

APOAEQUORIN AND CURCUMIN CONTAINING COMPOSITIONS AND METHODS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This International application claims the benefit of U.S. Provisional Application No. 62/980,785, filed February 24, 2020, and hereby incorporated by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR
DEVELOPMENT

[0002] Not Applicable.

FIELD OF THE INVENTION

[0003] This invention relates generally to compositions useful for the maintenance of human health. In particular, this invention is directed to apoaquorin and curcumin containing nutraceutical compositions.

SUMMARY OF THE INVENTION

[0004] The present invention provides various advantages over prior compositions and methods in the improvement and/or maintenance of human health. Such compositions include apoaquorin and curcumin formulations in combination with acceptable carriers for administration to a subject by a variety of routes.

[0005] Accordingly, the present invention is directed to compositions comprising effective amounts of apoaquorin and curcumin in combination with an acceptable carrier. In certain embodiments, the present invention is directed to nutraceutical compositions including effective amounts of apoaquorin and curcumin in combination with an acceptable carrier. In certain embodiments, nutraceutical compositions include, in addition to apoaquorin and curcumin, at least one other component recognized as providing nutraceutical benefit such as, for example, an immune boosting agent, anti-inflammatory agent, anti-oxidant agent, anti-viral agent, or a mixture thereof. Apoaquorin and curcumin compositions in certain embodiments are provided in a unit dosage form selected from a tablet, a capsule, a solution, a suspension, a syrup, a beverage, or an oral or ophthalmic formulation.

[0006] In another aspect, the invention is directed to a method for treating a symptom or disorder associated with calcium imbalance, comprising administering to a subject in need of such treatment an effective amount of apoaquorin and curcumin.

[0007] Methods according to the invention are useful in treating a wide variety of symptoms or disorders associated with human health, including but not limited to mental disorder, anxiety, cognitive function, sleep quality, energy quality, mood quality, pain, memory quality. In certain embodiments, the symptom of disorder is physiologically-related to neuronal excitability, muscle contraction, membrane permeability, cell division, hormone secretion, bone mineralization, or cell death following ischemia. In such methods, apoaquorin and curcumin are preferably administered to the subject in the form of a nutraceutical composition.

[0008] In yet another embodiment, the invention encompasses the use of apoaquorin and curcumin for the manufacture of a nutraceutical composition for treating a symptom or disorder associated with human health in a subject administered the nutraceutical composition. Exemplary symptoms or disorders treated by such compositions include those associated with mental disorder, anxiety, cognitive function, sleep, energy, mood, pain, or memory.

[0009] Accordingly, the present invention further contemplates apoaquorin and curcumin for use in treating a symptom or disorder described above in a subject, including those symptoms or disorders associated with, e.g., mental disorder, anxiety, cognitive function, sleep, energy, mood, pain, or memory in a subject.

[0010] The present invention provides various advantages over prior compositions and methods in that it provides for the general improvement of a subject's mental and physical health.

[0011] Other objects, features and advantages of the present invention will become apparent after review of the specification and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Figure 1 provides a graph showing the percent change from baseline of scores from areas: overall quality of sleep, energy, mood, pain and general health vs. days 0 through 90.

[0013] Figure 2 depicts a graph showing data in which apoaquorin (10mg) was taken daily by 56 participants. The participants were evaluated from eight days to 30 days. The memory study showed a statistically significant improvement in memory after 30 days ($p < .05$). 57% of participants had improvement in general memory, 51% in retaining information, 84% in remembering driving directions and 66% in word recall. N=56; 66% female, 34% male, mean age = 56 years; range 20-78 years.

[0014] Figure 3 provides a graph showing the percent change, from baseline, of scores from standardized cognitive battery questionnaire vs. day 0 through 90.

DETAILED DESCRIPTION OF THE INVENTION

I. IN GENERAL

[0015] Before the present materials and methods are described, it is understood that this invention is not limited to the particular methodology, and materials described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

[0016] It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. As well, the terms "a" (or "an"), "one or more" and "at least one" can be used interchangeably herein. It is also to be noted that the terms "comprising", "including", and "having" can be used interchangeably.

