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(54) **Title**: COMPOSITIONS AND METHODS FOR NUTRITIONAL PREVENTION AND TREATMENT OF ALZHEIMER'S-ASSOCIATED CONDITIONS

(57) **Abstract**: The present invention provides nutraceutical compositions containing an aluminum-blocking component and a calcium-enhancing (and magnesium-enhancing) component, and optionally additional nutrients that address the harmful effects of aluminum on the brain. The compositions find use in nutritional methods for treating and/or preventing Alzheimer's and related conditions. The methods generally involve oral administration of the nutraceutical composition to an individual having or at risk for Alzheimer's.

COMPOSITIONS AND METHODS FOR NUTRITIONAL PREVENTION AND TREATMENT OF ALZHEIMER'S-ASSOCIATED CONDITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims the benefit of U.S. Provisional Application No. 61/144,060, filed January 12, 2009, which is hereby incorporated by reference in its entirety.

FIELD OF INVENTION

[002] The present invention relates to nutraceutical compositions and methods of using the same for preventing and treating dementia and other conditions associated with Alzheimer's disease (Alzheimer's).

BACKGROUND

[003] Alzheimer's disease (AD), Alzheimer's, or Senile Dementia of the Alzheimer Type (SDAT), is a common form of dementia, named after a German psychiatrist who was the first to describe the condition. Enserink, M. (1998). "First Alzheimer's diagnosis confirmed". Science, 279(5359): 2037. The condition is associated with protein plaques and tangles in the brain, and involves progressive degeneration of a host of cognitive and functional abilities, generally divided into four stages - predementia, early dementia, moderate dementia and advanced dementia. The mean life expectancy following diagnosis is about seven years, with fewer than three percent of patients living past fourteen years after diagnosis. Mölsä, PK, et al. (March 1995). "Long-term survival and predictors of mortality in Alzheimer's disease and multi-infarct dementia". ActaNeurol. Scand. 91(3): 159–64. Alzheimer's is currently a pandemic, involving tens of millions of victims around the world. Foster, H.D. (2004). What really causes Alzheimer's disease. (Trafford Publishing). In 2006, an estimated 26.6 million people had the disease worldwide, and this number is expected to quadruple by 2050. Brookmeyer, R., et al. (July 2007). "Forecasting the global burden of Alzheimer's disease". Alzheimer's and Dementia 3(3): 186–91.

[004] Despite enormous effort and expense, there remains no cure for this terminal condition. Moreover, current treatments offer small symptomatic benefits, as they address only one or a few of the multitude of biochemical abnormalities associated with Alzheimer's. For example, cholinesterase inhibitors, currently in use to treat Alzheimer's, aim to increase availability of just one of many affected neurotransmitters, acetylcholine, and generally only slow disease progression by a few months. Small, G.W., et al. (1997). "Diagnosis and treatment of Alzheimer's disease and related disorders". Journal of the AMA, 278, 1363-1371. Further, some other recognized treatments are associated with such severe side effects that they are typically not used to treat Alzheimer's. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce the risk of Alzheimer's,

but prolonged use is associated with gastrointestinal and renal toxicity. Etminan, M., et al. (2003). "Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer's disease: Systematic review and meta-analysis of observational studies". British Medical Journal, 327(7407): 128.

[005] In addition to such therapies, some investigators have considered nutritional approaches. However, these earlier studies generally focused on supplementing individual nutrients or small groups of nutrients, and failed to provide correct combinations addressing the numerous biochemical pathologies associated with the progression of Alzheimer's. For example, it has been demonstrated that providing a daily dose of phosphatidylserine can improve memory and behavior in elderly patients suffering from cognitive impairment, but in this approach many other significant biochemical abnormalities associated with Alzheimer's remain unaddressed. Cenacchi, T., et al. (1993) "Cognitive decline in the elderly: A double-blind, placebo-controlled multicenter study of efficacy of phosphatidylserine administration." Aging (Milano) 5(2): 123-133. Similarly, a mixture of B vitamins and several mineral ascorbates has been shown to restore memory in elderly patients, but again the combination used failed to address other Alzheimer's-associated problems. Bobkova, N.V. (2001). "The impact of mineral ascorbates on memory loss." Paper presented at the III World Congress on Vitamin C, Committee for World Health, Victoria, BC, Canada, June 2001. Thus, while various approaches have targeted select problems by correcting one or a few of the pathologies seen in Alzheimer's, other abnormal aspects of Alzheimer's biochemistry, and their corresponding symptoms, have not been addressed concomitantly.

[006] With the increasing prevalence of Alzheimer's and the lack of safe effective therapies to address the myriad of biochemical abnormalities associated with Alzheimer's, there remains a need for improved nutritional approaches. The present invention provides methods, compositions, and kits for use in the prevention and treatment of Alzheimer's and Alzheimer's-related conditions.

SUMMARY

[007] The present invention addresses the aforementioned problems in the art through the provision of neutraceutical compositions that help correct the biochemical abnormalities associated with Alzheimer's, and accordingly find use in preventing and/or treating Alzheimer's-associated conditions and the clinical symptoms thereof.

[008] In one aspect, the invention provides a nutraceutical composition for treating and/or preventing Alzheimer's, comprising or consisting essentially of an aluminum-blocking component, a calcium supplement, and a calcium-enhancing component. In preferred embodiments, the invention further comprises a magnesium supplement.

[009] In one embodiment, the aluminum-blocking component comprises boron. In another embodiment, the aluminum-blocking component comprises a mixture of silica and boron.

[0010] In one embodiment, the calcium-enhancing component comprises cholecalciferol.

[0011] In further embodiments, additional brain repair components directed to normalizing brain biochemistry and/or eliminating abnormal proteins such as *e.g.*, beta-amyloid and tau, are included. In one embodiment, these additional repair components include at least one of niacinamide, acetyl-l-carnitine, alpha lipoic acid, vitamin B12, SAM-e, and/or extra virgin coconut oil. In a further embodiment, the repair components include one or more of selenium, hyperzine A, grape seed extract, vitamin B1, folate, vitamin E, and phosphatidyl serine.

[0012] In another aspect, the invention provides a method for treating and/or preventing Alzheimer's in a patient in need thereof, comprising administering to said patient a nutraceutical composition as described above.

DETAILED DESCRIPTION

Nutraceutical Compositions

[0013] One aspect of the present invention provides nutraceutical compositions. The nutraceutical compositions provide one or more nutrients to block aluminum absorption and/or reduce or repair its harmful effects on the brain. Without being limited to a particular hypothesis or theory, it is believed that aluminum that reaches the brain can replace metal co-factors in enzymes, and impair numerous others, eventually leading to abnormal brain biochemistries characteristic of Alzheimer's and its associated conditions. In particular, aluminum acts antagonistically towards divalent metals, such as calcium and magnesium, zinc and phosphorus, which are involved in multiple aspects of normal brain biochemistry. Foster, H.D. (2000) "How Aluminum Causes Alzheimer's Disease: The Implications for Prevention and Treatment of Foster's Multiple Antagonist Hypothesis". Journal of Orthomolecular Medicine 15(1): 21-51. The nutraceutical compositions thus provide combinations of nutrients that can block aluminum absorption and/or encourage calcium and preferably magnesium utilization; and optionally that can repair brain damaged tissues and/or correct nutrient deficiencies in individuals having, or at risk for, Alzheimer's. The nutraceutical compositions of the present invention find use as nutritional therapies for such individuals and for preventing and/or treating Alzheimer's-associated conditions.

[0014] As used herein, "nutraceutical composition" refers to any edible material that comprises one or more nutrients, e.g., in a nutrient combination. "Edible material" includes material in any form that can be ingested and/or in a form that can be converted to an ingestible form, such as, by dissolving in water. For example, the nutraceutical composition can be in the form of a powder, capsule, or tablet, which contains a combination of nutrients described herein. Alternatively, the nutraceutical composition can be any food and/or drink, such as a foodstuff enriched with one or more nutrients disclosed herein or a drink formulated to contain such nutrients.

[0015] "Nutrients" as used herein refers to the components of nutraceutical compositions that serve a biochemical and/or physiological role in the human or animal body. "Nutrients" includes such substances as vitamins, minerals and trace elements and minerals, micronutrients, and the like, as well as other bioactive materials, such as components of enzymes or compounds biosynthetically produced by human or animal enzymes; as well as herbs and herbal extracts; fatty acids, amino acids and derivatives thereof. "Nutrients" is used herein interchangeably with related terms such as "nutrient supplements" or "supplements", "nutrient substances" or "substances".

[0016] The individual nutrient components may be provided in any form or combination of forms, preferably in a form allowing adequate or high bioavailability and little or no toxicity. Mineral components, for example, can be provided in the free form and/or as mineral chelates. The commercially available nutrient components useful in the practice of the present invention can be used as supplied in pharmaceutically acceptable purity. A reference to a substance includes the essentially pure substance, as well as the substance having the kinds and amounts of impurities as the skilled artisan knows or expects to be present in the commercially available substance.

[0017] Exemplary forms and sources of the components are described below. Individual nutrients also can be provided in various amounts and in various relative proportions, e.g., depending on the intended use of the nutraceutical composition. In addition to the exemplary embodiments explicitly described below, other forms, sources, amounts and proportions of the nutrient components useful in the present invention would be apparent to one of skill in the art, based on the teachings presented herein, and are also contemplated as within the scope of the invention.

Aluminum-blocking components

[0018] In some embodiments, the nutraceutical composition comprises one or more nutrients that block aluminum absorption. As used herein the term "aluminum-blocking components" refers to substances that reduce the amount of aluminum passing through the blood brain barrier, e.g. competitive antagonists such as, e.g., calcium, magnesium and boron, and compounds that inhibit aluminum's bioactivity such as, e.g., silicic acid. Preferred nutrients for blocking aluminum include boron and/or silica.

[0019] Boron is a trivalent metalloid element with atomic number 5, represented by the chemical symbol B. Boron is considered to be an ultra-trace nutrient, although its physiological role in humans remains poorly understood. Because a biochemical function has not been defined for boron, its nutritional significance has not been firmly established. It has been hypothesized that boron's small size enables it to form complexes with various organic compounds, such as carbohydrates, vitamins, enzymes and nucleotides, as well as oxygen, putting boron in a position to influence many biochemical activities. Anthony, M. (2005). "Nutrition beyond the trends: boron's a beneficial bone builder" http://www.foodprocessing.com/articles/2005/417.html. Retrieved on 05-27-2009. Boron is

also believed to help in bone growth, and to possibly play a role in preventing osteoporosis and arthritis. Schaafsma, A., et al. (May 2001). "Delay of natural bone loss by higher intakes of specific minerals and vitamins". Crit. Rev. Food Sci. Nutr. 41(4): 225-49.

