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Canadian Intellectual Property Office

CA 2925318 C 2021/01/19

(11)(21) 2 925 318

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2014/09/27
(87) Date publication PCT/PCT Publication Date: 2015/04/02
(45) Date de délivrance/Issue Date: 2021/01/19
(85) Entrée phase nationale/National Entry: 2016/03/23
(86) N° demande PCT/PCT Application No.: US 2014/057923
(87) N° publication PCT/PCT Publication No.: 2015/048590
(30) Priorités/Priorities: 2013/09/27 (US61/883,433); 2014/09/06 (US62/046,953); 2014/09/07 (US62/047,055)

(51) Cl.Int./Int.Cl. *A61K 31/353* (2006.01), *A61K 31/352* (2006.01), *A61K 36/28* (2006.01), *A61K 36/36* (2006.01)

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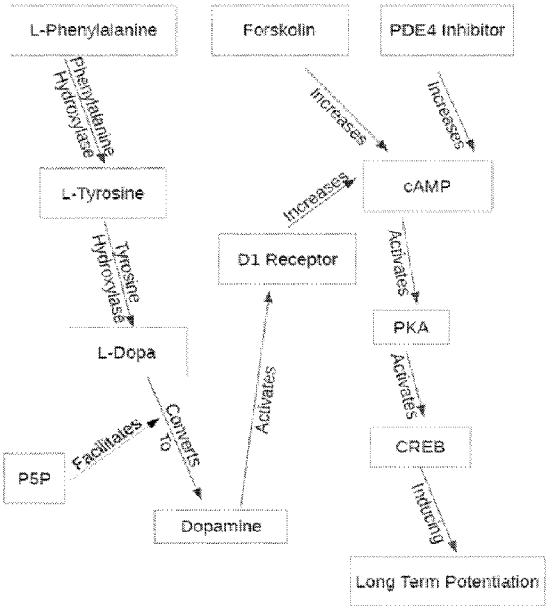
(54) Titre : COMPOSITION NUTRACEUTIQUE PERMETTANT L'INHIBITION DE PDE4, UN MEILLEUR METABOLISME DE LA DOPAMINE ET UNE POTENTIALISATION A LONG TERME

(54) Title: NUTRACEUTICAL COMPOSITION FOR PDE4 INHIBITION, ENHANCED DOPAMINE METABOLISM AND LONG TERM POTENTIATION



(57) Abrégé/Abstract:
A nootropic combination for increasing cognitive functioning. The combination includes a phosphodiesterase 4 inhibitor and a cyclic adenosine monophosphate increasing agent. In some versions, the phosphodiesterase inhibitor is a flavonoid such as luteolin, and the cyclic adenosine monophosphate increasing agent is a labdane diterpene such as forskolin. The combination can also include one or a combination of L-phenylalanine, L-carnitine, acetyl-L-carnitine, and vitamin B6. In some versions, plant extracts, such as artichoke extract can be used as a source of the PDE4 inhibitor. Methods of using the combination to increase cognitive functioning are also included.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 April 2015 (02.04.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/048590 A1

(51) International Patent Classification:
A61K 38/24 (2006.01)

(21) International Application Number:
PCT/US2014/057923

(22) International Filing Date:
27 September 2014 (27.09.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/883,433 27 September 2013 (27.09.2013) US
62/046,953 6 September 2014 (06.09.2014) US
62/047,055 7 September 2014 (07.09.2014) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: NUTRACEUTICAL COMPOSITON FOR PDE4 INHIBITION, ENHANCED DOPAMINE METABOLISM AND LONG TERM POTENTIATION

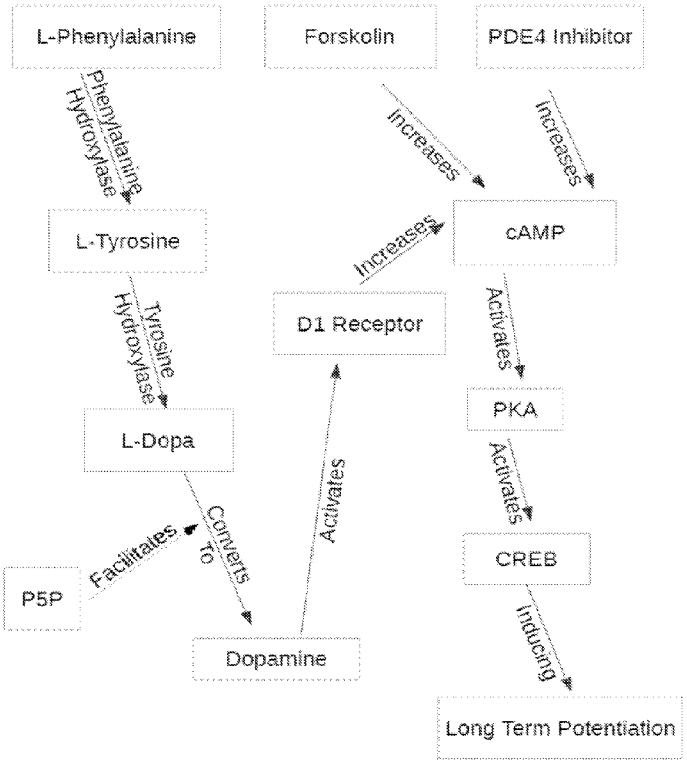

FIG. 2

(57) Abstract: A nootropic combination for increasing cognitive functioning. The combination includes a phosphodiesterase 4 inhibitor and a cyclic adenosine monophosphate increasing agent. In some versions, the phosphodiesterase inhibitor is a flavonoid such as luteolin, and the cyclic adenosine monophosphate increasing agent is a labdane diterpene such as forskolin. The combination can also include one or a combination of L-phenylalanine, L-carnitine, acetyl-L-carnitine, and vitamin B6. In some versions, plant extracts, such as artichoke extract can be used as a source of the PDE4 inhibitor. Methods of using the combination to increase cognitive functioning are also included.

WO 2015/048590 A1

WO 2015/048590 A1

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

NUTRACEUTICAL COMPOSITION FOR PDE4 INHIBITION, ENHANCED DOPAMINE METABOLISM AND LONG TERM POTENTIATION

BACKGROUND

FIELD OF THE INVENTION

[0002] The invention relates to nutritional supplements and methods of use thereof.

RELATED ART

[0003] There has been a significant amount of research into the benefits of PDE4 inhibitors. In animal models synthetic PDE4 inhibitors have been shown to enhance object memory, and to reverse deficits to learning, working and reference memory induced by scopolamine, NMDA antagonists and under conditions of depleted tryptophan and serotonin (references 1-6).

[0004] Several articles have been published in the literature that discuss the potential of PDE4 inhibitors for cognitive enhancement in those with Alzheimer's disease, dementia, and other neurodegenerative conditions. PDE4 inhibitors have also provided improvements in performance to aged animal brains and have been shown, in animal models, to provide protection from damage from certain types of ischemic strokes. Experimental new PDE4 inhibitors are regularly being developed with the intention of treating long-term memory loss and mild cognitive impairment. Unfortunately, one of the most studied PDE4 inhibitors, rolipram, has had the side effect of emesis (vomiting) at low doses. Much work remains for developing memory enhancing PDE4 inhibitors with better side-effect profiles than rolipram (references 7-13).

SUMMARY

[0005] In one aspect, a nootropic combination for increasing cognitive functioning in a human, or other mammal, is provided. The combination includes effective amounts of a phosphodiesterase 4 (PDE4) inhibitor and a cyclic adenosine monophosphate (cAMP) increasing agent. In embodiments of the nootropic combination: a) the combination includes an effective amount of acetyl-L-carnitine or a physiologically acceptable salt thereof; b) the PDE4 inhibitor includes a flavonoid, an alkaloid, or a stilbenoid, or any combination thereof; c) the PDE4 inhibitor includes luteolin, quercetin, hesperidin, biochanin A, genistein, mesembrenone, or resveratrol, or a glycoside thereof, a physiologically acceptable salt thereof, or any combination thereof; d) the cAMP increasing agent is a labdane diterpene; e) the cAMP increasing agent is forskolin, a glycoside thereof, or a physiologically acceptable salt thereof; f) when the cAMP increasing agent is forskolin, the forskolin is in a range of about 0.9 mg to about 4.4 mg per daily dose of the combination; g) when the cAMP increasing agent is forskolin, the ratio of acetyl-L-carnitine to forskolin is about 200:1 by weight; h) the combination further includes effective amounts of one or any combination of components selected from the group consisting of L-phenylalanine, L-carnitine, acetyl-L-carnitine, vitamin B6, and a physiologically acceptable salt thereof; i) the PDE4 inhibitor, the cAMP increasing agent, or both, can be added to the combination in the form of one or more plant extracts; j) the combination can be a nutritional supplement; or k) any combination of a) – j).