[0017] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications and patents specifically mentioned herein are incorporated by reference for all purposes including describing and disclosing the chemicals, instruments, statistical analysis and methodologies which are reported in the publications which might be used in connection with the invention. All references cited in this specification are to be taken as indicative of the level of skill in the art. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

II. THE INVENTION

[0018] Aequorin is a photo-protein originally isolated from luminescent jellyfish and other marine organisms. The aequorin complex comprises a 22,285-dalton apoequorin protein, molecular oxygen and the luminophore coelenterazine. When three Ca^{2+} ions bind to this complex, coelenterazine is oxidized to coelenteramide, with a concomitant release of carbon dioxide and blue light. Aequorin is not exported or secreted by cells, nor is it compartmentalized or sequestered within cells. Accordingly, aequorin measurements have

been used to detect Ca^{2+} changes that occur over relatively long periods. In several experimental systems, aequorin's luminescence was detectable many hours to days after cell loading. It is further known that aequorin also does not disrupt cell functions or embryo development.

[0019] Because of its Ca^{2+} -dependent luminescence, the aequorin complex has been extensively used as an intracellular Ca^{2+} indicator. *Aequorea victoria* aequorin has been specifically used to: (1) analyze the secretion response of single adrenal chromaffin cells to nicotinic cholinergic agonists; (2) clarify the role of Ca^{2+} release in heart muscle damage; (3) demonstrate the massive release of Ca^{2+} during fertilization; (4) study the regulation of the sarcoplasmic reticulum Ca^{2+} pump expression in developing chick myoblasts; and (5) calibrate micropipets with injection volumes of as little as three picoliters.

[0020] Apoequorin has an approximate molecular weight of 22 kDa. Apoequorin can be used to regenerate aequorin by reducing the disulfide bond in apoequorin. The calcium-loaded apoequorin retains the same compact scaffold and overall folding pattern as unreacted photoproteins containing a bound substrate.

[0021] Conventional purification of aequorin from the jellyfish *Aequorea victoria* requires laborious extraction procedures and sometimes yields preparations that are substantially heterogeneous or that are toxic to the organisms under study. Two tons of jellyfish typically yield approximately 125mg of the purified photoprotein. In contrast, recombinant aequorin is preferably produced by purifying apoequorin from genetically engineered *Escherichia coli*, followed by reconstitution of the aequorin complex *in vitro* with pure coelenterazine. Apoequorin useful in the present invention has been described and is commercially-obtainable through purification schemes and/or syntheses known to those of skill in the art. S. Inouye, S. Zenno, Y. Sakaki, and F. Tsuji. *High level expression and purification of apoequorin*. (1991) Protein Expression and Purification 2, 122-126.

[0022] The present invention is directed to the administration of apoequorin and curcumin containing compositions to a subject in order to correct or maintain the calcium balance in that subject thereby improving, but not limited to, mental disorder, anxiety, cognitive function, sleep quality, energy quality, mood quality, pain, memory quality. Curcumin (diferuloylmethane; 1,7-bis[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione) is a liposoluble molecule and a hydrophobic polyphenol derivative. Curcumin's known identifier is CAS Number:458-37-7. Its chemical formula is $\text{C}_{21}\text{H}_{20}\text{O}_6$ with a molar mass of $368.39 \text{ g}\cdot\text{mol}^{-1}$ and melting point of 183°C . (361°F ; 456 K).

[0023] Curcumin and its mono- and dimethoxy derivatives known as curcuminoids, bisdemethoxy curcumin, demethoxy curcumin, and tetrahydro curcumin, are major constituents of the curcumin formulation derived from the extraction process. Commercial curcumin can sometimes contain approximately, 77% diferuloylmethane, 17% demethoxycurcumin, and 6% bisdemethoxycurcumin. Curcumin is obtained by extraction with solvent from the dried and ground rhizome of the *Curcuma longa* (turmeric) plant. Turmeric was historically used in Indian Ayurvedic medicine to treat a wide variety of disorders, but it was not until the 20th century that scientific research identified curcumin as the factor responsible for most of its biological activity.