[0020] Boron is commonly found in fruits, especially prunes, vegetables, especially dark leafy vegetables, legumes, and nuts. Other rich sources include, e.g., cheese, sardines, salmon, and sesame seeds, as well as applesauce, grape juice, and red wine. Naghii, M.R., et al. (Dec. 1996) "The boron content of selected foods and the estimation of its daily intake among free-living subjects." J. Am. Coll. Nutr. 15(6): 614-9.

[0021] In some embodiments, the nutraceutical composition comprises boron in an amount from about 1 to about 20 mg, preferably from about 2 to about 15 mg, and more preferably about 3 to about 10 mg. In some still more preferred embodiments, the nutraceutical composition comprises boron in an amount from about 3 mg to about 7 mg. In some embodiments, the composition comprises from at least about 3.5, at least about 4, at least about 5, or at least about 5.5 mg of boron. In some embodiments, the composition comprises less than about 6.5, less than about 6, less than about 5, or less than about 4.5 mg of boron. In a particularly preferred embodiment, about 5 mg of boron are provided. Boron can be used in the nutraceutical compositions of the instant invention to block aluminum absorption, with or without silica.

[0022] Silica is the chemical compound silicon dioxide, which is an oxide of silicon with a chemical formula SiO_2. Silica is most commonly found in nature as sand or quartz, as well as in the cell walls of diatoms. Silicon also is found in body tissues, such as nails and connective tissues, including bone, blood vessels, cartilage, and tendons. Silica is used as a food additive, for example, as a "flow agent" in powdered foods and pharmaceutical products, or to absorb water. Silicon also is used in herbal therapies, for example, to promote healthy hair, skin, and nails.

[0023] Without being bound to a particular hypothesis or theory, it is believed that silica acts to block aluminum by promoting the formation of aluminosilicate species, which limits the gastrointestinal absorption of aluminum. Silica's high affinity for aluminum influences aluminum absorption by the intestinal tract, thereby providing a protective effect at adequately high levels of silica.

[0024] Silicon is widely available in foodstuffs. It forms part of plant fibers, and is found in high amounts in the hulls of wheat, rice, and oats, in beet and cane pulp, as well as in alfalfa and the herbs horsetail, comfrey, and nettles. Horsetail, *Equisetum arvensa*, is a common source used to make silica supplements. A preferred source is Spring Horsetail, available, e.g., from Flora Manufacturing & Distributing Ltd., British Columbia, Canada, which comprises about 2% organic silica by weight. Silicon is also present, for example, in avocados, cucumbers, dandelions and other dark greens, lettuce, onions, and strawberries. Hard drinking water provides still another source. Haas, E., et al. (2006) Staying Healthy with Nutrition: The Complete Guide to Diet and Nutritional Medicine. Potable

water having silica of at least about 3 mg per liter is preferred, more preferably at least about 3.5 mg/liter, at least about 5 mg/liter, at least about 10 mg/liter, at least about 11.25 mg/liter, at least about 12 mg/liter, or at least about 15 mg/liter, particularly where the water pH is high. See, e.g., Rondeau, V., et al. (2000). Relationship between aluminum concentrations in drinking water and Alzheimer's disease: An 8-year follow-up study. American Journal of Epidemiology, 154(3), 288-290.

[0025] In some embodiments, the nutraceutical composition comprises silicon in an amount from about 5 mg to about 50 mg, preferably from about 7 to about 40 mg, and more preferably from about 10 to about 35 mg. In some still more preferred embodiments, the nutraceutical composition comprises silica in an amount from about 7 mg to about 13 mg. In some embodiments, the composition comprises from at least about 8, at least about 9, at least about 10, or at least about 11 mg of silica. In some embodiments, the composition comprises less than about 12, less than about 11, less than about 10, or less than about 9 mg of silica. In a particularly preferred embodiment, about 10 mg of silica, more preferably organic silica, are provided, for example as about 500 mg of Spring Horsetail. Silica can be used in the nutraceutical compositions of the instant invention to block aluminum absorption, with or without boron, as described above.

[0026] Preferred embodiments use both silica and boron in combination. The combined protective properties of these nutrients have a synergistic effect in preventing aluminum from reaching the brain.

Calcium-enhancing components

[0027] In some embodiments, the nutraceutical composition comprises one or more nutrients that encourage calcium utilization. As used herein the term "calcium-enhancing components" refers to substances that improve/increase the absorption and/or bioavailability of calcium *in vivo*, e.g. calcium transporters such as, e.g., pectin; compounds involved in calcium metabolism such as, e.g., cholecalciferol (vitamin D3); and the like. Vitamin D3 is a preferred nutrient for enhancing the use of calcium.

[0028] Vitamin D3 (cholecalciferol or calciol) is one of two major forms of vitamin D, a group of fat-soluble pro-hormones. It is structurally similar to steroids, such as testosterone, cholesterol, and cortisol. Vitamin D3 itself has a number of forms, including cholecalciferol, (sometimes called calciol) which is an inactive unhydroxylated form; calcidiol (also called 25-hydroxyvitamin D3), which is the form measured in the blood to assess vitamin D status; and calcitriol (also called 1,25-dihydroxyvitamin D3), which is the active form of the vitamin. As used herein, vitamin D3 refers to any of these forms as well as to metabolites or other analogues of the vitamin.

[0029] Vitamin D3 is produced in skin when exposed to sunlight, specifically ultraviolet B radiation. Whether produced in the skin or consumed in food, vitamin D3 is converted in the liver and kidney to the physiologically active form. Vitamin D3 is known to regulate calcium and phosphorus levels in the

blood by promoting their absorption from food in the intestines, and by promoting re-absorption of calcium in the kidneys, which enables normal bone growth and remodeling. van den Berg, H. (January 1997). "Bioavailability of vitamin D". Eur. J. Clin. Nutr. 51 Suppl. 1: S76–9; Cranney, A., et al., (August 2007). "Effectiveness and safety of vitamin D in relation to bone health". Evid. Rep. Technol. Assess 158: 1–235. Vitamin D3 also is known to affect the immune system, e.g., by promoting phagocytosis, anti-tumor activity, and immunomodulatory functions. Tavera-Mendoza, L.E. et al., (November 2007). "Cell defenses and the sunshine vitamin". Sci. Am. 297 (5): 62–5, 68–70.

[0030] Without being bound to a particular hypothesis or theory, it is believed that vitamin D3 encourages calcium utilization in the body by working with the parathyroid hormone to regulate the level of calcium in the blood.

[0031] While cholecalciferol can be synthesized in the skin, it is also the form of vitamin D3 commonly added to fortify foods. High levels of vitamin D3 are also naturally found in certain foods, e.g., cod liver oil, salmon, mackerel, tuna, sardines and milk. Cholecalciferol can be produced industrially, for example, by the irradiation of 7-dehydrocholesterol, which can be extracted from lanolin found in sheep's wool. In some embodiments, the nutraceutical composition comprises vitamin D3, preferably in the cholecalciferol form.

[0032] In some embodiments, the nutraceutical composition comprises vitamin D3 in an amount from about 2000 IU to about 4000 IU. In some embodiments, the composition comprises from at least about 2250, at least about 2500, at least about 2750, or at least about 3000 IU of vitamin D3. In some embodiments, the composition comprises less than about 3750, less than about 3500, less than about 3250, or less than about 3000 IU of vitamin D3. In a particularly preferred embodiment, about 3000 IU of vitamin D3 are provided.

[0033] Vitamin D3 can be used in the nutraceutical compositions of the instant invention to enhance calcium utilization, in combination with one or more nutrients that block aluminum absorption. The combined actions of blocking aluminum absorption while concomitantly enhancing calcium (and magnesium) use, e.g., to counteract any aluminum that does cross the blood brain barrier, have a synergistic effect in protecting the brain from aluminum and its deleterious metabolic consequences. For example, calcium can replace aluminum as the correct cofactor of one or more brain enzymes, allowing the enzyme(s) to resume normal function. Such brain enzymes may include, e.g., glucose-6-phosphate dehydrogenase, hexokinase, phosphofructokinase, choline acetyltransferase, adenylate cyclase, dihydropteridine reductase, glutamae decarboxylase, calcium/ calmodulin kinase II, alkaline phosphatase, phospholipase A2, Na^+ K^+ ATPase, and 2'3'-cyclic nucleotide phosphohydrolase.

[0034] Pectin is another nutrient that can enhance the use of calcium, as it is a calcium transporter. Good sources of pectin include, for example, apples, oranges, lemons, broccoli, cabbage, kale,

tomatoes, and carrots. In some embodiments, the nutraceutical composition comprises pectin, with or without vitamin D3, as the calcium-enhancing component.

Brain-repairing components

[0035] In some embodiments, the nutraceutical composition comprises one or more nutrients that help repair brain tissue, for example, by reversing the effect of aluminum neurotoxicity. As used herein the term "brain-repairing components" refers to nutrient supplements that help repair brain damage. Preferred nutrients for repairing brain damage include (1) niacinamide, (2) acetyl-l-carnitine, (3) alpha lipoic acid, (4) vitamin B12, (5) S-adenosylmethionine, and (6) coconut oil or components. Each of these six components are discussed below.

[0036] (1) Niacinamide ($C_6H_5NO_2$) is a water-soluble B-complex vitamin. Niacinamide, also known as nicotinamide or nicotinic acid amide, is the amide of nicotinic acid or niacin, which itself is vitamin B3. Niacin, is converted to niacinamide *in vivo*, and incorporated into nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which are coenzymes for in a wide variety of enzymatic oxidation-reduction reactions.

[0037] Without being bound to a particular hypothesis or theory, it is believed that niacinamide helps repair brain damage caused by aluminum by acting to help remove the abnormal protein tau, which is largely responsible for the abnormal tangles seen in the brains of Alzheimer's patients. The human brain has comparatively little ability to repair itself, so that aluminum's damage tends to be cumulative, if not aided by specifically-supplied combinations of nutrients.

[0038] Niacinamide can be found in many foods, including yeast, turkey, chicken, meat, (particularly pork, veal, and beef liver), fish (particularly halibut, tuna, swordfish, and salmon), milk, eggs, green vegetables, sunflower seeds, peanuts, and cereal grains. Dietary tryptophan is also converted to niacin in the body. Niacinamide can also be produced commercially by aqueous ammonolysis of 3-cyanopyridine (nicotinonitrile) and subsequent crystallization. Niacinamide is also widely available commercially, e.g., as a supplement found in many health food stores.

[0039] In some embodiments, the nutraceutical composition comprises niacinamide in an amount from about 100 mg to about 5 grams, preferably from about 200 mg to about 4 grams, and more preferably from about 250 mg to about 3 grams. In still more preferred embodiments, the nutraceutical composition comprises niacinamide in an amount from about 1 g to about 3 g. In some embodiments, the composition comprises from at least about 1.2, at least about 1.5, at least about 1.8, or at least about 2 g of niacinamide. In some embodiments, the composition comprises less than about 2.8, less than about 2.5, less than about 2.2, or less than about 2 g of niacinamide. In a particularly preferred embodiment, about 2 g of niacinamide are provided.