[0006] In another aspect, a nutritional supplement for increasing cognitive functioning in a human, or other mammal, is provided. The nutritional supplement includes effective amounts of forskolin and acetyl-L-carnitine, and further includes a plant extract including an effective amount of a PDE4 inhibitor. In embodiments of the nutritional supplement: a) the ratio of acetyl-L-carnitine to forskolin is about 200:1 by weight; b) the forskolin is in a range of about 0.9 mg to about 4.4 mg per daily dose of the supplement; c) the PDE4 inhibitor includes a flavonoid, an alkaloid, or a stilbenoid, or any combination thereof; d) the PDE4 inhibitor includes luteolin, quercetin, hesperidin, biochanin A, genistein, mesembrenone, or resveratrol, or a

glycoside thereof, a physiologically acceptable salt thereof, or any combination thereof; e) the forskolin can be added to the nutritional supplement in the form of a Coleus forskohlii extract; or f) any combination of a) – e).

[0007] In a further embodiment, a method of increasing cognitive functioning in a human or other mammalian subject in need thereof is provided. The method includes administering any of the nootropic combinations for increasing cognitive functioning described in this application, including any of the nutritional supplements. Thus, in some embodiments, the method includes administering to the subject a nutritional supplement that includes effective amounts of a cyclic adenosine monophosphate (cAMP) increasing agent and acetyl-L-carnitine, and further includes a plant extract that includes an effective amount of a PDE4 inhibitor. In embodiments of the method: a) the cAMP increasing agent is forskolin, a glycoside thereof, or a physiologically acceptable salt thereof; b) the PDE4 inhibitor includes a flavonoid, an alkaloid, or a stilbenoid, or any combination thereof; c) the PDE4 inhibitor includes luteolin, quercetin, hesperidin, biochanin A, genistein, mesembrenone, or resveratrol, or a glycoside thereof, a physiologically acceptable salt thereof, or any combination thereof; d) the cAMP increasing agent is forskolin; e) when the nootropic combination includes forskolin, the ratio of acetyl-L-carnitine to forskolin is about 200:1 by weight; or f) when the nootropic combination includes forskolin, the forskolin can be added to the nutritional supplement in the form of a Coleus forskohlii extract; or g) any combination of a)– f).

[0008] In another aspect, a nutritional supplement for increasing cognitive functioning in a human, or other mammal, is provided. The nutritional supplement includes effective amounts of a phosphodiesterase 4 (PDE4) inhibiting flavonoid and a cyclic adenosine monophosphate (cAMP) increasing labdane diterpene. In some embodiments: a) the flavonoid can be luteolin, a glycoside thereof, or a physiologically acceptable salt thereof; b) the nutritional supplement can include artichoke extract as a source of the flavonoid; c) the labdane diterpene can be forskolin, a glycoside thereof, or a physiologically acceptable salt thereof; d) the nutritional supplement can further include effective amounts of one or any

combination of components selected from the group consisting of L-phenylalanine, L-carnitine, acetyl-L-carnitine, vitamin B6, and piperine, and a physiologically acceptable salt thereof; or e) any combination of a) – d).

[0009] In some embodiments, the nutritional supplement includes in daily dosage form about 202.5 mg to about 990 mg of artichoke extract standardized to 5% cynarin, and about 0.9 mg to about 4.4 mg of forskolin. In some embodiments: a) the nutritional supplement further includes one or any combination of components selected from the group consisting of about 180 mg to about 880 mg of acetyl-L-carnitine per daily dosage of the nutritional supplement, about 112.5 mg to about 550 mg of L-phenylalanine per daily dosage of the nutritional supplement, about 2.25 mg to about 11 mg of vitamin B6 per daily dosage of the nutritional supplement, and about 10 mg to about 20 mg of piperine per daily dosage of the nutritional supplement; b) in embodiments containing acetyl-L-carnitine, the ratio of acetyl-L-carnitine to forskolin can be about 200:1 by weight; c) particular embodiments of the nutritional supplement can include about 180 mg to about 880 mg of acetyl-L-carnitine per daily dosage of the nutritional supplement; about 112.5 mg to about 550 mg of L-phenylalanine per daily dosage of the nutritional supplement; about 2.25 mg to about 11 mg of vitamin B6 per daily dosage of the nutritional supplement; or d) any combination of a) – c). In a particular embodiment, the nutritional supplement comprises, per daily dosage: about 900 mg of artichoke extract standardized to 5% cynarin; about 4 mg of forskolin; about 750 mg of acetyl-L-carnitine; about 500 mg of L-phenylalanine; and about 5 mg vitamin B6.

[0010] In a further aspect, a method of increasing cognitive functioning in a human or other mammalian subject in need thereof is provided. The method includes administering to the subject a nutritional supplement that includes therapeutically effective amounts of a phosphodiesterase 4 (PDE4) inhibiting flavonoid and a cyclic adenosine monophosphate (cAMP) increasing labdane diterpene. In some embodiments: a) the flavonoid can be luteolin, a glycoside thereof, or a physiologically acceptable salt thereof; b) the nutritional supplement can include artichoke extract as a source of the flavonoid; c) the labdane diterpene can be

forskolin, a glycoside thereof, or a physiologically acceptable salt thereof; d) the nutritional supplement can further include therapeutically effective amounts of one or any combination of components selected from the group consisting of L-phenylalanine, L-carnitine, acetyl-L-carnitine, vitamin B6, and piperine, and a physiologically acceptable salt thereof; or e) any combination of a) – d).

[0011] In some embodiments, the method includes administering to the subject a nutritional supplement that includes in daily dosage form about 202.5 mg to about 990 mg of artichoke extract standardized to 5% cynarin, and about 0.9 mg to about 4.4 mg of forskolin. In some embodiments: a) the nutritional supplement further includes one or any combination of components selected from the group consisting of about 180 mg to about 880 mg of acetyl-L-carnitine per daily dosage of the nutritional supplement, about 112.5 mg to about 550 mg of L-phenylalanine per daily dosage of the nutritional supplement, about 2.25 mg to about 11 mg of vitamin B6 per daily dosage of the nutritional supplement, and about 10 mg to about 20 mg of piperine per daily dosage of the nutritional supplement; b) in embodiments containing acetyl-L-carnitine, the ratio of acetyl-L-carnitine to forskolin can be about 200:1 by weight; c) particular embodiments of the nutritional supplement can include about 180 mg to about 880 mg of acetyl-L-carnitine per daily dosage of the nutritional supplement; about 112.5 mg to about 550 mg of L-phenylalanine per daily dosage of the nutritional supplement; and about 2.25 mg to about 11 mg of vitamin B6 per daily dosage of the nutritional supplement; or d) any combination of a) – c). In a particular embodiment, the nutritional supplement comprises, per daily dosage: about 900 mg of artichoke extract standardized to 5% cynarin; about 4 mg of forskolin; about 750 mg of acetyl-L-carnitine; about 500 mg of L-phenylalanine; and about 5 mg vitamin B6.

[0012] In a further aspect, a nutritional supplement for increasing cognitive functioning in a human, or other mammal, is provided. The nutritional supplement includes an effective amount of means for inhibiting phosphodiesterase 4 (PDE4), an effective amount of means for increasing cyclic adenosine monophosphate (cAMP), and an effective amount of means for increasing acetylcholine. In some embodiments, the nutritional supplement also includes effective amounts of one or any combination

of components selected from the group consisting of L-phenylalanine, L-carnitine, vitamin B6, and piperine.

[0013] In another aspect, a method of increasing cognitive functioning in a human or other mammalian subject in need thereof is provided. The method includes administering to the subject a nutritional supplement that includes therapeutically effective amounts of means for inhibiting phosphodiesterase 4 (PDE4), means for increasing cyclic adenosine monophosphate (cAMP), and means for increasing acetylcholine. In some embodiments, the nutritional supplement also includes effective amounts of one or any combination of components selected from the group consisting of L-phenylalanine, L-carnitine, vitamin B6, and piperine.