[0024] Curcumin has formed the subject of numerous preclinical and clinical studies, so its anti-inflammatory and antioxidant power is well documented: it possesses the ability to regulate the oxidative balance of the cells, intervening in numerous mechanisms in different ways; in particular, it inhibits a series of factors with strongly inflammatory activity (COX 1 and 2, TNF, lipoxygenase and interferon-gamma). Finally, its efficacy as an antitumoral has been demonstrated in vitro (Bengmark S., JPEN, 2006, 30(1):45-51).

[0025] The curcumin (with the derivatives thereof, such as its esters which act as prodrugs) can be acquired as such (generally associated with other curcuminoids present in smaller proportions, such as Curcumin Complex), or as Biocurcumin (BCM-95®) associated with oils and polymers that increase its bioavailability (US20070148263), or formulated in combination with piperine (Shobha et al., Planta Med, 1998, 64: 353-56), or obtained as micro- or nanoemulsions/nanodispersions that use lecithin and/or fatty acids and/or triglycerides and optionally also surfactants, such as Tween 80, to stabilize the molecule and make it more bioavailable.

[0026] It is also to be appreciated that diarylheptanoids are considered a class of compounds to which curcuminoids (e.g. curcumin) belongs. Other similar diarylheptanoids, such as those that may be obtained from ginger may possess similar properties as curcuminoids (e.g. curcumin). It will be appreciated that while curcuminoids (e.g. curcumin) may be described in detail herein, it will be appreciated that other diarylheptanoids may have similar or the same biological properties and effects, and which may be included in such compositions as described herein and may be used in the methods of treatment as described herein.

[0027] Furthermore, there is an increasing interest in the development of therapeutic compounds that may be used to improve focus, learning, memory and alertness, in both elderly and young people, individuals who need especially high memory and attention in their daily work, including students, construction workers, drivers, pilots, physicians, salespeople, executives, housewives, "high performance professionals" and people who are under mental or daily stress as

well as persons who are prone to psychiatric instability and dramatic mood swings. A therapeutic product that can provide a balanced mental state would contribute to a more productive life for a large percentage of people who live a high stress, high performance life.

[0028] Thus, in certain embodiments, the methods of the present invention comprise administering apoaquorin and curcumin as the active ingredients for improving attention span. In other embodiments, the invention provides methods which comprise administering apoaquorin and curcumin containing compositions in combination with one or more additional agents having known therapeutic or nutraceutical value. Particularly preferred applications of apoaquorin and curcumin are in treating one or more symptoms and disorders related to attention span.

[0029] As used herein, the terms “vigilance,” “sustained attention,” and “attention span” refer to an individual’s ability to attend to a stimulus or object over a period of time. In other words, the ability to maintain focus and alertness over a period of time.

[0030] As used herein, the term “treating” includes preventative as well as disorder remittent treatment. As used herein, the terms “reducing”, “alleviating”, “suppressing” and “inhibiting” have their commonly understood meaning of lessening or decreasing. As used herein, the term “progression” means increasing in scope or severity, advancing, growing or becoming worse. As used herein, the term “recurrence” means the return of a disease after a remission.

[0031] As used herein, the term “administering” refers to bringing a patient, tissue, organ or cell in contact with apoaquorin and curcumin. As used herein, administration can be accomplished *in vitro*, i.e., in a test tube, or *in vivo*, i.e., in cells or tissues of living organisms, for example, humans. In preferred embodiments, the present invention encompasses administering the formulations or compositions useful in the present invention to a patient or subject. A “patient” or “subject”, used equivalently herein, refers to a mammal, preferably a human, that either: (1) has a calcium imbalance-related disorder remediable or treatable by administration of apoaquorin and curcumin; or (2) is susceptible to a calcium imbalance-related disorder that is preventable by administering apoaquorin and curcumin.