[0040] (2) Acetyl-l-carnitine (3-acetyloxy-4-trimethylammonio-butanonate or ALCAR) is an acetylated form of L-carnitine, which itself is derived from the amino acids lysine and methionine. It is known that acetyl-l-carnitine in the body acts at cholinergic neurons, helps with membrane stabilization, and improves mitochondrial function, for example, by transporting fatty acids into mitochondria, facilitating their oxidation and energy utilization. Hudson, S., et al. (2003) "Acetyl-l-carnitine for dementia". Cochrane Database of Systematic Reviews, (2), CD003158.

[0041] Without being bound to a particular hypothesis or theory, it is believed that acetyl-l-carnitine helps repair brain damage caused by aluminum by stimulating production of the brain chemical acetylcholine, removing toxic fatty-acid metabolites from mitochondria, and helping to regenerate free radical-damaged neurons, e.g., facilitating myelin repair.

[0042] Food sources for L-carnitine include, e.g., red meat (particularly beef and lamb). It is also found in pork, bacon, cod, nuts, and seeds. Acetyl-l-carnitine also is commercially available as supplements, e.g., supplements claiming to help burn unwanted fat, or to supplement a vegetarian diet.

[0043] In some embodiments, the nutraceutical composition comprises acetyl-l-carnitine in an amount from about 300 mg to about 700 mg. In some embodiments, the composition comprises from at least about 350, at least about 400, at least about 450, or at least about 500 mg of acetyl-l-carnitine. In some embodiments, the composition comprises less than about 650, less than about 600, less than about 550, or less than about 500 mg of acetyl-l-carnitine. In a particularly preferred embodiment, about 500 mg of acetyl-l-carnitine are provided.

[0044] (3) Alpha lipoic acid, also known as lipoic acid, thioctic acid, or 6,8-dithiooctanoic acid, has molecular formula $C_8H1_{14}O_2S_2$ and a yellow crystalline appearance. The compound is a carboxylic acid with a cyclic disulfide functional group. In cells, the R-enantiomer is biosynthesized and functions as an enzyme cofactor, for example in aerobic metabolism. Alpha lipoic acid mostly exists as reduced dihydrolipoic acid inntracellularly, and as lipoate, the conjugate base of lipoic acid, at physiological conditions.

[0045] Without being bound to a particular hypothesis or theory, it is believed that alpha lipoic acid helps repair brain damage caused by aluminum by acting to greatly reduce oxidative stress.

[0046] Alpha lipoic acid is found in almost all foods, but slightly more so in kidney, heart, liver, spinach, broccoli, and yeast extract. However, as it is present only in very low amounts from natural sources, alpha lipoic acid supplements are generally always chemically synthesized, usually resulting in a racemic mixture of the R and S enantiomers. Alpha lipoic acid supplements are commercially available, e.g., from many health food stores.

[0047] In some embodiments, the nutraceutical composition comprises alpha lipoic acid in an amount from about 100 mg to about 300 mg. In some embodiments, the composition comprises from at least about 125, at least about 150, at least about 175, or at least about 200 mg of alpha lipoic acid. In some embodiments, the composition comprises less than about 275, less than about 250, less than about 225, or less than about 200 mg of alpha lipoic acid. In a particularly preferred embodiment, about 200 mg of alpha lipoic acid are provided.

[0048] (4) Vitamin B12, or α-(5,6-dimethylbenzimidazolyl)cobamidcyanide, is a water soluble vitamin, having a complicated structure and containing the biochemically rare element cobalt. Biosynthesis of the basic structure of the vitamin is accomplished only by bacteria, but conversion between different forms can be accomplished in the human body. The vitamin is normally involved in the metabolism of every cell of the body, affecting DNA synthesis and regulation in particular, as well as fatty acid synthesis and energy production. It also plays key roles in the normal functioning of the brain and nervous system, as well as in blood formation.

[0049] Without being bound to a particular hypothesis or theory, it is believed that vitamin B12 helps repair brain damage caused by aluminum by reducing homocysteine production and maintaining normal homocysteine levels. As the amino acid methionine is metabolized, homocysteine is produced before it is recycled to methionine or converted into a final breakdown product, cystathionine. Vitamin B12 plays a role is these processes, with the result that vitamin B12 deficiency in part may lead to slowed homocysteine metabolism, where abnormal levels of homocysteine build up, creating a condition known as homocysteinemia. It has been hypothesized that abnormally high homocysteine levels can impair cognitive function and increase the risk of Alzheimer's. See, e.g., Seshadri, S., et al., (2002). Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. New England Journal of Medicine, 346(7), 476-483; and Miller, J.W., Green, R., Ramas, M.I., Allen, L.H., Mungas, D.M., et al., (2003). Homocysteine and cognitive function in the Sacramento area Latino study on aging. American Journal of Clinical Nutrition, 78(3), 441-447.

[0050] Vitamin B12 is found in foods that come from animals, including fish, meat (especially liver and shellfish), poultry, milk, and milk products. Vitamin B12 is biochemically synthesized by species of several genera, including, for example, *Aerobacter, Corynebacterium, Flavobacterium, Micromonospora, Streptococcus* and *Xanthomonas*, and industrial production of B12 involves fermentation of selected microorganisms. Martens, J.H., et al. (2002). "Microbial production of vitamin B12". Applied Microbiology and Biotechnology 58: 275–285. A common synthetic form of the vitamin, cyanocobalamin, does not occur in nature, but is used in many pharmaceuticals and supplements, and as food additive, e.g., in energy drinks. In the body it is converted to the physiological forms. Related forms, hydroxocobalamin, methylcobalamin, and adenosylcobalamin, also can be found in pharmacological products and food supplements.

[0051] In some embodiments, the nutraceutical composition comprises vitamin B12 in an amount from about 25 to about 250 mg, preferably from about 50 to about 200 mg, and more preferably from about 75 to about 150 mg. In some still more preferred embodiments, the nutraceutical composition comprises vitamin B12 in an amount from about 2 mg to about 4 mg. In some embodiments, the composition comprises from at least about 2.2, at least about 2.5, at least about 2.8, or at least about 3 mg of vitamin B12. In some embodiments, the composition comprises less than about 3.8, less than about 3.5, less than about 3.2, or less than about 3 mg of vitamin B12. In a particularly preferred embodiment, about 3 mg of vitamin B12 are provided.

[0052] (5) S-adenosylmethionine, abbreviated SAM, SAMe, or SAM-e, is a co-enzyme, normally involved in methyl group transfers. It is made from adenosine triphosphate (ATP) and methionine. It is involved in transmethylations, transsulfurations, and aminopropylations, anabolic reactions that occur throughout the body. SAM-e is needed for cellular growth and repair, and is involved in the biosynthesis of several hormones and neurotransmitters that affect mood, including dopamine and serotonin.

[0053] SAM-e is generally commercially available, e.g., as a nutritional supplement sold in many health food stores. Because of SAM-e's structural instability, stable salt forms are preferred, e.g., for oral administration. Commonly used salts include, without limitation, butanedisulfonate, tosylate, disulfate tosylate, disulfate monotosylate, and disulfate ditosylate.

[0054] In some embodiments, the nutraceutical composition comprises SAM-e in an amount from about 200 to about 1800 mg, preferably from about 400 to about 1600 mg, and more preferably from about 600 to about 1400 mg. In some embodiments, the composition comprises from at least about 400, at least about 600, at least about 700, or at least about 800 mg of SAM-e. In some embodiments, the composition comprises less than about 1600, less than about 1400, less than about 1200, or less than about 1000 mg of SAM-e.

[0055] (6) Coconut oil is a tropical oil extracted from copra, the meat or "jelly" of a coconut. Coconut oil is a fat containing predominantly medium chain triglycerides, with about 92% saturated fatty acids, about 6% monounsaturated fatty acids, and about 2% polyunsaturated fatty acids. The saturated fatty acids include about 44.6% lauric acid, about 16.8% myristic acid, about 8.2% palmitic acid, and about 8% caprylic acid. The monounsaturated fatty acid component is oleic acid; and the polyunsaturated fatty acid is linoleic acid. As well as or in place of the coconut oil component, a suitably selected oil having a similar medium chain triglyceride content, and/or similar saturation composition, may be used in some embodiments.

[0056] In the human body, the lauric acid of coconut oil is converted into monolaurin. Hegde B. (2006). "Coconut oil - ideal fat next to mother's milk". JIACM. 7:16-19. Without being bound to a particular hypothesis or theory, it is believed that one or more components of coconut oil help repair

brain damage caused by aluminum by providing an alternative energy source beyond glucose to brain neurons. For example, medium chain triglyceride oils (present in virgin coconut oil) can be converted in the liver to ketone bodies, which in turn can be used by the brain as an energy source, in the event of low glucose. It is also believed that coconut oil reduces the transport of aluminum across the blood brain barrier.

[0057] Coconut oil may be virgin, refined, hydrogenated or fractionated. Virgin oil in preferred in some embodiments of the instant invention, more preferably extra virgin coconut oil. Virgin coconut oil is derived from fresh (rather than dried) coconuts. Virgin coconut oil can be produced by quick-drying or wet-milling the coconut milk or shredded meat. In the quick-drying technique, oil is pressed out of fresh coconut meat. Wet-milling involves extracting the oil from fresh coconut milk without drying, and then separating the oil from the water component. Wet-milling the shredded meat, also called direct micro-expulsion, involves shredding and then partly-drying fresh coconut meat, and then pressing the moist shredded coconut to expel virgin coconut oil. About 85% of all coconuts are produced by an 18 member Asian and Pacific Coconut Community (APCC) that has published an Interim Standard for Virgin Coconut Oil.

[0058] As would be known to one skilled in the art, any edible oil having a similar fatty acid composition to that of coconut oil would be suitable, for example, other oils containing a high content of saturated fatty acids and/or that comprise medium chain triglycerides. A non-limiting example of such an oil is palm oil.

[0059] In some embodiments, the nutraceutical composition comprises coconut oil (or a suitably selected oil having a similar medium chain triglyceride content and/or similar saturation), for example, from about 20 to about 75 grams, preferably from about 30 to about 60 grams, and more preferably about 35 to about 50 grams. In some still more preferred embodiments, the nutraceutical composition comprises coconut oil, preferably virgin coconut oil, more preferably extra virgin coconut oil, in an amount from about 1 to about 5 tablespoons. In some embodiments, the composition comprises from at least about 1.5, at least about 2, at least about 2.5, or at least about 3 tablespoons of coconut oil. In some embodiments, the composition comprises less than about 4.5, less than about 4, less than about 3.5, or less than about 3 tablespoons of coconut oil. In a particularly preferred embodiment, about 2 to about 4 tablespoons of coconut oil are provided, more preferably virgin coconut oil, and still more preferably extra virgin coconut oil.