[0014] In another aspect, a nutritional supplement for increasing cognitive functioning in a human, or other mammal, is provided. The nutritional supplement includes effective amounts of mesembrenone, a glycoside thereof, or a physiologically acceptable salt thereof, and a cyclic adenosine monophosphate (cAMP) increasing labdane diterpene is provided. In some embodiments: a) the labdane diterpene can be forskolin, a glycoside thereof, or a physiologically acceptable salt thereof; b) the nutritional supplement can further include effective amounts of one or any combination of components selected from the group consisting of L-phenylalanine, L-carnitine, acetyl-L-carnitine, vitamin B6, and piperine, and a physiologically acceptable salt thereof; or c) any combination of a) – b).

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] For a more complete understanding of the present invention, reference is now made to the following descriptions taken in conjunction with the accompanying drawings, in which:

[0016] Figure 1 is a panel showing the chemical structures of various compounds; and

[0017] Figure 2 is a diagram showing suggested interactions of components of a nutritional supplement.

DETAILED DESCRIPTION

[0019] In one aspect, a nootropic combination for increasing cognitive functioning is provided, comprising effective amounts of a phosphodiesterase 4 (PDE4) inhibitor and a cyclic adenosine monophosphate (cAMP) increasing agent. PDE4 inhibitors and cAMP increasing agents can be natural or synthetic. Examples of PDE4 inhibitors include, but are not limited to, theophylline, isobutylmethylxanthine, rolipram, and benzamide derivatives of rolipram. PDE4 inhibitors found in plant extracts include, but are not limited to, PDE4 inhibiting flavonoids, alkaloids, and stilbenoids. Phosphodiesterase 4 is a member of a family of phosphodiesterase enzymes that degrade 3',5'-cyclic nucleotides including cAMP. In humans, phosphodiesterase 4 is abundant in brain tissue.

[0020] A flavonoid is a plant compound having a three ring backbone structure, including flavonoid glycosides. Luteolin, shown in Fig. 1A, is a flavonoid that can inhibit 3',5'-cyclic nucleotide phosphodiesterase enzymes, including PDE4. Luteolin is found in certain plants such as artichoke (Cynara scolymus), and artichoke extracts containing luteolin are commercially available. An artichoke extract can be standardized based upon the amount of cynarin, a caffeoylquinic acid present in artichoke. Other examples of PDE4 inhibiting flavonoids include, but are not limited to, quercetin (Fig. 1B) found in many plants including onion (Allium cepa), hesperidin (Fig. 1C) found in citrus plants, biochanin A (Fig. 1D) found in many plants including red clover (Trifoleum pretense), and genistein (Fig. 1E) found in soy beans. Extracts containing these plant compounds are commercially available. A non-limiting example of a PDE4 inhibiting alkaloid is mesembrenone shown in Fig. 1F. Mesembrenone is found in the succulent herb Sceletium tortuosum, also known as

kanna, and kanna extracts containing mesembrenone are commercially available. Stilbenoids are stilbene derivatives having a C6-C2-C6 structure. A non-limiting example of a PDE4 inhibiting stilbenoid is resveratrol (Fig. 1G) found in grapes and other fruits. Grape extracts containing resveratrol are commercially available. Glycosides of luteolin, quercetin, hesperidin, biochanin A, genistein, mesembrenone, and resveratrol may also act as PDE4 inhibitors (references 46-51). PDE inhibitors are commercially available as purified components, for example, from Sigma-Aldrich Corp., St. Louis, Missouri, USA, and/or as plant extracts from, for example, Now Foods, Bloomingdale, Illinois, USA, Jarrow Formulas, Los Angeles, California, USA, Source Naturals, Scotts Valley, California, USA, Neutraceutical, Park City, Utah, USA, Swanson Health Products, Fargo, North Dakota, USA, Planetary Herbals, Soquel, California, USA, and Better Body Sports, Ventura, California, USA.

[0021] Agents that increase intracellular cAMP levels include, but are not limited to, hormones and other bioactive agents such as dopamine, isoproterenol, adenosine, carbacyclin, endothelin, epinephrine, glucagon, parathyroid hormone, prostaglandin, vasopressin, cholera toxin, pertussis toxin, and cAMP increasing labdane diterpenes. A labdane diterpene is a natural product having a bicyclic diterpene backbone structure. Forskolin, shown in Fig. 1H, is a labdane diterpene that can stimulate the enzyme adenylyl cyclase, which catalyzes the conversion of ATP to cAMP. Forskolin is found in the plant Coleus forskohlii, and Coleus forskohlii extracts containing forskolin are commercially available. Purified forskolin preparations are also commercially available. Synthetic and natural derivatives of forskolin, including but not limited to forskolin glycosides, 7-deacetylforskolin and 6-aminoacylforskolins, can stimulate adenylyl cyclase activity. In some embodiments, forskolin in the amount of about 1 to about 4 mg per daily dosage, or an amount of a forskolin derivative or other cAMP increasing agent producing an effect on cognitive functioning equivalent to about 1 to about 4 mg of forskolin per daily dosage, is included in the nootropic combination.

[0022] In some embodiments, the PDE4 inhibitor, the cAMP increasing agent, or both, can be added to the nootropic combination in the form of one or more plant

extracts. For example, a nootropic combination can contain artichoke extract as a source of the PDE4 inhibitor luteolin and Coleus forskohlii extract as the source of forskolin. Plant extracts that can be used as sources of PDE4 inhibitors include, but are not limited to, onion, citrus, red clover and soy bean, or any combination thereof, as described above.

[0023] Cyclic AMP appears to play a role in long term potentiation and other nervous system processes. Combining an adenylyl cyclase stimulator with a PDE4 inhibitor can lead to enhanced cAMP production with decreased cAMP degradation, resulting in increased levels of cAMP in the body and increased intracellular cAMP levels. Thus, embodiments of the nootropic combination, including nutritional supplements, can affect nervous system functioning when administered to a subject.

[0024] In some embodiments, the nootropic combination includes physiologically acceptable or pharmaceutically acceptable salts of a PDE4 inhibitor, a cAMP increasing agent, and/or other components of the combination. Physiologically acceptable salts and pharmaceutically acceptable salts are well known in the art and include salts prepared from pharmaceutically acceptable non-toxic acids, including inorganic acids and organic acids. Suitable non-toxic acids can include inorganic and organic acids such as acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, p-toluenesulfonic, hydrochloric, hydrobromic, phosphoric, sulfuric acids, and the like. Salts formed with, for example, a free carboxy group of an amino acid, can be derived from inorganic bases including, but not limited to, sodium, potassium, ammonium, calcium or ferric hydroxides, and organic bases including, but not limited to, isopropylamine, trimethylamine, histidine, and procaine.

[0025] The nootropic combination, or any individual components of the nootropic combination, can be taken orally in the form of a capsule, pill or tablet, for example, and can contain pharmaceutically or physiologically acceptable carriers. For example,

inert, pharmaceutically or physiologically acceptable solid carriers can be one or more substances which may also act as diluents, flavoring agents, colorizers, solubilizers, lubricants, suspending agents, or binders. The solid carrier material can also include encapsulating material. Examples of carriers include, but are not limited to. inert diluents, such as calcium carbonate, sodium carbonate, sodium citrate, lactose, calcium phosphate, sodium phosphate, microcrystalline cellulose, corn starch, potato starch, and cellulose esters such as cellulose acetate, ethyl cellulose; granulating and disintegrating agents, for example, corn starch, or alginic acid, or complex silicates; binding agents, for example starch, polyvinylpyrrolidone, PEG-8000, gelatin or gum acacia, and lubricating agents, for example magnesium stearate, stearic acid, sodium lauryl sulfate, or talc.

[0026] Although oral administration of the nootropic combination or any of its components is the preferred route of administration, other means of administration such as intravenous, nasal or rectal administration, or by injection or inhalation, are also contemplated. Depending on the intended mode of administration, the combination or any of its components may be in the form of solid, semi-solid or liquid dosage forms, such as, for example, liquids, suspensions, suppositories, or powders. In some embodiments, the nootropic combination can be administered in unit dosage form suitable for single administration of a precise dosage. One skilled in this art may further formulate the composition or any of its components in an appropriate manner, and in accordance with accepted practices, such as those disclosed in Remington's Pharmaceutical Sciences, Gennaro, Ed., Mack Publishing Co., Easton, Pa. 1990.