[0032] As used herein, the terms “effective amount” and “therapeutically effective amount” refer to the quantity of active agents sufficient to yield a desired therapeutic response without undue adverse side effects such as toxicity, irritation, or allergic response. The specific “effective amount” will, obviously, vary with such factors as the particular condition being treated, the physical condition of the patient, the type of animal being treated, the duration of the treatment, the nature of concurrent therapy (if any), and the specific formulations employed and the structure of the compounds or its derivatives. In this case, an amount would be deemed

therapeutically effective if it resulted in one or more of the following: the prevention, the reversal, the stabilization, or the improvement in mental disorder, anxiety, cognitive function, sleep quality, energy quality, mood quality, pain, memory quality in a subject as compared to a subject not administered the combination. In certain embodiments, the symptom of disorder is physiologically-related to neuronal excitability, muscle contraction, membrane permeability, cell division, hormone secretion, bone mineralization, or cell death following ischemia. The optimum effective amounts can be readily determined by one of ordinary skill in the art using routine experimentation.

[0033] In certain preferred compositions for oral administration to subjects, apoaquorin is formulated in a formulation at a dosage of approximately 10 mg/dose to 80 mg/dose, preferably 20 mg/dose to 70 mg/dose, and more preferably 30 mg/dose to 60 mg/dose. Curcumin, on the other hand, is formulated in a formulation at a dosage approximately between 80 mg/dose to 1200 mg/dose, with a preferable dosage for a subject approximately 600 mg/dose to 800 mg/dose.

[0034] Conventional excipients such as diluents, ligands, bufferings, sweeteners, flavorings, colorings, solubilizers, disintegrants, wetting agents and other excipients of common use may be added to the formulation. Suitable flavoring agents include natural flavors, artificial flavors, and mints, such as peppermint, menthol, artificial vanilla, cinnamon, various fruit flavors, both individual and mixed, and the like are contemplated. The flavorings are generally utilized in amounts that will vary depending upon the individual flavor, and may, for example, range in amounts of about 0.5 to about 3% by weight of the final composition weight.

[0035] In the instance where sweeteners are utilized, the present invention contemplates the inclusion of those sweeteners well known in the art, including both natural and artificial sweeteners. Thus, additional sweeteners may be chosen from the following non-limiting list: sugars such as sucrose, glucose (corn syrup), invert sugar, fructose, and mixtures thereof; saccharin and its various salts such as the sodium or calcium salt; cyclamic acid and its various salts such as the sodium salt; the dipeptide sweeteners such as aspartame; dihydrochalcone; glycyrrhizin; Stevia rebaudiana (Stevioside); and sugar alcohols such as sorbitol, sorbitol syrup, mannitol, xylitol, and the like. Also contemplated as an additional sweetener is the nonfermentable sugar substitute (hydrogenated starch hydrolysate) which is described in U.S. Pat. No. Re 26,959. Also contemplated is the synthetic sweetener 3,6-dihydro-6-methyl-1-1-2,3-oxathiazin-4-one-2,2-dioxide particularly the potassium (Acesulfame-K), sodium and calcium salts thereof as described in German Pat. No.

2,001,017.7. In general, the amount of sweetener will vary according to the type of sweetener and the desired taste of the final product. For example, natural sweeteners may be used in amounts up to about 5% by weight, while artificial sweeteners may be in amounts up to about 1% by weight.

[0036] The colorants useful in the present invention include pigments, such as titanium dioxide, that may be incorporated in amounts of up to about 1% by weight, and preferably up to about 0.6% by weight. Also, the colorants may include other dyes suitable for food, drug and cosmetic applications, and known as F.D. & C. dyes and the like. The materials acceptable for the foregoing spectrum of use are preferably water-soluble. Illustrative examples include indigoid dye, known as F.D. & C. Blue No. 2, which is the disodium salt of 5,5'-indigotin disulfonic acid. Similarly, the dye known as F.D. & C. Green No. 1, comprises a triphenylmethane dye and is the monosodium salt of 4-[4-N ethyl-p-sulfobenzylamino)diphenylmethylene][1-(N-ethyl-N-p-sulfoniumbenzyl)-2,5-cyclohexadienimine]. A full recitation of all F.D. & C. and D. & C. dyes and their corresponding chemical structures may be found in the Kirk-Othmer Encyclopedia of Chemical Technology, in Volume 5, at Pages 857-884, which text is accordingly incorporated herein by reference.