[0060] Coconut oil, SAM-e, vitamin B12, alpha lipoic acid, acetyl-l-carnitine, and/or niacinamide can be used in the nutraceutical compositions of the instant invention to repair aluminum-related degenerative effects on brain tissues. The combination of two of more of these nutrients provides synergistic benefits in bringing about this repair, e.g., in that they address different forms of brain damage. As discussed above, for example, medium chain triglycerides in virgin coconut oil address

glucose deficiency; acetyl-l-carnitine helps repair free radical-damaged neurons; niacinamide helps remove tau proteins; and so on.

[0061] In some embodiments, the nutraceutical composition comprises one or more additional nutrients that help repair brain damage caused by aluminum. In a particularly preferred embodiment, the nutraceutical composition comprises grape seed extract, or one or more components thereof. In some embodiments, the nutraceutical composition provides from about 50 to about 100 mg of grape seed extract, and a particularly preferred embodiment provides about 75 mg.

[0062] In some embodiments, the nutraceutical composition further includes one or more of the six nutrients listed in Table 1 below, to further help repair brain damage. In some preferred embodiments, the nutraceutical composition comprises the amounts suggested in the Table, for the corresponding nutrient component.

Table 1.

Additional nutrients for brain repair	Suggested amounts
Selenium	200 mcg
Hyperzine A	200 mcg
Vitamin B1	50 mg
Vitamin B9 (folate)	2 mg
Vitamin E	200 IU
Phosphatidyl serine	500 IU

[0063] In some embodiments, selenium is provided as L-selenomethionine or L-selenocysteine or a combination of both. In some embodiments, the selenomethionine form is particularly preferred. In some embodiments, selenomethionine or selenium is provided in an amount from about 100 to about 600 µg, preferably from about 150 to about 500 µg, and more preferably from about 200 to about 400 µg (if provided as selenium, approximately the same dosage is recommended, as the uptake of selenium is less than selenomethionine; however, if the same dosage is desired, then the values should be multiplied by 0.4 to arrive at the same actual amount of selenium ingested).

[0064] In some embodiments hyperzine A is provided as Club moss (Lycopodium) extract, for example, in an amount from about 20 to about 250 µg, or from about 40 to about 225 µg, or from about 50 to about 200 µg.

[0065] In some embodiments, vitamin B1 is provided in an amount from about 25 to about 250 mg, from about 50 to about 200 mg, or from about 75 to about 150 mg.

[0066] In some embodiments, folic acid is provided in an amount from about 200 µg to about 5 mg, from about 300 µg to about 4 mg, or from about 400 µg to about 3 mg.

[0067] In some embodiments, phosphatidyl serine is provided in an amount from about 100 to about 1000 mg, from about 200 to about 900 mg, or from about 300 to about 800 mg. Without being bound to a particular hypothesis or theory, phosphatidyl serine may stimulate the cerebral metabolic rate for glucose, thus aiding in repair of damaged brain tissue.

[0068] As with the nutrients discussed above, these additional nutrients may be provided in any form, preferably in a form allowing adequate or high bioavailability and no or low toxicity. The additional nutrients may also be provided in various amounts and relative proportions, e.g., depending on the intended use of the nutraceutical composition. In addition to the exemplary embodiments explicitly described, other forms, sources, amounts and proportions of these six additional nutrient supplements useful in the present invention would be apparent to one of skill in the art, based on the teachings presented herein, and are also contemplated as within the scope of the invention.

[0069] In some preferred embodiments, one or more nutrients for repairing brain damage is used in combination with one or more nutrients that block aluminum; and/or in combination with one or more nutrients that enhance calcium (and magnesium) utilization. A particularly preferred combination comprises, for example, one or more nutrients selected from coconut oil, SAM-e, vitamin B12, alpha lipoic acid, acetyl-l-carnitine, and niacinamide; in combination with boron and/or silica; and/or in combination with vitamin D3. Some embodiments further include grape seed extracts (or components thereof) in the nutraceutical composition. The combined actions of blocking aluminum absorption while concomitantly enhancing the utilization of calcium (and magnesium), as well as concomitantly repairing any aluminum-related damage already done, is believed to have synergistic effects in protecting and restoring normal brain biochemistry. For example, nutrient combinations in preferred embodiments will act to address different forms of brain damage, as described above, with synergistic results.

Nutrition-supplementing components

[0070] In some embodiments, the nutraceutical composition comprises one or more nutrients that correct nutritional deficiencies, for example, nutritional deficiencies that exacerbate the harmful effects of aluminum on brain biochemistry. Preferred nutrients to correct such deficiencies include calcium and magnesium, preferably calcium ascorbate and magnesium ascorbate.

[0071] Calcium is a chemical element with symbol Ca and atomic number 20. Calcium is essential for living organisms, particularly in cell physiology, where the movement of calcium ions into and out of the cytoplasm acts as a signal for many cellular processes. Calcium is also a major material needed for the mineralization of bones. Calcium ascorbate is the calcium salt of ascorbic acid, aka vitamin C.

[0072] Without being bound to a particular hypothesis or theory, it is believed that calcium reduces the harmful effects of aluminum on the brain. It is believed that aluminum crossing the blood brain barrier replaces calcium cofactors in various enzymes involved in normal brain biochemistry, such as calcium/calmodulin kinase II, especially where calcium itself is deficient, causing the brain enzyme to malfunction. Other possibly affected brain enzymes include glucose-6-phosphate dehydrogenase, hexokinase, phosphofructokinase, choline acetyltransferase, adenylate cyclase, dihydropteridine reductase, glutamae decarboxylase, alkaline phosphatase, phospholipase A2, Na^+ K^+ ATPase, and/or 2'3'-cyclic nucleotide phosphohydrolase. Higher dietary levels of calcium can replace aluminum as the correct cofactor of one or more of these brain enzymes, allowing the enzyme(s) to resume normal function. Further, dietary calcium, especially calcium ascorbate, reduces aluminum's absorption into the blood stream from the gastrointestinal tract, by competing with it for absorption. Providing additional amounts of calcium, particularly as a calcium ascorbate supplement, can thus reduce aluminum neurotoxicity.

[0073] Calcium is found in many foods, including, for example, nuts (such as almonds, Brazil nuts, hazelnuts, and sunflower seeds); vegetables (such as black beans, bok choy, broccoli, collards, kale, pinto beans, spinach, and turnip greens); meats (such as beef flan steak, rabbit and chili con carne with beans); seafood (such as agar-agar, carp, crab, hijiki, kombu, oysters, salmon, sardines, shrimp, and wakame); grains and baked foods (such as bran muffins, fortified oat flakes, peanut butter cookies, baked custard, blackstrap molasses, and rice pudding); as well as cheddar cheese, edam, gruyere, parmesan, ricotta, sour cream, dry whole milk, yogurt, figs, dried pears, and papaya. Preferred food sources include salmon, sardines, broccoli, spinach, and bok choy, which are all high in calcium. Garland, C., et al. (1989). "The calcium connection". New York: Simon and Schuster, Inc. Further, calcium ascorbate can be manufactured by reacting ascorbic acid with calcium carbonate in aqueous solution, releasing carbon dioxide, drying the reaction product, and then milling the dried product to the desired particle size. Calcium supplements, including calcium ascorbate supplements, are commercially available, e.g., Super-Gram II from Alacer Corporation, California supplies calcium ascorbate; and Emer'gen-C is a fizzing drink mix that provides vitamin C and calcium.

[0074] In some embodiments, the nutraceutical composition comprises calcium, preferably as calcium ascorbate or calcium d-pantothenate, in an amount from about 100 to about 700 mg, preferably from about 150 to about 600 mg, and more preferably from about 200 to about 500 mg (these values should be multiplied by approximately 1.2 if calcium d-pantothenate is provided). In still more preferred embodiments, the nutraceutical composition comprises calcium, preferably calcium ascorbate, in an amount from about 400 mg to about 800 mg. In some embodiments, the composition comprises from at least about 450, at least about 500, at least about 550, or at least about 600 mg of calcium ascorbate. In some embodiments, the composition comprises less than about 750, less than about 700, less than about 650, or less than about 600 mg of calcium ascorbate. In a particularly preferred embodiment, about 600 mg of calcium ascorbate are provided.

[0075] Magnesium is a chemical element with the symbol Mg and atomic number 12. Magnesium is a vital dietary component. Magnesium ions are essential to the basic nucleic acid chemistry of life, and over 300 known enzymes use magnesium ions in their catalytic activities, including all enzymes that use or synthesize ATP or the other DNA or RNA nucleotides. Magnesium ascorbate is the magnesium salt of ascorbic acid, aka vitamin C.

[0076] Without being bound to a particular hypothesis or theory, it is believed that magnesium reduces the harmful effects of aluminum on the brain. It is believed that aluminum crossing the blood brain barrier interferes with the role magnesium plays in various enzymes and biological structures involved in normal brain biochemistry, especially if magnesium is itself deficient, causing the brain enzymes to malfunction. Brain enzymes possibly affected include, e.g., calcium/ calmodulin kinase II, glucose-6-phosphate dehydrogenase, hexokinase, phosphofructokinase, choline acetyltransferase, adenylate cyclase, dihydropteridine reductase, glutamae decarboxylase, alkaline phosphatase, phospholipase A2, Na^+ K^+ ATPase, and/or 2'3'-cyclic nucleotide phosphohydrolase. Higher dietary levels of magnesium can displace aluminum, allowing the enzyme(s) to resume normal function. Further, dietary magnesium, like calcium, competitively affects aluminum's absorption into the blood stream from the gastrointestinal tract. Providing additional amounts of magnesium, particularly as a magnesium ascorbate supplement, can thus reduce aluminum neurotoxicity.

[0077] Magnesium is found in many foods, including, for example, nuts (such as almonds, Brazil nuts, cashews, hazelnuts, peanuts, and pumpkin seeds); vegetables (such as black eyed peas, Swiss chard, collards, kohlrabi, green peas, spinach, turnip greens, yams); meats (such as beef flansteak, lean ground beef, beef round stead, ham venison and goose); seafood (such as cod, crab, flat fish, haddock, mackerel, oysters, shrimp, and snapper); grains and baked goods (such as whole wheat muffins, taco shells, bran flakes, granola, toasted wheat germ, blackstrap molasses, and brown whole grain rice); as well as dry whole or nonfat milk, eggnog, avocado, figs, dried peaches and pears, and raisins. Preferred sources from food include pumpkin seeds, almonds, Brazil nuts, and whole grain brown rice. Magnesium ascorbate can be manufactured by reacting ascorbic acid with magnesium carbonate in aqueous solution, releasing carbon dioxide, drying the reaction product, and then milling the dried product to the desired particle size. Magnesium supplements, including magnesium ascorbate supplements, are commercially available, e.g., Super-Gram II from Alacer Corporation, California supplies magnesium ascorbate; and Emer'gen-C is a fizzing drink mix that provides vitamin C and magnesium.