[0027] The effective amount of the nootropic combination and any of its components can vary according to, for example, the weight of the subject administered to, the mode of administration, and the general health of the subject. The dose or effective amount will be ascertainable by one skilled in the art using known techniques (for example, see Ansel, et al., Pharmaceutical Dosage Forms and Drug Delivery; Lieberman (1992) Pharmaceutical Dosage Forms (vols. 1-3), Dekker, ISBN 0824770846, 082476918X, 0824712692, 0824716981; and Lloyd (1999) The Art, Science and Technology of Pharmaceutical Compounding).

[0028] In some embodiments, the nootropic combination can be administered simultaneously or sequentially and in any order. For example, the PDE4 inhibitor, the cAMP increasing agent, and other components of the combination can be administered as a combination simultaneously or sequentially in any order, depending on the embodiment.

[0029] The nootropic combination can be in a form to be administered as a single preparation, such as a capsule or tablet, and can be in a daily dosage form. In some embodiments, the combination is a nutritional supplement.

[0030] The nootropic combination can be administered to a subject to increase or enhance cognitive functioning. Cognitive functioning refers to higher-order brain processes such as concentration, alertness, focus, attention, motivation, wakefulness, and long-term memory. An effective amount, or a therapeutically effective amount, of a substance is an amount that increases or enhances cognitive functioning in the subject.

[0031] In some cases, cognitive functioning can be assessed using cognitive tests such as long-term recall of studied material, spatial search and grammatical reasoning tests.

[0032] The subject can be a human or other mammal.

[0033] The primary means by which PDE4 inhibitors are theorized to improve learning and memory is by lengthening the duration during which the secondary messenger cyclic-adenosine monophosphate (cAMP) is present in cells, where it can activate the cAMP response element binding protein CREB and thus increase CREB's gene transcription activities in the nucleus and mitochondria. These gene transcription activities are what are theorized to lead to long term potentiation (LTP) activity which is crucial to learning and memory. Additionally, increased transcription of brain-derived neurotrophic factor (BDNF) by CREB has been linked to improved short-term memory in studies (references 14-20).

[0034] Forskolin is a chemical derived from the plant Coleus forskohlii which has been widely used in traditional Ayurvedic medicine. It has also has been extensively studied due to its ability to increase levels of intracellular cAMP (references 21-23).

[0035] Luteolin can inhibit the family of phosphodiesterase enzymes (PDE 1 through 5) that degrade 3',5'-cyclic nucleotides. Inhibition of phosphodiesterase 1 and phosphodiesterase 5 have both shown beneficial activity with regard to synaptic plasticity (references 24-27). PDE 4 specific inhibitors are also known, such as rolipram (reference 28).

[0036] CREB's activities in the cell have been shown to increase the transcription of enzymes which are key enzymes in dopamine metabolism, such as tyrosine hydroxylase. Increased transcription of these enzymes leads to increased processing of dopamine precursors. The essential amino acid L-phenylalanine is converted into L-tyrosine by phenylalanine hydroxylase and then converted into L-dopa by tyrosine hydroxylase. Vitamin B6 can support the conversion of L-dopa to dopamine by dopa decarboxylase (references 29-32). Thus, L-phenylalanine and/or Vitamin B6 can be added to embodiments of the nutritional supplement.

[0037] Some embodiments of the nootropic combination may lead to afternoon sleepiness and a temporary decrease in short term memory. Studies have provided evidence that forskolin increases transcription of the enzyme acetylcholinesterase. Acetylcholinesterase breaks down acetylcholine in the brain. Sleepiness is a common symptom of medicines that are anti-cholinergic so it would follow that excess acetylcholinesterase could lead to lower acetylcholine levels and thus sleepiness. Acetyl-L-carnitine has been shown to increase the levels of acetylcholine in the brain and thus could be helpful in counteracting increased transcription of acetylcholinesterase by forskolin (references 33-35). Thus, acetyl-L-carnitine, or L-carnitine, can be added to the nutritional supplement. In embodiments containing acetyl-L-carnitine or L-carnitine, afternoon drowsiness and short-term memory issues can be largely mitigated.

[0038] Kanna extract and mesembrenone have been shown to significantly inhibit PDE4 (reference 38). Embodiments containing kanna extract were effective at increasing cognitive functioning, although less beneficial than artichoke extract.

[0039] In particular embodiments, multiple components are combined to create a synergistic combination for improving synaptic and cognitive functions in the mammalian brain. These components include: a cyclic adenosine monophosphate (cAMP) increasing labdane diterpene such as forskolin; a PDE4 inhibiting flavonoid such as Luteolin contained within artichoke extract; the amino acid L-phenylalanine; vitamin B6; and the quaternary ammonium compound L-carnitine or its acylated derivative acetyl-L-carnitine.

[0040] Although not wishing to be bound by theory, it is believed that when these components are taken together orally in the form of a nutritional supplement, PDE-4 is inhibited and cAMP is increased leading to sustained activation of CREB (cAMP response element binding protein), which helps to maintain effective long-term potentiation (LTP) and thus memory. In addition, L-phenylalanine is believed to provide adequate precursors to the dopaminergic metabolic pathway to accommodate upregulation of tyrosine hydroxylase by PDE4 inhibition, and vitamin B6 is believed to behave as a dopamine metabolic co-factor (see Fig. 2). Also, L-carnitine and acetyl-L-carnitine are believed to counteract the upregulation of acetylcholinesterase caused by forskolin. Thus, it is believed that the dopamine co-factors provide a steady supply of co-factors to the enhanced D1/PKA/DARPP-32 signaling cascade caused by PDE-4 inhibition and the subsequent increase in dopamine synthesis and turnover due to increases in tyrosine hydroxylase gene transcription (references 36-45).

[0041] Some particular embodiments for an adult human that have been determined through experimentation include:

200 mg acetyl-L-carnitine;

1 mg forskolin;

225 mg artichoke extract standardized to 5% cynarin;

125 mg L-phenylalanine; and

2.5 mg vitamin B6.

[0042] Alternative formulas include:

200 mg acetyl-L-carnitine

1 mg forskolin

225 mg artichoke extract standardized to 5% cynarin;

or

1 mg forskolin

225 mg artichoke extract standardized to 5% cynarin

125 mg L-phenylalanine

[0043] These particular embodiments are exemplary and the weight of each ingredient may be varied by 10% without significant degradation of efficacy. Also, from 1 to 2, 1 to 3, 1 to 4, 2 to 3, 2 to 4, 3 to 4, or 1, 2, 3 or 4 doses may be taken per day. Thus, in some embodiments, the range of ingredients per daily dosage can be:

about 202.5 mg to about 495 mg, about 202.5 mg to about 742.5 mg, or about 202.5 mg to about 990 mg artichoke extract standardized to 5% cynarin; and

about 0.9 mg to about 2.2 mg, about 0.9 mg to about 3.3 mg, or about 0.9 mg to about 4.4 mg forskolin.

[0044] Alternatively, the daily dosage can be about 225 mg, about 450 mg, about 675 mg or about 900 mg artichoke extract standardized to 5% cynarin; and about 1 mg, about 2 mg, about 3 mg, or about 4 mg forskolin, or can be varied by 10 % of such amounts.

[0045] Further, in some embodiments, the nutritional supplement can include one or a combination of the following ingredients, in ranges per daily dosage:

about 180 mg to about 440 mg, about 180 mg to about 660 mg, or about 180 mg to about 880 mg acetyl-L-carnitine;

about 112.5 mg to about 275 mg, about 112.5 mg to about 412.5 mg, or about 112.5 mg to about 550 mg L-phenylalanine; and

about 2.25 mg to about 5.5 mg, about 2.25 mg to about 8.25 mg, or about 2.25 mg to about 11 mg vitamin B6.

[0046] Alternatively, the daily dosage can be about 200 mg, about 400 mg, about 600 mg, or about 800 mg acetyl-L-carnitine; about 125 mg, about 250 mg, about 375 mg, or about 500 mg L-phenylalanine; and about 2.5 mg, about 5 mg, about 7.5 mg, or about 10 mg vitamin B6, or can be varied by 10 % of such amounts.