[0037] Inventive compositions may further include liquids or lyophilized or otherwise dried formulations and include diluents of various buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength, additives such as albumin or gelatin to prevent absorption to surfaces, detergents (e.g., Tween 20, Tween 80, Pluronic F68, bile acid salts), solubilizing agents (e.g., glycerol, polyethylene glycerol), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimerosal, benzyl alcohol, parabens), bulking substances or tonicity modifiers (e.g., lactose, mannitol), covalent attachment of polymers such as polyethylene glycol to the protein, complexation with metal ions, or incorporation of the material into or onto particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, or hydrogels, or onto liposomes, microemulsions, micelles, lamellar or multilamellar vesicles, erythrocyte ghosts or spheroplasts. Such compositions will influence the physical state, solubility, stability, rate of *in vivo* release, and rate of *in vivo* clearance. Controlled or sustained release compositions include formulation in lipophilic depots (e.g., fatty acids, waxes, oils).

[0038] The preparation of compositions which contain an active component is well understood in the art. The active therapeutic ingredient is often mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient. Suitable excipients include, for example, water, saline, dextrose, glycerol, ethanol, or the like or any

combination thereof. In addition, the composition can contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents which enhance the effectiveness of the active ingredient.

[0039] An active component can be formulated into the composition as neutralized pharmaceutically acceptable salt forms. Pharmaceutically acceptable salts include the acid addition salts, which are formed with inorganic acids such as, for example, hydrochloric, or phosphoric acids, or such organic acids as acetic, tartaric, mandelic, and the like. Salts formed from the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like.

[0040] Salts of active ingredients are preferably pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compositions according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts include acid addition salts which may, for example, be formed by mixing a solution of active ingredients with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

[0041] In addition, “supplement” for the purpose of this specification, refers to a food item, or a part of a food item, that offers medical health benefits, including prevention and/or treatment of disease. A supplement composition according to the present invention may contain only apoaquorin and curcumin as active ingredients, or alternatively, may further comprise, in admixture with dietary supplements including vitamins, co-enzymes, minerals, herbs, amino acids and the like which supplement the diet by increasing the total intake of that substance.

[0042] Therefore, the present invention provides methods of providing health benefits to a patient comprising the step of administering to the subject a supplement composition containing apoaquorin and curcumin. Such compositions generally include an “acceptable carrier” which, as referred to herein, is any carrier suitable for oral delivery including aforementioned pharmaceutically-acceptable carriers suitable for the oral route. Thus, the invention provides a more favorable mechanism for orally delivering a medicament to a patient.

[0043] In certain embodiments, compositions according to the invention comprise dietary supplements which, defined on a functional basis, include immune boosting agents, anti-inflammatory agents, anti-oxidant agents, anti-viral agents, or mixtures thereof.

[0044] Immune boosters and/or anti-viral agents are useful for accelerating wound- healing and improved immune function; and they include extracts from the coneflowers, or herbs of the genus *Echinacea*, extracts from herbs of the genus *Sambuca*, and Goldenseal extracts. Herbs of the genus *Astragalus* are also effective immune boosters in either their natural or processed forms. *Astragalus* stimulates development of stem cells in the marrow and lymph tissue active immune cells. Zinc and its bioactive salts, such as zinc gluconate and zinc acetate, also act as immune boosters in the treatment of the common cold.

[0045] Antioxidants include the natural, sulfur-containing amino acid allicin, which acts to increase the level of antioxidant enzymes in the blood. Herbs or herbal extracts, such as garlic, which contain allicin, are also effective antioxidants. The catechins, and the extracts of herbs such as green tea containing catechins, are also effective antioxidants. Extracts of the genus *Astragalus* also show antioxidant activity. The bioflavonoids, such as quercetin, hesperidin, rutin, and mixtures thereof, are also effective as antioxidants. The primary beneficial role of the bioflavonoids may be in protecting vitamin C from oxidation in the body. This makes more vitamin C, or ascorbic acid, available for use by the body.