[0078] In some embodiments, the nutraceutical composition comprises magnesium, preferably magnesium ascorbate or magnesium stearate, in an amount from about 100 to about 700 mg, preferably from about 150 to about 600 mg, and more preferably from about 200 to about 500 mg for magnesium ascorbate (these values should be multiplied by approximately 1.6 if magnesium stearate is provided). In some still more preferred embodiments, the nutraceutical composition comprises

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magnesium, preferably magnesium ascorbate, in an amount from about 400 mg to about 800 mg. In some embodiments, the composition comprises from at least about 450, at least about 500, at least about 550, or at least about 600 mg of magnesium ascorbate. In some embodiments, the composition comprises less than about 750, less than about 700, less than about 650, or less than about 600 mg of magnesium ascorbate. In a particularly preferred embodiment, about 600 mg of magnesium ascorbate are provided.

[0079] In some embodiments, the nutraceutical composition further includes one or more of the six nutrients listed in Table 2 below, to further correct nutritional deficiencies that otherwise exacerbate the harmful effects of aluminum on brain chemistry. In some preferred embodiments, the nutraceutical composition comprises the amounts suggested in the Table, for the corresponding nutrient component.

Table 2.

Additional nutrient supplements	Suggested amounts
Manganese ascorbate	2 mg
Chromium ascorbate	120 mcg
Molybdenum ascorbate	100 mcg
Potassium ascorbate	140 mg
Citrus bioflavonoid complex	400 mg
Quercetin	30 mg

[0080] In some embodiments, vitamin C is added (in addition to or instead of using ascorbate), preferably as ascorbic acid, for example, from about 1 to about 20 grams, preferably from about 2 to about 15 grams, and more preferably from about 2 to about10 grams.

[0081] In some embodiments, manganese (preferably as manganese ascorbate) is provided in an amount from about 0.3 to about 1.5 mg, or from about 0.4 to about 1.2 mg, or from about 0.5 to about 1.0 mg.

[0082] In some embodiments, chromium (preferably as chromium ascorbate) is provided in an amount from about 30 to about 200 µg, or from about 50 to about 175 µg, or from about 60 to about 150 µg. Chromium may also or instead be provided in other forms, for example, as chromium picolinate (noting that if the same dosage of chromium is desired as that of chromium picolinate, the values should be multiplied by about 8.2 to arrive at the same actual amount of chromium ingested).

[0083] In some embodiments, molybdenum (preferably as molybdenum ascorbate) is provided in an amount from about 30 to about 200 µg, or from about 40 to about 175 µg, or from about 50 to about 100 µg.

[0084] In some embodiments, potassium (preferably as potassium ascorbate) is provided in an amount from about 50 to about 350 mg, or from about 75 to about 300 mg, or from about 100 to about 250 mg.

[0085] In some embodiments, citrus bioflavonoid complex is provided in an amount from about 150 to about 450 mg, or from about 175 to about 400 mg, or from about 200 to about 350 mg.

[0086] In some embodiments, Quercetin is provided in an amount from about 5 to about 500 mg, or from about 10 to about 350 mg, or from about 15 to about 250 mg

[0087] As with the nutrients discussed above, these additional nutrients may be provided in any form, preferably in a form allowing adequate or high bioavailability and no or low toxicity. The additional nutrients may also be provided in various amounts and relative proportions, e.g., depending on the intended use of the nutraceutical composition. In addition to the exemplary embodiments explicitly described, other forms, sources, amounts and proportions of these six additional nutrient supplements useful in the present invention would be apparent to one of skill in the art, based on the teachings presented herein, and are also contemplated as within the scope of the invention.

[0088] Mineral components, e.g., calcium and magnesium, may be provided in the free form or as mineral chelates or the chelating agents may be replaced. For example, ascorbate may be replaced with an alterative chelating agent, for example, but not limited to glycine, aspartate, and other suitable amino acids, citrate and other suitable Kreb's cycle compounds, and picolinate. Similarly picolinate may be replaced with alternative chelating agents, for example, but not limited to glycine, aspartate, and other suitable amino acids, citrate and other suitable Kreb's cycle compounds, and ascorbate. Appropriate calculations to adjust the dosage would need to be undertaken, taking into consideration both the molecular weight and the relative bioavailability of the minerals in the various formats contemplated, as would be known to one skilled in the art.

[0089] In some preferred embodiments, one or more nutrients that correct nutrient deficiencies is used in combination with one or more nutrients from the other functional categories described above, that is, with one or more nutrients that repair brain damage; and/or enhance calcium utilization; and/or block aluminum absorption. A particularly preferred combination comprises, for example, calcium ascorbate and/or magnesium ascorbate; in combination with one or more nutrients selected from coconut oil, SAM-e, vitamin B12, alpha lipoic acid, acetyl-l-carnitine, and niacinamide; and/or in combination with vitamin D3; and/or in combination with boron and/or silica. Preferred embodiments further include one or more of molybdenum ascorbate; citrus bioflavonoid complex; and Quercetin; and/or grape seed extract (or components thereof).

[0090] The combined actions of blocking aluminum absorption while concomitantly enhancing calcium utilization, over any aluminum that does cross the blood brain barrier, as well as

concomitantly repairing any aluminum-related damage, and further simultaneously addressing nutritional deficiencies that exacerbate aluminum's harmful effects, is believed to have synergistic effects in protecting and restoring normal brain biochemistry in Alzheimer's and Alzheimer's-associated conditions.

[0091] Without being bound to any particular theory or hypothesis, it is believed that aluminum that crosses the blood brain barrier can impair numerous enzymes involved in normal brain biochemistry, such as choline acetyltransferase and calcium/calmodulin kinase II, as discussed above, as well as alkaline phosphatase and phospholipase A2, which leads to the diverse brain pathologies seen in Alzheimer's and related conditions. Replacement of calcium by aluminum in the calmodulin complex, for example, leads to hyperphosphorylation of the protein tau in the brain, which in turn causes neurofibrillary tangles characteristic of Alzheimer's brains. Similarly, aluminum inhibition of choline acetyltransferase leads to overproduction of beta-amyloid, a protein fragment of amyloid precursor protein, which forms the neuritic plaques also characteristic of Alzheimer's. As noted above, dietary deficiencies in certain nutrients, particularly calcium and magnesium, exacerbate the aluminum-related degenerative processes. Furthermore, particular genetic aberrations can affect an individual's ability to overcome aluminum's neurotoxicity, predisposing such individuals to Alzheimer's.

[0092] The present invention provides nutritional approaches to preventing and/or treating Alzheimer's-associated conditions by addressing the hypothesized cause for the multiple brain abnormalities and deleterious metabolic consequences characteristic of Alzheimer's, as well as, optionally, providing additional nutrient substances that may be affected by aluminum neurotoxicity. For example, in some embodiments, the nutraceutical composition further includes one or more of the following nutrients:

[0093] Vitamin B2, B6: preferably from about 25 to about 250 mg, more preferably from about 50 to about 200 mg, and still more preferably from about 75 to about 150 mg.

[0094] Phytoalexins: preferably from about 5 to about 25 mg, more preferably from about 10 mg to about 20 mg, and still more preferably from about 15 mg.

[0095] Salvestrol™ (preferably as Platinum salvestrol 350 mg): preferably 1 capsule, more preferably 2 capsules, and still more preferably 3 capsules, e.g., 1, 2 or 3 capsules a day.

[0096] Lion's Mane mushroom (Hericium erinaceus): preferably from about 2 to about 20 grams dry weight, more preferably from about 3 to about 15 grams dry weight, and still more preferably from about 5 to about 10 grams dry weight (or an amount calculated to provide the same dry weight quantity if fresh or freeze dried). Without being bound to a particular theory or hypothesis, Hericium erinaceum may be an inducer of brain tissue regeneration.

[0097] Omega 3 fatty acids (docosahexaenoic acid [DHA]and eicosapentaenoic acid [EPA]): preferably from about 200 to about 1200 mg, more preferably from about 400 to about 1000 mg, and still more preferably from about 500 to about 900 mg.

[0098] Low Dose Naltrexone: (17-(cyclopropylmethyl)-4,5a-epoxy- 3,14-dihydroxy-morphinan-6-one): preferably from about 0.5 to about 8 mg, more preferably from about 1 to about 7 mg, and still more preferably from about 1 to about 5 mg.

[0099] As with the nutrients discussed above, these additional substances may be provided in any form, preferably in a form allowing adequate or high bioavailability and no or low toxicity. The additional nutrients may also be provided in various amounts and/or relative proportions, e.g., depending on the intended use of the nutraceutical compound. In addition to the exemplary embodiments explicitly described, other forms, sources, amounts, and/or relative proportions useful in the present invention would be apparent to one of skill in the art, based on the teachings presented herein, and are also contemplated as within the scope of the invention.

[00100] In some embodiments, the nutraceutical composition further comprises curcumin (or components thereof). Curcumin is a component of curry spice and is known to be a strong antioxidant. Lim, G.P., et al. (2001). "The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer's transgenic mouse". Journal of Neuroscience 21, (21), 8370-8377. Without being bound to any particular theory or hypothesis, it is believed that curcumin reduces oxidative stress, inflammation, and amyloid deposition.

Prevention and Treatment of Alzheimer's

[00101] Another aspect of the present invention provides methods of using the nutraceutical compositions disclosed herein in the prevention and/or treatment of Alzheimer's-associated conditions. The term "Alzheimer's-associated conditions" is used herein interchangeably with "Alzheimer's" and "Alzheimer's-related conditions", and refers to the symptoms and/or conditions characteristic of Alzheimer's patients and commonly associated with Alzheimer's. These can include, for example, progressive dementia, involving memory loss (particularly short-term memory loss), apathy, cognitive impairment, language difficulties, difficulties with perception (agnosia) and movement (apraxia), irritability, mood swings, aggression, delusions, failure to recognize loved ones, and ultimately complete dependence on caregivers. The degenerative progress seen in Alzheimer's has been termed retrogenesis, as the patient progressively loses abilities in cognition, coordination, behavior, language, mobility, etc., which in turn leads to other conditions, such as pressure ulcers and/or pneumonia where the patient becomes bedridden, and ultimately to death. Such related symptoms and conditions stemming from Alzheimer's are also included as Alzheimer's-associated conditions.

