitor). The third agent can be a compound possessing or maintaining at least one of serotonin's activities and, when used in combination with the first and second agents, effectively treats one or more of the target diseases of this invention. Examples include serotonin (e.g., serotonin sulfate, a serotonin creatinine sulfate complex, or serotonin hydrochloride) and a serotonin re-uptake inhibitor. A preferred composition contains metformin hydrochloride, aspirin, and a serotonin creatinine sulfate complex. The three agents mentioned above can treat a target disease via biological mechanisms other than those described therein. For example, metformin may treat a target disease (e.g., osteoporosis) via a mechanism other than inhibiting oxidative phosphorylation or activating AMPK.

The composition described above can contain 5-5,000 mg (e.g., 5-3,000 mg, 5-1,500 mg, or 5-1,000 mg) of the first agent, 1-5,000 mg (e.g., 1-3,000 mg, 1-1,000 mg, 1-500 mg, or 1-100 mg) of the second agent, and 0.1-1,000 mg (e.g., 0.1-100 mg, 0.1-50 mg, or 0.1-30 mg) of the third agent, or in quantities of the same ratio as that calculated based on the above amounts.

In another aspect, the present invention features a method for reducing aging or fatigue by administering the above-described composition to a subject in need of the treatment.

In yet another aspect, this invention features a method for treating sleep apnea, erectile dysfunction, McArdle disease, or a carbohydrate metabolism disorder by administering the above-described composition to a subject in need of the treatment.

Also within the scope of this invention is the use of the above-described composition for the manufacture of a medicament for any of the diseases and disorders mentioned above.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

## DETAILED DESCRIPTION

Disclosed herein is use of a composition for treating various diseases/disorders, e.g., Alzheimer's disease, osteoporosis, sleep apnea, erectile dysfunction, McArdle disease, or a carbohydrate metabolism disorder, or for reducing aging or fatigue. The composition includes at least three active agents which are described immediately below and also in US Patent Application Nos. 60/885,212 and 12/014,932.

The first agent can be an oxidative phosphorylation inhibitor, an ionophore, or an adenosine 5'-monophosphate-activated protein kinase (AMPK) activator. The first agent can include, in addition to those described above, 4,6-dinitro-o-cresol, uncoupling proteins (e.g., UCP1, UCP2, or UCP3), carbonyl cyanide p-(trifluoromethoxy)phenyl-hydrazone, carbonyl cyanide m-chlorophenyl-hydrazone, C5 gene products, dinitrophenol (e.g., 2,4-dinitrophenol), efrapeptin (A23871), guanethidine, chlorpromazine, amytal, secobarbital, rotenone, progesterone, antimycin A, naphthoquinone, 8-hydroxyquinoline, carbon monoxide, cyanides, azides (e.g., $NaN_3$), dicoumarin, bilirubin, bile pigment, ephedrine, hydrogen sulfide, tetraiodothyronine, quercetin, 2,4-bis(p-chloroanilino)pyrimidine, glyceraldehyde-3-phosphate dehydrogenase, oligomycin, tributyltin chloride, aurovertin, rutamycin, venturicidin, mercurials, dicyclohexylcarbdiimide, Dio-9, m-chlorophenyl-hydrazone mesoxalonitrile, ionomycin, calcium ionophores (e.g., A23187, NMDA, CA 1001, or enniatin B), compounds that increase the $Ca^{+2}$ concentration in mitochondria (e.g., atractyloside, bongkrekic acid, thapsigargin, amino acid neurotransmitters, glutamate, N-methyl-D-aspartic acid, carbachol, ionophores, inducers of potassium depolarization), apoptogens (i.e., compounds that induce apoptosis), valinomycin, gramicidin, nonactin, nigericin, lasalocid, and monensin. The first agent can be an AMPK activator (e.g., metfomin or phenformin, buformin, 5'-aminoimidazole-4-carboxyamide-ribonucleoside, thienopyridones, resveratrol, nootkatone, thiazole, or adiponectin).