[0047] The alkaloid piperine (Fig. 1I) can also be included as a component of the nootropic combination, including the nutritional supplement. Piperine is present in black pepper and has been used in nutritional products to enhance the bioavailability of flavonoids by blocking glucuronidation in the liver and digestive tract. Piperine has been found to enhance the bioavailability of curcumin by 2000%, and enhance the bioavailability of resveratrol (references 52-53). In embodiments of the nutritional supplement, piperine can be included in the range of about 10 mg to about 20 mg per daily dose of the nootropic combination.

[0048] Additional inactive ingredients such as different types of color, filler, binder, capsule, and coating are permissible.

[0049] In embodiments containing acetyl-L-carnitine, a ratio of acetyl-L-carnitine to forskolin of about 200:1 by weight appears to provide particularly good effects on cognitive functioning.

[0050] Forskolin in the amount of 1-4 mg per daily dosage is less than the amount typically provided in forskolin supplements (25 mg to 50 mg). The 1-4 mg daily dosage was found by the inventor to provide positive cognitive benefits, while larger amounts produced side effects and diminished or eliminated cognitive benefits.

[0051] As used herein, the term "about" in reference to an amount of a substance indicates an amount within experimental error.

[0052] It is to be understood that the ranges and limits mentioned herein include all sub-ranges located within the prescribed limits, inclusive of the limits themselves unless otherwise stated.

[0053] The present invention may be better understood by referring to the accompanying examples, which are intended for illustration purposes only and should not in any sense be construed as limiting the scope of the invention.

EXAMPLE 1

Artichoke extract and forskolin

[0054] The inventor ingested 900mg artichoke extract standardized to 5% cynarin (Now Foods, Bloomingdale, Illinois) and 385 mg Coleus forskhohlii root standardized to 1% forskolin yielding 3.85 mg forskolin (Neutraceutical, Park City, Utah). The combination was administered once per morning. After taking the combination, the inventor performed better on spatial search and grammatical reasoning tests compared to baseline. The inventor felt increased motivation and could study for longer periods of time. He also had subjectively better recall of material that was studied. The inventor experienced excessive tiredness in the afternoon, and short term memory, as measured by a paired-associate-learning test "Paired Associates" (Cambridge Brain Sciences, Ontario, Canada) in which a pair of items is learned (an object and its location), was slightly negatively affected.

EXAMPLE 2

Artichoke extract, forskolin and L-phenylalanine

[0055] The inventor ingested artichoke extract and forskolin as in Example 1, and also ingested up to 1500 mg L-Phenylalanine (Now Foods, Bloomingdale, Illinois). The combination was administered once per morning. After taking the combination, the inventor performed better on spatial search and grammatical reasoning tests compared to baseline, felt increased motivation, could study for longer periods of time, and had subjectively better recall of material that was studied. Compared to the

combination containing just artichoke extract and forskolin, the inventor experienced less tiredness in the afternoon. Short term memory, as measured by the paired-associate-learning test "Paired Associates" (Cambridge Brain Sciences, Ontario, Canada), was slightly negatively affected.

EXAMPLE 3

Artichoke extract, forskolin, L-phenylalanine and vitamin B6

[0056] The inventor ingested artichoke extract, forskolin and L-phenylalanine as in Example 2, and also ingested 5 mg vitamin B6 as part of a B vitamin complex (Neutraceutical, Park City, Utah). The combination was administered once per morning. After taking the combination, the inventor performed better on spatial search and grammatical reasoning tests compared to baseline, felt increased motivation, could study for longer periods of time, and had subjectively better recall of material that was studied. The inventor experienced less tiredness in the afternoon and the effects of the stack did not diminish over several days of taking it. Short term memory, as measured by the paired-associate-learning test "Paired Associates" (Cambridge Brain Sciences, Ontario, Canada), was slightly negatively affected.

EXAMPLE 4

Artichoke extract, forskolin, L-phenylalanine, vitamin B6 and acetyl-L-carnitine

[0057] The inventor ingested artichoke extract, forskolin, L-phenylalanine and vitamin B6 as in Example 3, and also ingested 750 mg of acetyl-L-carnitine (Primaforce, Burlington, North Carolina). The combination was administered once per morning. After taking the combination, the inventor performed better on spatial search and grammatical reasoning tests compared to baseline, felt increased motivation, could study for longer periods of time, and had subjectively better recall of material that was studied. The inventor experienced no tiredness in the afternoon. The amount of acetyl-L-carnitine relative to forskolin was increased until the inventor's paired associates scores no longer fell after taking the combination.

EXAMPLE 5

[0058] This example is based on a testimonial by a subject. The subject was a female with concentration and memory problems. The nutritional supplement was in capsular form, with a capsule including 300 mg artichoke extract standardized to 5% cynarin, ~ 4/3 mg forskolin, 167 mg L-phenylalanine, 5/3 mg vitamin B6, and 250 mg acetyl-L-carnitine. Also included were cellulose, vegetable stearate and silica as carriers. After taking the nutritional supplement, the subject reported increased focus, energy and memory.

EXAMPLE 6

[0059] This example is based on a testimonial by a male subject. The nutritional supplement was in capsular form, with a capsule including 300 mg artichoke extract standardized to 5% cynarin, ~ 4/3 mg forskolin, 167 mg L-phenylalanine, 5/3 mg vitamin B6, and 250 mg acetyl-L-carnitine. Also included were cellulose, vegetable stearate and silica as carriers. After taking the nutritional supplement, the subject reported increased focus and mental vision.

EXAMPLE 7

[0060] This example is based on a testimonial by a male subject. The nutritional supplement was in capsular form, with a capsule including 300 mg artichoke extract standardized to 5% cynarin, ~ 4/3 mg forskolin, 167 mg L-phenylalanine, 5/3 mg vitamin B6, and 250 mg acetyl-L-carnitine. Also included were cellulose, vegetable stearate and silica as carriers. After taking the nutritional supplement, the subject reported increased focus and concentration.

EXAMPLE 8

[0061] The inventor ingested 25 mg kanna extract (Zembrin®, Organic African Red Tea Imports, Los Angeles, California), 1500 mg L-phenylalanine, and 4 mg forskolin (Better Body Sports LLC, Ventura, California). This combination was administered

once per morning. After taking the combination, the inventor obtained much better scores on "Polygons" and "Odd One Out" tests (Cambridge Brain Sciences, Ontario, Canada). Studying was much easier and more enjoyable.

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[0062]

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[0063] Although the present invention has been described in connection with the preferred embodiments, it is to be understood that modifications and variations may be utilized without departing from the principles and scope of the invention, as those

skilled in the art will readily understand. Accordingly, such modifications may be practiced within the scope of the invention and the following claims.

CLAIMS

What is claimed is:

1. A nutritional supplement for increasing cognitive functioning in a human subject, comprising effective amounts of a phosphodiesterase 4 (PDE4) inhibiting flavonoid, a cyclic adenosine monophosphate (cAMP) increasing labdane diterpene in the form of forskolin, and acetyl-L-carnitine, wherein the nutritional supplement comprises about 202.5 mg to about 247.5 mg of artichoke extract standardized to 5% cynarin, as a source of the PDE4 inhibiting flavonoid, per about 0.9 mg to about 1.1 mg of the forskolin, and about 180 mg to about 220 mg of the acetyl-L-carnitine per about 0.9 mg to about 1.1 mg of the forskolin.

2. The nutritional supplement of claim 1, further comprising effective amounts of one or any combination of components selected from the group consisting of L-phenylalanine, L-carnitine, vitamin B6, and piperine.

3. The nutritional supplement of claim 1, further comprising an effective amount of piperine.

4. The nutritional supplement of claim 1, further comprising an effective amount of L-phenylalanine.

5. The nutritional supplement of claim 1, further comprising an effective amount of vitamin B6.

6. The nutritional supplement of claim 1, further comprising one or any combination of components selected from the group consisting of about 112.5 mg to about 137.5 mg of L-phenylalanine per about 0.9 mg to about 1.1 mg of the forskolin, and an effective amount of vitamin B6.