[00102] Alzheimer's-associated conditions that may be treated and/or prevented according to the instant invention also include conditions and/or symptoms arising from deleterious effects of aluminum in the body, as well as effects that mimic aluminum-related degenerative processes. Again without being bound to any particular theory or hypothesis, it is believed that certain genetic variants predispose individuals to Alzheimer's by increasing susceptibility to the harmful effects of aluminum and/or mimicking its effects in the body, particularly in the brain. These genetic variants include, for example, the APO E4 allele, as well as variants in one or more of the genes for beta-amyloid precursor protein, presenilin-1, presenilin-2, and apolipoprotein E. Individuals with the APO E4 allele, for example, are believed to be less capable of repairing aluminum-caused damage, e.g., be being less efficient at removing beta-amyloid and tau proteins, which form the abnormal plaques and tangles characteristic of Alzheimer's, as discussed above. Conditions and/or symptoms arising from these genetic variants may include some features also seen in Alzheimer's, such as, for example, dementia, memory loss, and/or impaired cognitive abilities.

[00103] Alzheimer's patients are also often very glucose deficient, having low blood glucose levels, sometimes long before other typical symptoms appear. Without being bound to a particular theory or hypothesis, low glucose may be due to aluminum binding and inhibition of enzymes involves in the glycolytic pathway, such as, hepatic phosphofructokinase, hexokinase, and glucose-6-phosphate dehydrogenase. Any of the symptoms and/or conditions associated with glucose deficiency are also considered Alzheimer's-associated conditions that may be treated and/or prevented according to the present invention.

[00104] The present invention provides methods, nutraceutical compositions, and kits for treating and/or preventing Alzheimer's-associated conditions in animal subjects. The term "animal subject" as used herein includes humans as well as other mammals.

[00105] The term "treating and/or preventing" as used herein includes achieving a therapeutic benefit and/or a prophylactic benefit, respectively. Therapeutic benefits generally occur from remedial treatments, that is, treatments aimed at slowing progress of an Alzheimer's-associated condition after the condition initiates. By therapeutic benefit is meant the eradication, reversal, halting, or amelioration of the underlying disorder being treated; or the eradication or amelioration of one or more symptoms associated with the disorder, even if the underlying condition is not cured. For example, in an Alzheimer's patient, therapeutic benefit includes eradicating or alleviating one or more of the myriad of conditions and symptoms associated with Alzheimer's, such that an improvement is observed in the patient, notwithstanding the fact that the patient may still be afflicted with the underlying disorder. For example, treatment provides a therapeutic benefit to an Alzheimer's patient not only when retrogenesis is halted and/or reversed, but also when an improvement is observed in the patient with respect to one or more symptoms that accompany Alzheimer's, such as a decrease in irritability, aggression, and/or apathy, or an improvement in memory, cognitive ability, and/or language

use. Therapeutic benefits also include, e.g., fewer or less severe symptoms, slower disease progression, and/or reduced mortality.

[00106] For prophylactic benefit, a neutraceutical composition of the present invention may be administered to a patient at risk of developing Alzheimer's, but generally before onset of symptoms or diagnosis of Alzheimer's. Individuals at risk for Alzheimer's include individuals predisposed to developing the condition, or at risk for developing the condition earlier or more severely than the general population. The cause for the higher risk may be genetic, environmental, metabolic, or a combination of these or other factors.

[00107] Individuals with a genetic predisposition for Alzheimer's include, for example, individuals having one or more genetic variants shown to be associated with Alzheimer's, such the APO E4 allele or variation in the beta-amyloid precursor protein, presenilin-1, presenilin-2, and/or apolipoprotein E genes, as discussed above. APO E4 is linked to developing late-onset Alzheimer's, while most other variants are linked to developing early-onset Alzheimer's. Depending on the affected gene, for example, prophylactic treatment may begin prior to the usual or expected age for early- or late-onset of Alzheimer's.

[00108] Environments associated with increased risk for Alzheimer's include areas where drinking water is high in aluminum, especially monomeric aluminum. Other environments associated with increased risk include areas where soils and/or potable water lack or are low in one of more of magnesium, calcium and silica or silicic acid; or where the soil and/or potable water are acidic, which allows for a higher content of dissolved aluminum. Foster, H.D., Fluoride and its antagonists. Journal of Orthomolecular Medicine 1993, (8): 149-153; and Foster, H.D., How aluminum causes Alzheimer's disease: Implications for prevention and treatment of Foster's multiple antagonist hypothesis. Journal of Orthomolecular Medicine. 2000, 15(1): 21-51. Individuals living in such areas also are considered at risk for developing Alzheimer's.

[00109] At risk individuals also include patients with low glucose levels, or those with conditions that cause glucose levels to vary beyond the normal range, such as diabetes, particularly if not controlled with insulin, and/or obesity. Other individuals at risk for Alzheimer's that may benefit from prophylactic treatment with a nutraceutical composition described herein, include, for example, individuals having condition(s) that correlate with a higher risk of developing Alzheimer's, such as, for example, hypertension, high cholesterol, high plasma levels of homocysteine, depression, stress, osteoporosis, diabetes mellitus (type II), and head trauma. Individuals of advanced age, for example, over about 55, about 60 or about 65 years of age, may also benefic from prophylactic administration of a nutraceutical composition taught herein.

[00110] Such prophylactic treatment can reduce the risk of developing Alzheimer's-associated conditions. A prophylactic benefit is achieved where onset of Alzheimer's is delayed, symptoms are

fewer and/or less severe; progress of the disease is retarded; and/or later stages are avoided. In particularly preferred embodiments, administration of a nutraceutical composition described herein to an at risk individual prevents the onset of Alzheimer's.

[00111] The instant invention also facilitates approaches to treating and/or preventing Alzheimer's-related conditions that generally cause no or few adverse side effects, including, for example, fewer adverse side effects than conventionally-used therapies, such as cholinesterase inhibitors, and fewer adverse side effects than some other potential therapies, such as NSAID. Moreover, the nutraceuticals described herein address multiple biochemical abnormalities that occur in the Alzheimer's brain, rather than just one or a few of the processes affected.

[00112] The present invention provides nutraceutical compositions comprising one or more nutrients to address aluminum neurotoxicity that can be administered to a patient in need thereof. In preferred embodiments, the nutracetical compositions of the present invention produce a benefit, including either a prophylactic benefit, a therapeutic benefit, or both, in preventing and/or treating one or more Alzheimer's-associated conditions. In preferred embodiments, the nutrient components are selected from different "functional categories", aimed at addressing the harmful effects of aluminum in different ways, including, for example, by blocking aluminum absorption; by enhancing calcium usage; by repairing brain damage; and/or by correcting nutritional deficiencies. Again without being bound to any particular theory or hypothesis, it is believed that Alzheimer's results from the accumulated effects of aluminum crossing the blood-brain barrier and interfering with numerous biological processes, e.g., replacing metal cofactors (such as calcium, magnesium, zinc, iron, and phosphorus) in enzymes involved in normal brain biochemistry; and also inhibiting other enzymes (such as the membrane-bound enzymes Na^+K^+ ATPase, acetylcholinesterase, and myelin-specific enzyme 2'3'-cyclic nucleotide phosphohydrolase). Addressing the aluminum problem by more than one approach, as taught herein, can provide compelling, superior and/or synergistic benefits.

[00113] For example, in some preferred embodiments, administration of a nutraceutical composition of the instant invention restores normal activity of one or more enzymes or biochemical processes in the brain, and/or returns one or more hormones, neurotrasmitters, co-enzymes, or other biochemicals, to optimal levels. The activity of the enzyme dihydropteridine reductase, for example, is known to be depressed in Alzheimer's, which in turn affects tetrahydrobioterin, an enzyme required in the synthesis of the neurotransmitters dopamine, norepinephrine and serotonin. Conversely, the activity of adenylate cyclase, a catecholamine sensitive enzyme, is abnormally elevated, affecting secretion of parathyroid hormone. The enzyme choline acetyltransferase also is inhibited, and choline deficiency leads to elevated homocysteine. In a cascade of biochemical abnormalities, deficiencies in acetylcholine and dopamine lead to malfunction in the catecholaminergic and cholinergic systems in Alzheimer's. In preferred embodiments of the instant invention, the enzymatic activities of one or more of dihydropteridine reductase, tetrahydrobioterin, adenylate cyclase, and choline

acetyltransferase are returned to normal; and/or the levels of one or more of dopamine, norepinephrine, serotonin, acetylcholine, parathyroid hormone, choline, and homocysteine are normalized.

[00114] Further, in some preferred embodiments, administration of a nutraceutical composition of the instant invention slows and/or restores myelinization. As noted above, myelin-specific enzyme 2'3'-cyclic nucleotide phosphohydrolase is impaired by aluminum in the brain. This can lead to thinning of the myelin sheath, and increased susceptibility to oxidative stress. Sarin, S., et al. (1997). "Alteration in lipid composition and neuronal injury in primates following chronic aluminum exposure". Biological Trace Element Research 59(1-3): 133-143; Golub, M.S., at al. (1999) "Morphometric studies of myelination of the spinal cord of mice exposed developmentally to aluminum". Neurotoxicology 20(6): 953-959. Without being bound to a specific theory or hypothesis, it is believed that such de-myelinization leads to the retrogenesis characteristic of Alzheimer's patients. Increased myelinization can indicate a therapeutic benefic, in providing, for example, a positive step towards halting and/or reversing retrogeneis.

[00115] Further, in some embodiments, administration of a nutraceutical composition of the instant invention corrects low glucose levels, seen with and even before onset of Alzheimer's. Restoring the activities of enzymes involves in the glycolytic pathway, such as, for example, hepatic phosphofructokinase, hexokinase, and glucose-6-phosphate dehydrogenase, can allow glucose levels to normalize and indicate therapeutic benefit.

[00116] Further, in some embodiments, administration of a nutraceutical composition of the instant invention corrects low SAM-e levels, often seen in the brains of Alzheimer's patients. Without being bound to a specific theory or hypothesis, abnormally low brain SAM-e levels in Alzheimer's may be linked to deficiencies of one or more of serotonin, melatonin, dopamine, and vitamin B12, also associated with Alzheimer's. SAM-e levels can be measured as known in the art and, in preferred embodiments of the instant invention, brain SAM-e levels are normalized.

[00117] In particularly preferred embodiments, more than one of the individually recited therapeutic and/or prophylactic effects are observed. That is, addressing the hypothesized aluminum toxicity from multiple angles, as taught herein, can correct multiple biochemical abnormalities and comprehensively treat and/or prevent Alzheimer's. In some preferred embodiments, administration of a nutraceutical composition of the instant invention prevents or delays onset of Alzheimer's-associated conditions. In some preferred embodiments, administration reduces the severity of symptoms and/or slows progression. In more preferred embodiments, administration halts and/or reverses the neurodegenerative progression characteristic of Alzheimer's. In still more preferred embodiments, administration leads to regression and/or eventual eradication of Alzheimer's, for example, to the point where no abnormal signs can be detected on the brain scans of previously-affected individuals, using,

e.g., advanced medical imagery, such as computed tomography (CT); magnetic resonance imaging (MRI); single photon emission computed tomography (SPECT); and/or positron emission tomography (PET).