The second agent can include steroidal anti-inflammatory drugs and non-steroidal anti-inflammatory drugs. Examples of steroidal anti-inflammatory drugs include glucocorticoids, hydrocortisone, cortisone, beclomethasone, dipropionate,

betamethasone, dexamethasone, prednisone, methylprednisolone, triamcinolone, fluocinolone acetonide, fludrocortisone, and beclometasone propionate. Examples of non-steroidal anti-inflammatory drugs (NSAIDs) include A183827, ABT963, aceclofenac, acemetacin, acetyl salicylic acid, AHR10037, alclofenac, alminoprofen, ampiroxicam, amtolmetin guacil, apazone, atliprofen methyl ester, AU8001, benoxaprofen, benzydamine flufenamate, bermoprofen, bezpiperylon, BF388, BF389, BIRL790, BMS347070, bromfenac, bucloxic acid, butibufen, BW755C, C53, C73, C85, carprofen, CBS1108, celecoxib, CHF2003, chlorobiphenyl, choline magnesium trisalicylate, CHX108, cimicoxib, cinnoxicam, clidanac, CLX1205, COX-2 inhibitors, CP331, CS502, CS706, D1367, darbufelone, deracoxib, dexketoprofen, DFP, DFU, diflunisal, DP155, DRF4367, E5110, E6087, eltenac, ER34122, esflurbiprofen, etoricoxib, F025, felbinac ethyl, fenbufen, fenclofenac, fenclozic acid, fenclozine, fenoprofen, fentiazac, feprazone, filenadol, flobufen, florifenine, flosulide, flubichin methanesulfonate, flufenamic acid, fluprofen, flurbiprofen, FPL62064, FR122047, FR123826, FR140423, FR188582, FS205397, furofenac, GR253035, GW406381, HAI105, HAI106, HCT2035, HCT6015, HGP12, HN3392, HP977, HX0835, HYAL AT2101, ibufenac, ibuproxam-beta-cyclodextrin, icodulinum, IDEA070, iguratimod, imrecoxib, indoprofen, IP751, isoxepac, isoxicam, KC764, ketoprofen, L652343, L745337, L748731, L752860, L761066, L768277, L776967, L783003, L784520, L791456, L804600, L818571, LAS33815, LAS34475, licofelone, LM 4108, lobuprofen, lornoxicam, lumiracoxib, mabuprofen, meclofenamic acid, meclofenamate sodium, mefenamic acid, meloxicam, mercaptoethylguanidine, mesoporphyrin, metoxibutropate, miroprofen, mofebutazone, mofezolac, MX1094, nabumetone, naproxen sodium, naproxen-sodium/metoclopramide, NCX1101, NCX284, NCX285, NCX4016, NCX4215, NCX530, niflumic acid, nitric oxide-based NSAIDs (NitroMed, Lexington, MA), nitrofenac, nitroflurbiprofen, nitronaproxen, NS398, ocimum sanctum oil, ONO3144, orpanoxin, oxaprozin, oxindanac, oxpinac, oxycodone/ibuprofen, oxyphenbutazone, P10294, P54, P8892, pamicogrel, parcetasal, parecoxib, PD138387, PD145246, PD164387, pelubiprofen, pemedolac, phenylbutazone, pirazolac, piroxicam,

piroxicam beta-cyclodextrin, piroxicam pivalate, pirprofen, pranoprofen, resveratrol, R-ketoprofen, R-ketorolac, rofecoxib, RP66364, RU43526, RU54808, RWJ63556, S19812, S2474, S33516, salicylsalicylic acid, satigrel, SC236, SC57666, SC58125, SC58451, SFPP, SKF105809, SKF86002, sodium salicylate, sudoxicam, sulfasalazine, sulindac, suprofen, SVT2016, T3788, TA60, talmetacin, talniflumate, tazofelone, tebufelone, tenidap, tenoxican, tepoxalin, tiaprofenic acid, tilmacoxib, tilnoprofen arbamel, tinoridine, tiopinac, tioxaprofen, tolfenamic acid, tolmetin, triflusal, tropesin, TY10222, TY10246, TY10474, UR8962, ursolic acid, valdecoxib, WAY120739, WY28342, WY41770, ximoprofen, YS134, zaltoprofen, zidometacin, and zomepirac.