[0046] Bioflavonoids such as quercetin are also effective anti-inflammatory agents, and may be used as such in the inventive compositions. Anti-inflammatory herbal supplements and anti-inflammatory compounds derived from plants or herbs may also be used as anti-inflammatory agents in the inventive composition. These include bromelain, a proteolytic enzyme found in pineapple; teas and extracts of stinging nettle; turmeric, extracts of turmeric, or curcumin, a yellow pigment isolated from turmeric.

[0047] Another supplement which may be used in the present invention is ginger, derived from herbs of the genus *Zingiber*. This has been found to possess cardiogenic activity due to compounds such as gingerol and the related compound shogaol as well as providing benefits in the treatment of dizziness, and vestibular disorders. Ginger is also effective in the treatment of nausea and other stomach disorders.

[0048] Supplements which assist in rebuilding soft tissue structures, particularly in rebuilding cartilage, are useful in compositions for treating the pain of arthritis and other joint disorders. Glucosamine, glucosamine sulfate, chondroitin may be derived from a variety of sources such as Elk Velvet Antler. Marine lipid complexes, omega 3 fatty acid complexes, and fish oil are also known to be useful in treating pain associated with arthritis.

[0049] Supplements useful in treating migraine headaches include feverfew and *Ginkgo biloba*. The main active ingredient in feverfew is the sesquiterpene lactone parthenolide, which inhibits the secretions of prostaglandin which in turn cause pain through vasospastic activity in

the blood vessels. Feverfew also exhibits anti-inflammatory properties. Fish oil, owing to its platelet-stabilizing and antivasospastic actions, may also be useful in treating migraine headaches. The herb *Ginkgo biloba* also assists in treatment of migraines by stabilizing arteries and improving blood circulation.

[0050] Although some of the supplements listed above have been described as to their pharmacological effects, other additives may also be utilized in the present invention and their effects are well documented in the scientific literature.

[0051] The invention will be more fully understood upon consideration of the following non-limiting Examples.

III. EXAMPLES

[0052] Example 1: Administration of apoeaquorin over a ninety (90) day time course results in improved quality of life for test subjects.

[0053] The present analysis, an open-label study, of 32 patients over a 90 day period shows an increase in overall quality of sleep, energy, mood, pain, general health. Changes in performance were measured via a standardized battery of questions. These included assessments of qualitative cognitive test, a sleep index, a headache index and a Quality of Life questionnaire. The study shows improved performance. No participants discontinued the study due to an adverse event.

[0054] The results illustrated in Fig. 1 show the percent change from baseline of scores from the areas mentioned; we have excluded the memory scores for another graph. The analysis here is shown as marked on the graph as 1, 2, 3, 4 and 5 vs. days 0 through 90. The graph shows an increase in overall quality of sleep, energy, mood, pain and general health. The baseline was known from a pre-study phase.

[0055] Example 2: Administration of apoeaquorin over a thirty (30) day time course results in improved quality of life for test subjects.

[0056] The present study was an open-label study for 56 participants over a 30 day period. Changes in performance were measured via a memory screening tool. As illustrated in Fig. 2, the study showed improved memory performance as early as eight days but with statistically greater improvement at day 30. No participants discontinued the study due to an adverse event.

[0057] Example 3: Administration of apoeaquorin over a ninety (90) day time course results in improved cognition for test subjects.

[0058] The present analysis, for an open-label study of 32 patients shows an increase in cognitive ability. Changes in performance were measured via a standardized cognitive battery. The study showed improved cognition as early as eight days but with statistically greater improvement at day 30, as well as 60-90. No participants discontinued the study due to an adverse event. The results shown in Fig. 3 demonstrate the significant percent increase from baseline of scores in cognitive ability. Note: Greater than 51% of participants had an increase in cognitive ability.

[0059] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

[0060] Other embodiments and uses of the invention will be apparent to those skilled in the art from consideration from the specification and practice of the invention disclosed herein. All references cited herein for any reason, including all journal citations and U.S./foreign patents and patent applications, are specifically and entirely incorporated herein by reference. It is understood that the invention is not confined to the specific reagents, formulations, reaction conditions, etc., herein illustrated and described, but embraces such modified forms thereof as come within the scope of the following claims.