Administration and Dosage

[00118] The nutraceutical compositions useful in the present invention can be delivered to a patient in need thereof using a number of routes or modes of administration. Nutraceutical compositions for use in accordance with the present invention may be formulated in any conventional manner, e.g., using one or more physiologically acceptable carriers, including excipients and/or auxiliaries, which facilitate processing of the nutrient components into preparations to be delivered to patients. Proper formulation is dependent upon the route of administration chosen.

[00119] In some embodiments, the nutraceutical composition may be administered in combination with one or more other therapeutic agents, e.g., as an adjunct to other treatments. The choice of therapeutic agent that can be co-administered with a composition of the invention will depend, for example, on the degree of disease progression, the severity of symptoms, and/or any contraindications to be considered. In some embodiments, the nutraceutical compositions can be co-administered with one or more cholinesterase or acetylcholinesterase inhibitors, including, for example, (1) donepexil (brand name Aricept); (2) tacrine (brand name Cognex); (3) galantamine (brand name Razadyne); (4) rivastigmine (brand name Exelon); (5) metrifonate; and the like. In some embodiments, the nutraceutical compositions can be co-administered with memantine (brand names Akatinol, Axura, Ebixa/Abixa, Memox, and Namenda), an antagonist for the NMDA receptor. In other embodiments, the nutraceutical composition is provided to a patient not receiving any other treatment for Alzheimer's, e.g., not receiving any of the treatments described above.

[00120] Administration of the nutraceutical compositions of the instant invention can begin at various points along disease progression, and can follow a variety of dosing schedules. For example, nutraceutical compositions of the instant invention can be administered to an individual in need thereof before and/or after symptoms associated Alzheimer's have developed. For example, in some embodiments, treatment begins just after an individual starts showing symptoms of pre-dementia. In some embodiments, treatment begins during the pre-dementia stage, or during the early, moderate, or advanced stages of dementia. Further, a nutraceutical composition of the instant invention may also be administered to a patient reporting one or more of the symptoms or conditions commonly associated with Alzheimer's, even though a diagnosis may not yet have been made.

[00121] In some embodiments, treatment is started prophylactically, before onset of any characteristic symptoms of Alzheimer's, for example, in individuals genetically at risk for Alzheimer's, or living in

areas with one or more environmental triggers for Alzheimier's, or having other conditions correlated with higher risk, as described above. For example in some embodiments, treatment is started prophylactically, before onset of any characteristic symptoms of Alzheimer's, but upon presentation of low glucose levels, believed to preface onset, especially in patients at higher risk for Alzheimer's, as discussed above. Individuals of advanced age, for example over about 55, about 60 or about 65 years of age, may also benefic from prophylactic administration of a nutraceutical composition taught herein, for example, where treatment is started at about 1, about 2, about 5, or about 10 years or more before the expected age of onset for the individual to be treated.

[00122] Nutraceutical compositions suitable for use in the present invention include compositions wherein the active nutrient components are present in an effective amount, i.e., in an amount sufficient to produce a therapeutic and/or a prophylactic benefit in at least one Alzheimer'-associated condition being treated. The actual amount effective for a particular application will depend on a number of factors, including, e.g., the severity of symptoms and the route of administration. In preferred embodiments, individual nutrient components are present in the nutraceutical composition in effective proportions relative to one another. Effective proportion refers to the effective amount of a given nutrient component relative to the amounts of one or more other nutrient(s) in combination with it in the nutraceutical composition. Determination of an effective amount and/or effective proportion is within the capabilities of those skilled in the art, based on the teachings provided herein. For example, the amounts disclosed herein, particularly preferred amounts per nutraceutical composition, represent preferred daily doses of the corresponding nutrient components. A person of ordinary skill using techniques known in the art also can determine other effective amounts and/or effective proportions of the nutrient components used together in the nutraceutical compositions. The amounts disclosed, along with the teachings presented herein, provide guidance to enable one of ordinary skill in the art to select those and other effective dosages of the corresponding nutrient components.

[00123] A person of ordinary skill in the art can determine efficacy, for example, by evaluating a number of quantifiable parameters, such as, for example, the parameters used in diagnosing Alzheimer's and determining the stage of dementia. Other techniques would be apparent to one of ordinary skill in the art. A person of ordinary skill in the art would also be able to monitor in a patient the effect of a nutraceutical composition of the present invention, e.g., by monitoring one or more such parameters over time.

[00124] For example, effective amounts and/or proportions may be determined and/or monitored by assessing intellectual function, including cognitive and memory testing, as well as by obtaining brain scans using advanced medical imaging, such as CT, MRI, SPECT and/or PET. Improvement in intellectual functional or memory, and/or a trend towards more normal brain scans, can indicate efficacy. Further, the activities of one or more enzymes or the levels of one or more hormones, neurotrasmitters, or other biochemicals affected in Alzheimer's can be monitored. Normalization or a

trend towards normal body levels or activities can indicate efficacy. For example, enzymatic activities of one or more of the following enzymes can be assessed: calcium/calmodulin kinase II, alkaline phosphatase, and phospholipase A2, as well as dihydropteridine reductase, tetrahydrobioterin, adenylate cyclase, and choline acetyltransferase, as well as hepatic phosphofructokinase, hexokinase, and glucose-6-phosphate dehydrogenase, and as well as Na^+K^+ ATPase, acetylcholinesterase, and myelin-specific enzyme 2'3'-cyclic nucleotide phosphohydrolase. Body levels of one or more of dopamine, norepinephrine, serotonin, acetylcholine, parathyroid hormone, choline, and homocysteine, for example, can also be determined. Techniques for determining enzymatic activities and levels of these substances in humans and animal models are known in the art. Effective dosage can also be determined and/or monitored by measurement of blood glucose levels, where increased levels can indicate efficacy.

[00125] Suitable doses for each of the various nutrient components in individual patients can vary and will depend on, e.g., previous diet and disease progression. Dosage can be varied accordingly, e.g., depending on the stage of Alzheimer's, severity of the symptoms, and the clinical judgment of a treating physician or other health service provider. Ongoing assessments of any of the above indicators, as well as the individual's status for calcium, magnesium, vitamin D3 and/or other dietary nutrients, can also be used to determine efficacy of treatment and/or whether a change in dosage is recommended at a particular point in treatment.

[00126] In some embodiments, treatment is continued until one of more benefits is realized and/or one or more of the parameters discussed herein shows an improvement. In preferred embodiments, effective amounts of the nutraceutical composition are administered on an ongoing basis, such as, e.g., for several months, years, a decade or several decades, or for the rest of the patient's life.

[00127] The effective amount can be administered in a single dose or in a series of doses separated by appropriate time intervals, such as hours. Dosage can be daily, twice daily, three times daily, or more. In preferred embodiments, the nutraceutical compositions are administered daily, and the daily dosage can be varied depending, e.g., on the abatement of symptoms in the individual being treated. In some embodiments, it is recommended that the daily dose is taken with food, e.g., the dose can be taken with breakfast, lunch, or dinner.

[00128] In some preferred embodiments, the daily dose comprises from about 3 mg to about 7 mg of boron. In some embodiments, the daily dose comprises from at least about 3.5, at least about 4, at least about 5, or at least about 5.5 mg of boron. In some embodiments, the daily dose comprises less than about 6.5, less than about 6, less than about 5, or less than about 4.5 mg of boron. In a particularly preferred embodiment, the daily dose comprises about 5 mg of boron.

[00129] In some preferred embodiments, the daily dose comprises from about 7 mg to about 13 mg of silica. In some embodiments, the daily dose comprises from at least about 8, at least about 9, at least

about 10, or at least about 11 mg of silica. In some embodiments, the daily dose comprises less than about 12, less than about 11, less than about 10, or less than about 9 mg of silica. In a particularly preferred embodiment, the daily dose comprises about 10 mg of silica, more preferably organic silica, as in, for example, about 500 mg of Spring Horsetail.

[00130] In some preferred embodiments, the daily dose comprises from about 2000 IU to about 4000 IU of vitamin D3. In some embodiments, the daily dose comprises from at least about 2250, at least about 2500, at least about 2750, or at least about 3000 IU of vitamin D3. In some embodiments, the daily dose comprises less than about 3750, less than about 3500, less than about 3250, or less than about 3000 IU of vitamin D3. In a particularly preferred embodiment, the daily dose comprises about 3000 IU of vitamin D3.

[00131] In some preferred embodiments, the daily dose comprises from about 1 g to about 3 g of niacinamide. In some embodiments, the daily dose comprises from at least about 1.2, at least about 1.5, at least about 1.8, or at least about 2 g of niacinamide. In some embodiments, the daily dose comprises less than about 2.8, less than about 2.5, less than about 2.2, or less than about 2 g of niacinamide. In a particularly preferred embodiment, the daily dose comprises about 2 g of niacinamide.

[00132] In some preferred embodiments, the daily dose comprises from about 300 mg to about 700 mg of acetyl-l-carnitine. In some embodiments, the daily dose comprises from at least about 350, at least about 400, at least about 450, or at least about 500 mg of acetyl-l-carnitine. In some embodiments, the daily dose comprises less than about 650, less than about 600, less than about 550, or less than about 500 mg of acetyl-l-carnitine. In a particularly preferred embodiment, the daily dose comprises about 500 mg of acetyl-l-carnitine.

[00133] In some preferred embodiments, the daily dose comprises from about 100 mg to about 300 mg of alpha lipoic acid. In some embodiments, the daily dose comprises from at least about 125, at least about 150, at least about 175, or at least about 200 mg of alpha lipoic acid. In some embodiments, the daily dose comprises less than about 275, less than about 250, less than about 225, or less than about 200 mg of alpha lipoic acid. In a particularly preferred embodiment, the daily dose comprises about 200 mg of alpha lipoic acid.

[00134] In some preferred embodiments, the daily dose comprises from about 2 mg to about 4 mg of vitamin B12. In some embodiments, the daily dose comprises from at least about 2.2, at least about 2.5, at least about 2.8, or at least about 3 mg of vitamin B12. In some embodiments, the daily dose comprises less than about 3.8, less than about 3.5, less than about 3.2, or less than about 3 mg of vitamin B12. In a particularly preferred embodiment, the daily dose comprises about 3 mg of vitamin B12.