The third agent includes serotonin and its functional equivalents. The functional equivalents of serotonin include serotonin metabolites (e.g., 5-hydroxyindoleacetic acid), serotonin transporter inhibitors (e.g., paroxetine, fluoxetine, fenfluramine, fluvoxamine, sertraline, imipramine, and those disclosed in WO 03/00663), serotonin receptor 2c modulators (e.g., BVT933, DPCA37215, IK264, PNU22394, WAY161503, R-1065, YM348, and those disclosed in U.S. Patent No. 3,914,250, WO 01/66548, WO 02/10169, WO 02/36596, WO 02/40456, WO 02/40457, WO 02/44152, WO 02/48124, WO 02/51844, and WO 03/033479), serotonin reuptake inhibitors (e.g., arylpyrrolidine compounds, phenylpiperazine compounds, benzylpiperidine compounds, piperidine compounds, tricyclic gamma-carbolines duloxetine compounds, pyrazinoquinoxaline compounds, pyridoindole compounds, piperidyindole compounds, milnacipran, citalopram, sertraline metabolite demethylsertraline, norfluoxetine, citalopram metabolite desmethylcitalopram, escitalopram, d,l-fenfluramine, femoxetine, ifoxetine, cyanodothiepin, litoxetine, dapoxetine, nefazodone, cericlamine, trazodone, mirtazapine, fluoxetine, fluvoxamine, indalpine, indeloxazine, milnacipran, paroxetine, sertraline, sibutramine, zimeldine, trazodone hydrochloride, dexfenfluramine, and those disclosed in U.S. Patent No. 6,365,633, WO 01/27060, and WO 01/162341), serotonin and noradrenaline reuptake inhibitors (e.g., venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, and clomipramine metabolite desmethylclomipramine), serotonin 1A receptor antagonists (e.g., arylpiperazine

compounds, azaheterocyclylmethyl derivatives of heterocycle-fused benzodioxans, or buspirone), serotonin 2A receptor antagonists (e.g., MDL100907 and fananserin), serotonin 2B or 2C receptor antagonists (e.g., pirazino(aza)indole compounds or serotonergic compounds), serotonin 6 receptor antagonists (e.g., 5-halo-tryptamine compounds), serotonin 7 receptor antagonists (e.g., 5-halo-tryptamine compounds or quinoline compounds), serotonin dopamine antagonists (e.g., olanzapine and ziperasidone), monoamine re-uptake inhibitors (e.g., amides), pyridazinone aldose reductase inhibitors (e.g., pyridazinone compounds), serotonergic agents, stimulants of serotonin receptors (e.g., ergoloid mesylate or pergolide mesylate), stimulants of serotonin synthesis (e.g., vitamin B1, vitamin B3, vitamin B6, biotin, S-adenosylmethionine, folic acid, ascorbic acid, magnesium, coenzyme Q10, or piracetam), or serotonin agonists (e.g., fenfluramine).

The first, second, and third agents can also be salts, prodrugs, or solvates of the above-described compounds. A salt can be formed between an anion and a positively charged group (e.g., amino) of an agent. Suitable anions include chloride, bromide, iodide, sulfate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, acetate, chlorophenyoxyacetate, malate, tosylate, tartrate, fumarate, glutamate, glucuronate, lactate, glutarate, benzoate, embonate, glycolate, pamoate, aspartate, parachlorophenoxyisobutyrate, formate, succinate, cyclohexanecarboxylate, hexanoate, octonoate, decanoate, hexadecanoate, octodecanoate, benzenesulphonate, trimethoxybenzoate, paratoluenesulphonate, adamantanecarboxylate, glycoxylate, pyrrolidonecarboxylate, naphthalenesulphonate, 1-glucosephosphate, sulphite, dithionate, and maleate. Likewise, a salt can also be formed between a cation and a negatively charged group (e.g., carboxylate) of an agent. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. The agents also include salts containing quaternary nitrogen atoms. Examples of prodrugs include esters and other pharmaceutically acceptable derivatives, which, upon administration to a subject, are capable of being transformed into active compounds. A solvate refers to a complex formed between an active

compound and a pharmaceutically acceptable solvent. Examples of pharmaceutically acceptable solvents include water, ethanol, isopropanol, ethyl acetate, acetic acid, and ethanolamine.

The three active agents mentioned above are known drugs and are readily available to the public. Some can be purchased from chemical companies, such as Sigma-Aldrich, St. Louis, MO. Regimens for administering these drug compounds are well known and, if necessary, can be easily re-established.

In addition to the three required agents, the composition used in the methods of this invention can include one or more additional active ingredients.

To practice the method of the present invention, an effective amount of the above-described composition can be administered to a subject in need parenterally, orally, buccally, nasally, topically, or rectally. "An effective amount" as used herein refers to the amount of each active agent required to confer a therapeutic effect on the subject, either alone or in combination with one or more other active agents.

Effective doses will vary, as recognized by those skilled in the art, depending on the type or degree of the disorder to be treated; the subject's size, weight, age, and sex; the route of administration; the excipient usage; and the possible co-usage with another therapeutic treatment. The daily dose of the compositions described above can be 5-5,000 mg (e.g., 10-2,500 or 10-3,000 mg) of the first agent, 1-5,000 mg (e.g., 2-1,000 or 2-3,000 mg) of the second agent, and 0.1-1,000 mg (e.g., 1-50 mg) of the third agent.