7. The nutritional supplement of claim 1, wherein the ratio of acetyl-L-carnitine to forskolin is about 200:1 by weight.

8. The nutritional supplement of claim 1, further comprising L-phenylalanine in an amount of about 112.5 mg to about 137.5 mg per about 0.9 to about 1.1 mg of the forskolin.

9. The nutritional supplement of claim 8, wherein the artichoke extract is in an amount of about 225 mg per about 1 mg of the forskolin, the acetyl-L-carnitine is in an amount of about 180 mg to about 220 mg per about 1 mg of the forskolin, and the L-phenylalanine is in an amount of about 125 mg per about 1 mg of the forskolin.

10. A nutritional supplement for increasing cognitive functioning in a human subject, comprising in daily dosage form about 900 mg of artichoke extract standardized to 5% cynarin, as a source of a PDE 4 inhibiting flavonoid, about 4 mg of forskolin, about 720 mg to about 880 mg of acetyl-L-carnitine, and about 500 mg of L-phenylalanine.

11. A nutritional supplement for increasing cognitive functioning in a human subject, consisting essentially of effective amounts of artichoke extract standardized to 5% cynarin, as a source of a PDE4 inhibiting flavonoid, a cAMP increasing labdane diterpene in the form of forskolin, acetyl-L-carnitine, L-phenylalanine, vitamin B6, and inactive ingredients, wherein the artichoke extract is in an amount of about 202.5 mg to about 247.5 mg per about 0.9 mg to about 1.1 mg of the forskolin, the acetyl-L-carnitine is in an amount of about 180 mg to about 220 mg per about 0.9 mg to about 1.1 mg of the forskolin, and the L-phenylalanine is in an amount of about 112.5 mg to about 137.5 mg per about 0.9 to about 1.1 mg of the forskolin.

12. The nutritional supplement of claim 11, wherein the artichoke extract is in an amount of about 225 mg per about 1 mg of the forskolin, the acetyl-L-carnitine is in an amount of about 180 mg to about 220 mg per about 1 mg of the forskolin, and the L-phenylalanine is in an amount of about 125 mg per about 1 mg of the forskolin.

13. A nutritional supplement for increasing cognitive functioning in a human subject, consisting essentially of, in daily dosage form, about 900 mg of artichoke extract standardized to 5% cynarin, as a source of a PDE4 inhibiting flavonoid, about 4 mg of forskolin, about 720 mg to about 880 mg of acetyl-L-carnitine, about 500 mg of L-phenylalanine, an effective amount of vitamin B6, and inactive ingredients.

14. A nootropic combination for increasing cognitive functioning in a human subject, comprising effective amounts of a PDE4 inhibitor and a cAMP increasing agent,

wherein the PDE4 inhibitor is luteolin, quercetin, hesperidin, biochanin A, genistein, mesembrenone, or resveratrol, or a glycoside thereof, a physiologically acceptable salt thereof, or a combination thereof, and

the cAMP increasing agent is forskolin in a range of about 0.9 mg to about 4.4 mg per daily dose of the combination.

15. The nootropic combination of claim 14, further comprising an effective amount of acetyl-L-carnitine or a physiologically acceptable salt thereof.

16. The nootropic combination of claim 14, further comprising an effective amount of acetyl-L-carnitine, and wherein the ratio of acetyl-L-carnitine to forskolin is about 200:1 by weight.

17. The nootropic combination of claim 14, further comprising effective amounts of one or a combination of components selected from the group consisting of L-phenylalanine, L-carnitine, acetyl-L-carnitine, vitamin B6, piperine, and a physiologically acceptable salt thereof.

18. The nootropic combination of claim 14, further comprising an effective amount of acetyl-L-carnitine.

19. The nootropic combination of claim 14, further comprising an effective amount of piperine.

20. The nootropic combination of claim 14, further comprising an effective amount of L-phenylalanine.

21. The nootropic combination of claim 14, further comprising an effective amount of vitamin B6.

22. The nootropic combination of claim 14, wherein the PDE4 inhibitor, the cAMP increasing agent, or both, are present in the combination in the form of one or more plant extracts.

23. The nootropic combination of claim 14, in the form of a nutritional supplement, further comprising an effective amount of acetyl-L-carnitine, and wherein the PDE4 inhibitor is present in the nutritional supplement in the form of a plant extract.

24. The nootropic combination of claim 23, wherein the ratio of acetyl-L-carnitine to forskolin is about 200:1 by weight.

25. The nootropic combination of claim 23, wherein the forskolin is present in the nutritional supplement in the form of a Coleus forskohlii extract.

26. The nootropic combination of claim 23, wherein the forskolin is present in the nutritional supplement in the form of a Coleus forskohlii extract, and the ratio of acetyl-L-carnitine to forskolin is about 200:1 by weight.

27. The nootropic combination of claim 23, further comprising effective amounts of one or any combination of components selected from the group consisting of L-phenylalanine, L-carnitine, vitamin B6, and piperine.

28. The nootropic combination of claim 23, further comprising an effective amount of piperine.

29. The nootropic combination of claim 23, further comprising an effective amount of L-phenylalanine.

30. The nootropic combination of claim 23, further comprising an effective amount of vitamin B6.

31. A nootropic combination, in the form of a nutritional supplement, comprising in daily dosage form:

about 202.5 mg to about 990 mg of artichoke extract standardized to 5% cynarin, as a source of a PDE4 inhibitor, per about 0.9 mg to about 4.4 mg of forskolin; and

about 180 mg to about 880 mg of acetyl-L-carnitine per about 0.9 mg to about 4.4 mg of forskolin.

32. The nootropic combination of claim 31, further comprising one or any combination of components selected from the group consisting of about 112.5 mg to about 550 mg of L-phenylalanine per daily dosage of the nutritional supplement, about 2.25 mg to about 11 mg of vitamin B6 per daily dosage of the nutritional supplement, and about 10 mg to about 20 mg of piperine per daily dosage of the nutritional supplement.

33. The nootropic combination of claim 31, wherein the ratio of acetyl-L-carnitine to forskolin is about 200:1 by weight.

34. The nootropic combination of claim 31, further comprising:

about 112.5 mg to about 550 mg of L-phenylalanine per daily dosage of the nutritional supplement; and

about 2.25 mg to about 11 mg of vitamin B6 per daily dosage of the nutritional supplement.

35. The nootropic combination of claim 31, in capsule form, comprising per capsule:

about 300 mg of artichoke extract standardized to 5% cynarin;

about 1.33 mg of forskolin;

about 250 mg of acetyl-L-carnitine; and

further comprising about 166.67 mg of L-phenylalanine and about 1.67 mg of vitamin B6.

36. Use of a nutritional supplement comprising effective amounts of a cAMP increasing agent and a PDE4 inhibitor for increasing cognitive functioning in a human subject in need thereof,

wherein the PDE4 inhibitor is luteolin, quercetin, hesperidin, biochanin A, genistein, mesembrenone, or resveratrol, or a glycoside thereof, a physiologically acceptable salt thereof, or a combination thereof, and

the cAMP increasing agent is forskolin in a range of about 0.9 mg to about 4.4 mg per daily dose of the nutritional supplement.

37. The use of claim 36, wherein the nutritional supplement further comprises an effective amount of acetyl-L-carnitine or a physiologically acceptable salt thereof.

38. The use of claim 36, wherein the nutritional supplement further comprises an effective amount of acetyl-L-carnitine and wherein the ratio of acetyl-L-carnitine to forskolin is about 200:1 by weight.

39. The use of claim 36, wherein the forskolin is present in the nutritional supplement in the form of a Coleus forskohlii extract.

40. The use of claim 36, wherein the PDE4 inhibitor, the cyclic cAMP increasing agent, or both, are present in the nutritional supplement in the form of one or more plant extracts.

41. The use of claim 36, wherein the nutritional supplement further comprises therapeutically effective amounts of one or any combination of components selected from the group consisting of L-phenylalanine, L-carnitine, acetyl-L-carnitine, vitamin B6, piperine, and a physiologically acceptable salt thereof.

42. The use of claim 36, wherein the nutritional supplement further comprises an effective amount of piperine.

43. The use of claim 36, wherein the nutritional supplement further comprises an effective amount of L-phenylalanine.

44. The use of claim 36, wherein the nutritional supplement further comprises an effective amount of vitamin B6.

45. The use of claim 36, wherein the nutritional supplement is for administration in a daily dosage form and comprises:

about 202.5 mg to about 990 mg of artichoke extract standardized to 5% cynarin, as a source of the PDE4 inhibitor, per about 0.9 mg to about 4.4 mg of forskolin; and

further includes about 180 mg to about 880 mg of acetyl-L-carnitine per about 0.9 mg to about 4.4 mg of forskolin.