A subject in need can be identified by a health care professional based on results from a suitable diagnostic method. The term "treating" or "treatment" used herein refers to administering an above-described compositions to a subject, who has a disease mentioned above, a symptom of such a disease, or a predisposition towards such a disease, with the purpose of conferring a therapeutic effect, e.g., to cure, relieve, alter, affect, ameliorate, or prevent the disease, the symptom of it, or the predisposition towards it. The term "reducing fatigue" used herein refers to lessening, ameliorating, or relieving one or more symptoms of fatigue (e.g., low energy, poor endurance, and attention deficits) in a subject. "Reducing aging" refers to lessening, ameliorating, or relieving the

deleterious effects of aging (e.g., low vigor, memory loss, weakened vision or hearing, and joint pain) in a subject.

The composition described herein can include a pharmaceutically acceptable carrier to form a pharmaceutical composition. The carrier must be "acceptable" in the sense that it is compatible with the active ingredients of the composition (and preferably, capable of stabilizing the active ingredients) and not deleterious to the subject to be treated. Conventional methods, known to those of ordinary skill in the art of medicine, can be used to administer the pharmaceutical compositions described herein to a subject.

A sterile injectable composition can be a solution or suspension in a non-toxic parenterally acceptable diluent or solvent. The term "parenterally" as used herein refers to subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional, or intracranial injection, as well as any suitable infusion technique. Among the acceptable vehicles and solvents that can be used are mannitol, water, 1,3-butanediol, Ringer's solution, and isotonic sodium chloride solution. In addition, fixed oils are conventionally employed as a solvent or suspending medium (e.g., synthetic mono- or diglycerides). Fatty acids, such as oleic acid and its glyceride derivatives, are useful in the preparation of injectables, as are natural pharmaceutically acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions can also contain a long chain alcohol diluent or dispersant, carboxymethyl cellulose, or similar dispersing agents. Other commonly used surfactants such as Tweens or Spans or other similar emulsifying agents or bioavailability enhancers, which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms can also be used for the purpose of formulation.

A composition for oral administration can be any orally acceptable dosage form including capsules, powders, tablets, emulsions and aqueous suspensions, dispersions, and solutions. In the case of tablets or capsules, commonly used carriers or diluents include lactose and corn starch. Lubricating agents, such as magnesium stearate, can be added. When aqueous suspensions or emulsions are administered orally, the active

ingredient can be suspended or dissolved in an oily phase combined with emulsifying or suspending agents. If desired, certain sweetening, flavoring, or coloring agents can be added.

A nasal aerosol or inhalation composition can be prepared according to techniques well known in the art of pharmaceutical formulation. For example, such a composition can be prepared as a solution in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

A composition for topical administration can be prepared in the form of an ointment, a gel, a plaster, an emulsion, a lotion, a foam, a cream of a mixed phase or amphiphilic emulsion system (oil/water-water/oil mixed phase), a liposome, a transfersome, a paste, or a powder.

Any of the compositions described above can also be administered in the form of suppositories for rectal administration. It can also be designed so that the composition is released in the intestine. For example, the composition is confined in a solid sub-unit or a capsule compartment that has a matrix or a wall or a closure comprising an enteric polymer which dissolves or disperses at the pH of the small or large intestine to release the drug substance in the intestine. Suitable enteric polymers have been described above and also in U.S. Patent No. 5,705,189.

A composition can be included in a drink or food product. Examples include tea (e.g., a tea drink and the contents of a tea bag), soft drinks, juice (e.g., a fruit extract and a juice drink), milk, coffee, cookies, cereals, candies, and snack bars.

The compositions described above can be preliminarily screened for their efficacy in treating an above-described disease or disorder by an *in vitro* assay and then confirmed by animal experiments and clinical trials. Other methods will also be apparent to those of ordinary skill in the art.

Without further elaboration, it is believed that one skilled in the art can, based on the description herein, utilize the present invention to its fullest extent. All of the

publications cited herein (including patents and patent applications) are incorporated by reference in their entirety.

## OTHER EMBODIMENTS

All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features.

From the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. Thus, other embodiments are also within the scope of the following claims.

**WHAT IS CLAIMED IS:**

1. A method for treating a disease, comprising administrating to a subject in need thereof an effective amount of a composition containing:

a first agent selected from the group consisting of an oxidative phosphorylation inhibitor, an ionophore, and an adenosine 5'-monophosphate-activated protein kinase (AMPK) activator;

a second agent that possesses anti-inflammatory activity; and

a third agent that possesses or maintains serotonin activity;

wherein the disease is Alzheimer's disease, osteoporosis, sleep apnea, erectile dysfunction, McArdle disease, or a carbohydrate metabolism disorder.

2. The method of claim 1, wherein the first agent is metformin, phenformin, buformin, ephedrine, thyroxine, salicylanilide, or salicylic acid.

3. The method of claim 2, wherein the first agent is metformin hydrochloride.

4. The method of claim 1, wherein the second agent is a non-steroidal anti-inflammatory compound.

5. The method of claim 1, wherein the second agent is aspirin, diclofenac, ibuprofen, indomethacin, acetaminophen, nimesulide, or a COX-2 inhibitor.

6. The method of claim 5, wherein the second agent is aspirin.

7. The method of claim 1, wherein the third agent is serotonin or a serotonin re-uptake inhibitor.

8. The method of claim 7, wherein the third agent is serotonin sulfate, a serotonin creatinine sulfate complex, or serotonin hydrochloride.

9. The method of claim 1, wherein the composition contains 5-5,000 mg of the first agent, 1-5,000 mg of the second agent, and 0.1-1,000 mg of the third agent; or in quantities of the same ratio.

10. The method of claim 9, wherein the composition contains 5-1,500 mg of the first agent, 1-1,000 mg of the second agent, and 0.1-100 mg of the third agent; or in quantities of the same ratio.

11. The method of claim 10, wherein the composition contains 5-1,000 mg of the first agent, 1-500 mg of the second agent, and 0.1-50 mg of the third agent; or in quantities of the same ratio.

12. The method of claim 1, wherein the composition contains metformin hydrochloride, aspirin, and a serotonin creatinine sulfate complex.

13. The method of claim 12, wherein the composition contains 5-5,000 mg of metformin hydrochloride, 1-5,000 mg of aspirin, and 0.1-1,000 mg of the serotonin creatinine sulfate complex; or in quantities of the same ratio.

14. The method of claim 13, wherein the composition contains 5-1,500 mg of metformin hydrochloride, 1-1,000 mg of aspirin, and 0.1-100 mg of the serotonin creatinine sulfate complex; or in quantities of the same ratio.

15. The method of claim 14, wherein the composition contains 5-1,000 mg of metformin hydrochloride, 1-500 mg of aspirin, and 0.1-50 mg of the serotonin creatinine sulfate complex; or in quantities of the same ratio.

16. The method of claim 1, wherein the composition further comprising a pharmaceutically acceptable carrier.

17. The method of claim 1, wherein the composition contains the first, second, and third agents as the only active ingredients.

18. The method of claim 1, wherein the first agent is an AMPK activator.

19. The method of claim 18, wherein the composition contains the first, second, and third agents as the only active ingredients.

20 The method of claim 18, wherein the AMPK activator is selected from the group consisting of metformin, phenformin, buformin, 5'-aminoimidazole-4-carboxyamide-ribonucleoside, thienopyridones, resveratrol, nootkatone, thiazole, and adiponectin.

21. The method of claim 1, wherein the first agent is an oxidative phosphorylation inhibitor or ionophore.

22. A method for reducing aging or fatigue, comprising administrating to a subject in need thereof an effective amount of a composition containing:

a first agent selected from the group consisting of an oxidative phosphorylation inhibitor, an ionophore, and an AMPK activator;

a second agent that possesses anti-inflammatory activity; and

a third agent that possesses or maintains serotonin activity.

23. The method of claim 22, wherein the first agent is metformin, phenformin, buformin, ephedrine, thyroxine, salicylanilide, or salicylic acid.

24. The method of claim 23, wherein the first agent is metformin hydrochloride.

25. The method of claim 22, wherein the second agent is a non-steroidal anti-inflammatory compound.

26. The method of claim 22, wherein the second agent is aspirin, diclofenac, ibuprofen, indomethacin, acetaminophen, nimesulide, or a COX-2 inhibitor.

27. The method of claim 26, wherein the second agent is aspirin.

28. The method of claim 22, wherein the third agent is serotonin or a serotonin re-uptake inhibitor.

29. The method of claim 28, wherein the third agent is serotonin sulfate, a serotonin creatinine sulfate complex, or serotonin hydrochloride.