46. The use of claim 45, wherein the nutritional supplement further comprises one or any combination of components selected from the group consisting of about 112.5 mg to about 550 mg of L-phenylalanine per daily dosage of the nutritional supplement, about 2.25 mg to about 11 mg of vitamin B6 per daily dosage of the nutritional supplement, and about 10 mg to about 20 mg of piperine per daily dosage of the nutritional supplement.

47. The use of claim 45, wherein the ratio of acetyl-L-carnitine to forskolin is about 200:1 by weight.

48. The use of claim 45, wherein the nutritional supplement further comprises:

about 112.5 mg to about 550 mg of L-phenylalanine per daily dosage of the nutritional supplement; and

about 2.25 mg to about 11 mg of vitamin B6 per daily dosage of the nutritional supplement.

49. The use of claim 36, wherein nutritional supplement is for administration in a daily dosage of two or three capsules, wherein each capsule comprises:

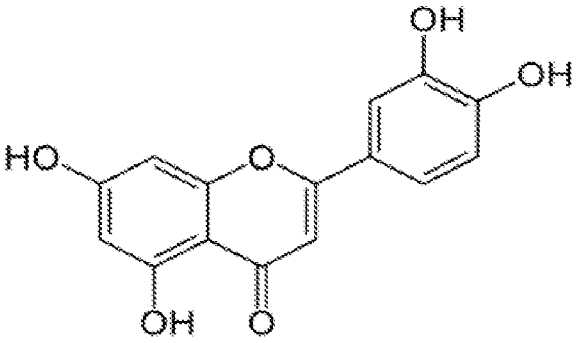
about 300 mg of artichoke extract standardized to 5% cynarin;

about 1.33 mg of forskolin;

about 250 mg of acetyl-L-carnitine; and

further comprising about 166.67 mg of L-phenylalanine and about 1.67 mg of vitamin B6.

(A)



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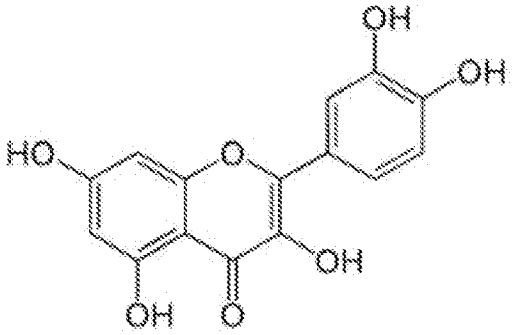

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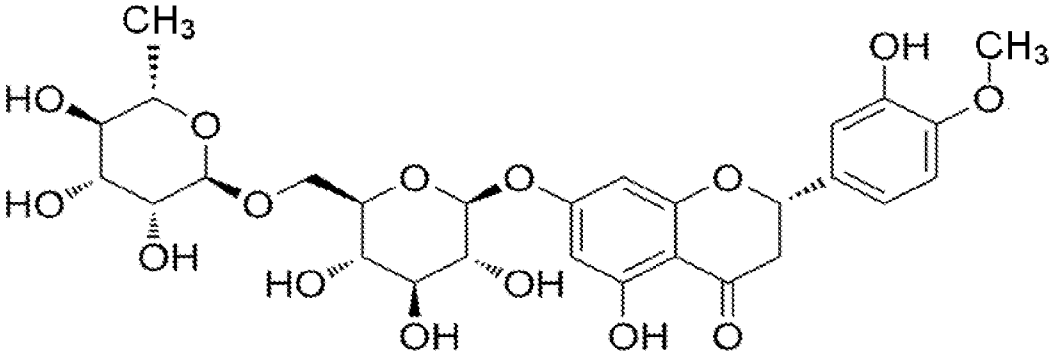

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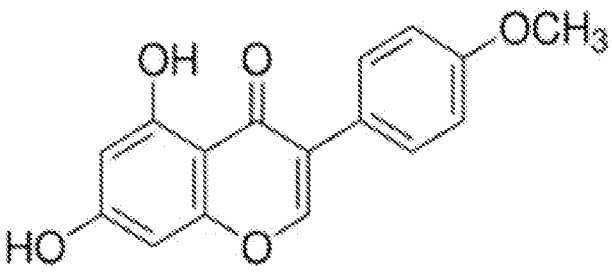
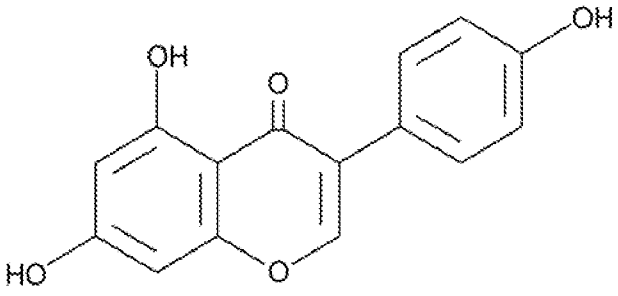


FIG. 1

(E)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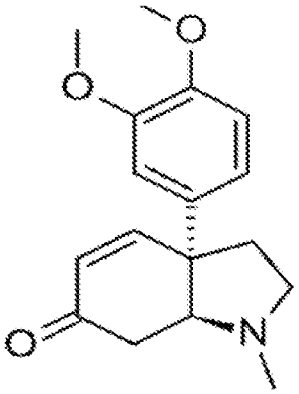
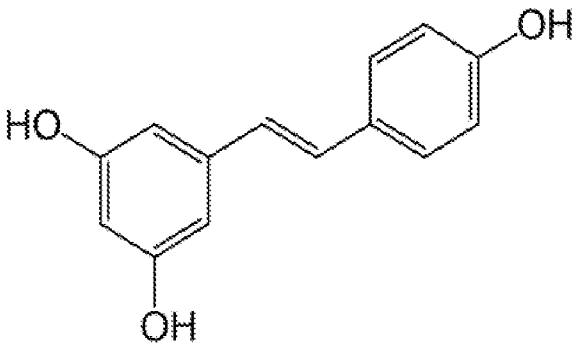
O
OH
HO
O

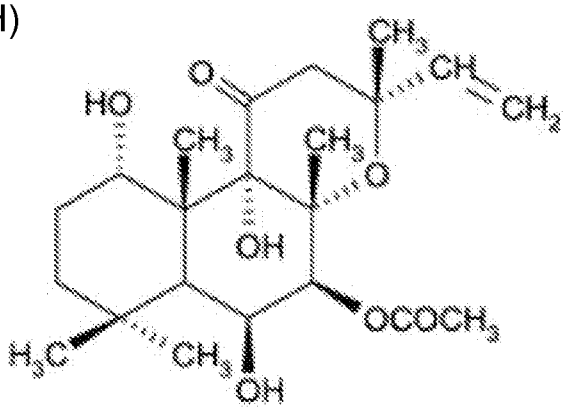
(F)


O
O
O
N

(G)


OH
HO
OH

(H)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CH
CH2
O
HO
CH3
CH3
O
OH
OCOCH3
H3C
CH3
OH

I)

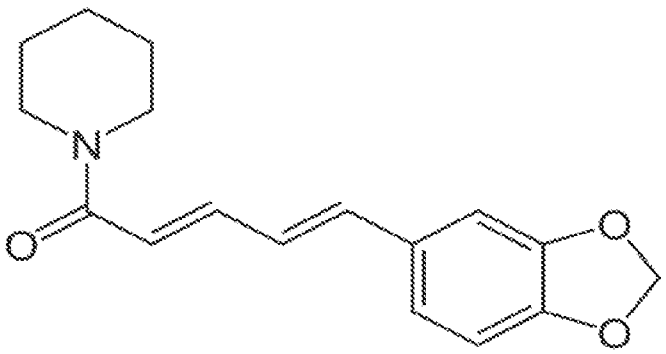

N
O
O
O

FIG. 1

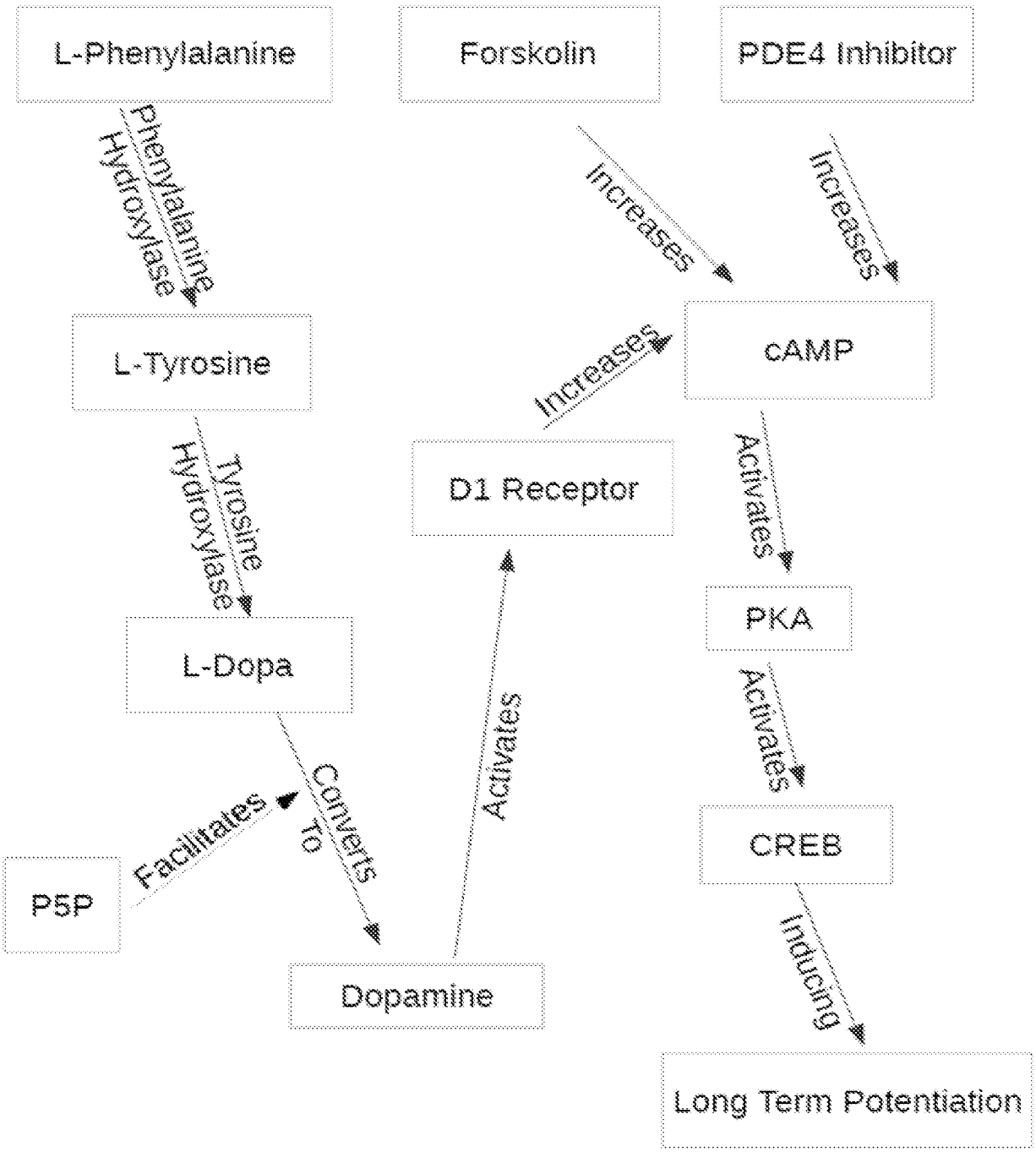
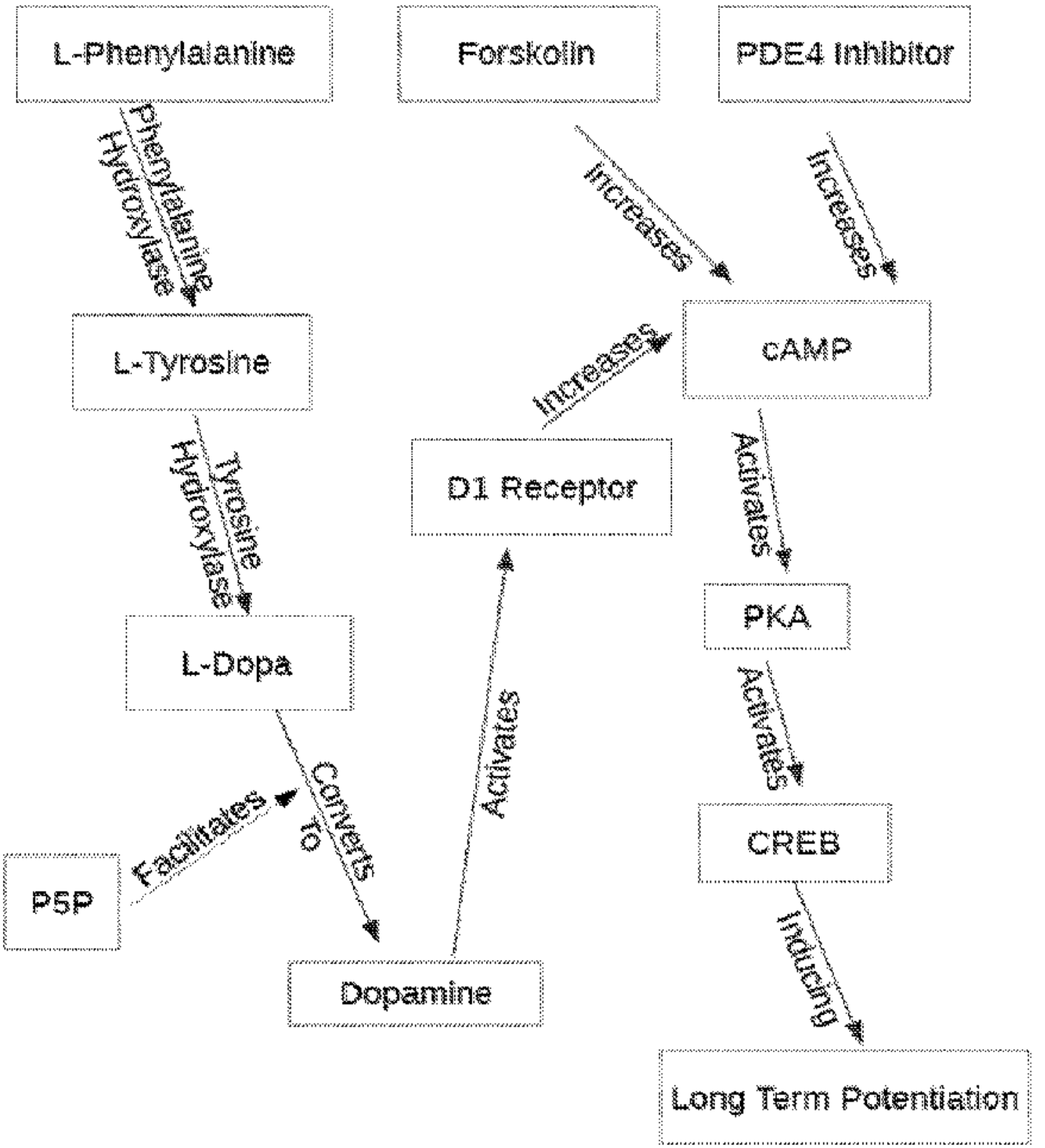

L-Phenylalanine
Forskolin
PDE4 Inhibitor
Phenylalanine Hydroxylase
Increases
Increases
L-Tyrosine
Increases
cAMP
D1 Receptor
Activates
Tyrosine Hydroxylase
PKA
L-Dopa
Activates
Activates
CREB
Converts To
Facilitates
P5P
Dopamine
Inducing
Long Term Potentiation

FIG. 2


L-Phenylalanine
Forskolin
PDE4 Inhibitor
Phenylalanine Hydroxylase
Increases
Increases
L-Tyrosine
Increases
cAMP
D1 Receptor
Activates
Tyrosine Hydroxylase
PKA
L-Dopa
Activates
Activates
Converts to
CREB
Facilitates
P5P
Inducing
Dopamine
Long Term Potentiation