30. The method of claim 22, wherein the composition contains 5-5,000 mg of the first agent, 1-5,000 mg of the second agent, and 0.1-1,000 mg of the third agent; or in quantities of the same ratio.

31. The method of claim 30, wherein the composition contains 5-1,500 mg of the first agent, 1-1,000 mg of the second agent, and 0.1-100 mg of the third agent; or in quantities of the same ratio.

32. The method of claim 31, wherein the composition contains 5-1,000 mg of the first agent, 1-500 mg of the second agent, and 0.1-50 mg of the third agent; or in quantities of the same ratio.

33. The method of claim 22, wherein the composition contains metformin hydrochloride, aspirin, and a serotonin creatinine sulfate complex.

34. The method of claim 33, wherein the composition contains 5-5,000 mg of metformin hydrochloride, 1-5,000 mg of aspirin, and 0.1-1,000 mg of the serotonin creatinine sulfate complex; or in quantities of the same ratio.

35. The method of claim 34, wherein the composition contains 5-1,500 mg of metformin hydrochloride, 1-1,000 mg of aspirin, and 0.1-100 mg of the serotonin creatinine sulfate complex; or in quantities of the same ratio.

36. The method of claim 35, wherein the composition contains 5-1,000 mg of metformin hydrochloride, 1-500 mg of aspirin, and 0.1-50 mg the serotonin creatinine sulfate complex; or in quantities of the same ratio.

37. The method of claim 22, wherein the composition further comprising a pharmaceutically acceptable carrier.

38. The method of claim 22, wherein the composition contains the first, second, and third agents as the only active ingredients.

39. The method of claim 22, wherein the first agent is an AMPK activator.

40. The method of claim 39, wherein the composition contains the first, second, and third agents as the only active ingredients.

41. The method of claim 39, wherein the AMPK activator is selected from the group consisting of metformin, phenformin, buformin, 5'-aminoimidazole-4-carboxyamide-ribonucleoside, thienopyridones, resveratrol, nootkatone, thiazole, and adiponectin.

42. The method of claim 22, wherein the first agent is an oxidative phosphorylation inhibitor or ionophore.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/27330

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/20, 9/22, 9/24 (2010.01)
USPC - 424/464, 424/468, 424/472
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)
USPC - 424/464, 424/468, 424/472

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/224.5, 514/250, 514/344, 514/477, 514/635 (see keywords below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); Medline, Google:
Search terms: ionophore, AMP, AMPK, metformin hydrochloride, HCl, aspirin, serotonin creatinine sulfate complex, 5-HT, NSAID, diclofenac, ibuprofen, indomethacin, acetaminophen , nimesulide, COX-2 inhibitor, phenformin, buformin, Alzheimer's, sleep apnea

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>---<br>Y | US 2007/0149466 A1 (MILBURN et al.) 28 June 2007 (28.06.2007) Abstract; para [0004], [0036], [0086], [1101], [1113], [1115], [1143], [1163], [1179], [1181], [1256]-[1258], [1267], [1275], [1298], [1301], [1435], [1484] | 1-2, 4-7, 16-20, 22-23, 25 -28, 37-41<br>---<br>3, 8-15, 21, 24, 29-36, 42 |
| Y | US 2007/0191351 A1 (COWEN et al.) 16 August 2007 (16.08.2007) para [0367], [0372], [0497]-[0498], [0507]; Table 1 | 3, 9-15, 24, 30-36 |
| Y | US 2007/0142291 A1 (Lin) 21 June 2007 (21.06.2007) para [0091], [0095], [0169] | 8-15, 29-36 |
| Y | US 2002/0045621 A1 (REINER et al.) 18 April 2002 (18.04.2002) Abstract; para [0010] | 21, 42 |
| A | SUDLOW et al. Cyclic AMP Levels, Adenylyl Cyclase Activity, and Their Stimulation by Serotonin Quantified in Intact Neurons. J Gen Physiol., 1997, Vol 110(3), pp 243-255; pg 244, col 1, last para: 5-HT (serotonin creatinine sulfate complex; Sigma Chemical Co.) | 1-42 |
| A | GRECO et al. Leptin regulates Tau phosphorylation and Amyloid through AMPK in Neuronal Cells. Biochem Biophys Res Commun., 2009 February, Vol 380(1): 98-104. | 1-42 |
| A | US 2004/0167114 A1 (Fliss) 26 August 2004 (26.08.2004) entire document | 1-42 |

☐ Further documents are listed in the continuation of Box C. ☐

* 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 April 2010 (18.04.2010) | 06 MAY 2010 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

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