[00135] In some preferred embodiments, the daily dose comprises from about 1 to about 5 tablespoons coconut oil, preferably extra virgin coconut oil, (or a suitably selected oil having a similar medium chain triglyceride content and/or similar saturation). In some embodiments, the daily dose comprises from at least about 1.5, at least about 2, at least about 2.5, or at least about 3 tablespoons of coconut oil. In some embodiments, the daily dose comprises less than about 4.5, less than about 4, less than about 3.5, or less than about 3 tablespoons of coconut oil. In a particularly preferred embodiment, the daily dose comprises about 2 to about 4 tablespoons of extra virgin coconut oil.

[00136] In some preferred embodiments, the daily dose comprises from about 400 mg to about 800 mg of calcium, more preferably calcium ascorbate. In some embodiments, the daily dose comprises from at least about 450, at least about 500, at least about 550, or at least about 600 mg of calcium ascorbate. In some embodiments, the daily dose comprises less than about 750, less than about 700, less than about 650, or less than about 600 mg of calcium ascorbate. In a particularly preferred embodiment, the daily dose comprises about 600 mg of calcium ascorbate.

[00137] In some preferred embodiments, the daily dose comprises from about 400 mg to about 800 mg of magnesium, more preferably magnesium ascorbate. In some embodiments, the daily dose comprises from at least about 450, at least about 500, at least about 550, or at least about 600 mg of magnesium ascorbate. In some embodiments, the daily dose comprises less than about 750, less than about 700, less than about 650, or less than about 600 mg of magnesium ascorbate. In a particularly preferred embodiment, the daily dose comprises about 600 mg of magnesium ascorbate.

[00138] In some embodiments, the daily dose comprises one or more of the nutrients listed in Table 1 above, in the suggested amounts indicated in the Table, for the corresponding nutrient being administered. In some embodiments, the daily dose comprises one or more of the nutrients listed in Table 2 above, in the suggested amounts indicated in the Table, for the corresponding nutrient being administered. In some embodiments, the daily dose further comprises one or more additional nutrients in the amounts provided in a nutraceutical composition, as described above. That is, the amounts suggested per nutraceutical composition refer to a preferred daily dosage for the corresponding nutrient component. For example, with respect to naltrexone, the daily does in some embodiments comprises preferably from about 0.5 to about 8 mg, more preferably from about 1 to about 7 mg, and still more preferably from about 1 to about 5 mg.

[00139] The nutraceutical compositions of the present invention are intended for administration to a mammal, in particular a human being, in a suitable dosage form, e.g., as known in the art. Suitable dosage forms known in the art include injectable, parenteral, enteral, oral or ingestible, and the like. Preferably, the nutraceutical composition comprising a combination of nutrient components is administered orally. Oral solid and liquid dosage forms are particularly preferred.

[00140] Oral solid dosage forms are well known in the art and include powders, capsules, pills, tablets, caplets, gelcaps, and edible food items. Oral solid dosage forms can be made with one or more pharmaceutically acceptable excipients. Pharmaceutically acceptable excipients assist or make possible the formation of a dosage form for a bioactive material and can include diluents, binding agents, lubricants, glidants, disintergents, coloring agents, and flavorants, along with the nutrient components. An excipient is pharmaceutically acceptable if, in addition to performing its desired function, it is non-toxic, well tolerated upon ingestion, and does not interfere with the action and/or absorption of bioactive materials.

[00141] Tablets can be made by well-known compression techniques using wet, dry, or fluidized bed granulation methods. The effective amounts and/or effective proportions of nutrient components disclosed herein can be combined with the desired amount of a pharmaceutically acceptable excipient (e.g. lactose, starch, dextrin, ethyl cellulose and the like) and, in the case of wet granulation, water. The ingredients can then be mixed in a blender. Useful blenders include the twin-shell type, the planetary mixer type, and the high-speed high-shear type; all of which are known to the skilled artisan. The blended combination can be sieved and dried to a granulate. The granulate can be then compressed into tablets, for example, using a tableting press as is known in the art. Preferably, the granulate is sieved before the compression to make sure that the granulate has the desired particle size. The proportion of components and excipients, binder and water (if used), etc., as well as the time and intensity of mixing, can be routinely optimized to obtain a granulate with the desired tableting characteristics. Tablets can be either coated or uncoated as is known in the art. Tablet making is well known to skilled artisan and is described, for example, by Edward Rudnic and Joseph B. Schwartz, Oral Solid Dosage Forms, in Volume II, Remington: The Science and Practice of Pharmacy, Chpt. 92, 1615, 1615-1637 (Alfonso R. Gennaro, ed., 19.sup.th ed. 1995).

[00142] Capsules, also known as dry-filled capsules, are oral solid dosage forms in which the composition is contained in a swallowable container of suitable size, typically made of gelatin. Hard empty capsules suitable for containing the nutraceutical composition of the present invention are available from several sources, for example, Tishcon Gel-Tec, 2410 N. Zion Rd., Salisbury, Md. 21801; the capsules are supplied in two halves and in various sizes. The sizes are typically designated by number. For example, 000 represents a large size commonly in use, while 5 represents a small size commonly in use. The capsule halves can be colored by a suitable coloring agent and each half can be the same or different colors.

[00143] In making a solid oral dosage form that is a capsule, the nutrient components are combined and mixed together, with or without a diluent such as lactose, mannitol, a carbonate, or the like, using any of the mixers described above. Prior to mixing, a granulate of one or more of the components can be prepared as in the making of tablets. In some embodiments, organic sugar is used as a filler.

[00144] The combined mixed components, along with any excipients and/or fillers, etc., are packed into one capsule half. The filled half-capsule is then closed with the other capsule half. Manual, semiautomatic, and automatic equipment for filling capsules are known in the art. The art of capsule filling is well known to the skilled artisan and is described, for example, by Edward Rudnic and Joseph B. Schwartz, Oral Solid Dosage Forms, in Volume II, Remington: the Sciemce and Practict of Pharmacy, Chpt. 92, 1615, 1642-1647 (Alfonso R. Gennaro, ed., 19.sup.th ed. 1995).

[00145] When the oral solid dosage form is either a tablet, gelcap, capsule, or caplet, administration can be more convenient when the nutraceutical composition is in the form of multiple oral solid dosage forms. That is, in the form of at least first and second oral solid dosage forms. The compositions of the at least first and second oral solid dosage forms can be the same or they can be different. Thus, in embodiments having multiple oral solid dosage forms, the entire effective amount and/or effective proportion of a component can be in one of the at least first and second oral dosage forms, or such effective amount and/or effective proportion can be distributed equally or unequally between each of the at least first and second oral sold dosage forms. In embodiments having at least first and second oral solid dosage forms, the effective amount and/or effective proportion of each nutrient component is preferably distributed equally among the multiple solid dosage forms

[00146] The oral solid dosage form used in the present invention can be a chewable food item that includes the nutraceutical composition. The oral solid dosage form can be formed of a mass having the desired ingredients, and into a shape, preferably a bar having a circular, semicircular, or rectangular cross-section by, for example, extrusion, and cut into chewable food item dosage forms of about 50 to about 175 grams each, whereby each such dosage form includes an effective amount of the nutraceutical composition.

[00147] Oral liquid dosage forms can be prepared with one or more vehicles and include solutions, emulsions, and suspensions. A vehicle can be any potable substance or mixture of potable substances that are liquid at room temperature and that do not interfere with the effectiveness of the nutraceutical composition. Water, ethanol, and oils, especially vegetable oils and seed oils, are preferred vehicles. Water is a particularly preferred vehicle. Emulsions and suspensions are preferred liquid oral dosage forms. In the case of an oral liquid dosage form that is an emulsion, two vehicles having limited mutual solubility can be used.

[00148] Oral liquid dosage forms may be hybrid. In one example of an oral liquid dosage form that is a hybrid, one or more nutrient components of the nutraceutical composition, or a fraction of them, are dissolved in a vehicle, and the remainder are in suspension in the vehicle. In another example of a liquid oral composition that is a hybrid, one or more nutrient components, or any fraction thereof, of the nutraceutical composition are dissolved in a first vehicle and the remainder are suspended or dissolved in a second vehicle that forms an emulsion with the first vehicle. Other hybrid liquid oral

dosage forms will be apparent to the skilled artisan and are within the scope of this invention. The making of oral liquid dosage forms is well known to the skilled artisan and is described, for example, by J. G. Narin, Solutions, Emulsions, Suspensions and Extracts, in Volume II Remington: the Science and Practice of Pharmacy, Chpt. 86, 1495, 1495-1521 (Alfonso R. Gennaro, ed., 19.sup.th ed., 1995). These oral liquid dosage forms can be ready-made, that is introduced into commerce in the liquid form in which they are to be administered. Preferred oral liquid dosage forms of the ready-made type are in the form of a beverage that can be carbonated.

[00149] Alternatively, a dry concentrate of the oral liquid dosage form can be supplied in the form of a powder that can be mixed by the practitioner or consumer with a potable liquid (e.g. milk, water, fruit juice) to form the oral liquid dosage form prior to administration. Powders can contain additives known in the art to prevent caking of the powder and maintain desirable free-flowing characteristics of the powder. In some embodiments, the nutraceutical composition is provided as a powered drink mix, e.g., sold in packets, to be mixed into drinks for oral consumption.

[00150] Further, oral forms may include additives that encourage the absorption and/or bioavailability of one or more nutrient components. Still further additives may be added that, for example, but not limited to, enhance the flavor, texture, integrity and/or color.

[00151] In some embodiments, the desired nutrient components, other than coconut oil, are provided as a solid or liquid dosage form, such as any of the solid or liquid dosage forms discussed above, and the dose is administered along with any desired dose of coconut oil. The coconut oil dose may be administered at about the same time as the other dosage form, or at a different time, e.g., minutes, a few hours, or several hours apart, but preferably within the same day. In some embodiments, the capsule, table or power may be mixed with the coconut oil dose prior to administration. In some embodiments, the coconut oil dose may be mixed with a liquid form to make, for example, an emulsion, suspension or hybrid, as discussed above, prior to administration.

[00152] In some embodiments, the nutraceutical composition comprises a foodstuff, for example a food source naturally providing a daily dose of one or more of the nutrient components provided herein or, for example, an enriched foodstuff. Foodstuffs may be enriched according to techniques known in the art. These include, for example, direct incorporation or by growth in enriched soils, to produce a food item or group of food items that can provide the combinations of nutrient components described herein. Direct incorporation can include, e.g., mixing or dissolving a capsule, tablet or powder, e.g., as described above, into the food item to be consumed; or blending in a liquid dosage form and/or a coconut oil component.

[00153] Soil and/or water enriched with one or more nutrients discussed herein can be produced according to methods known in the art. For example, drinking water can be enriched with boron to

reproduce or approximate the boron water content of Maracaibo, Venezuela, where only one case of Alzheimer's has been reported in a decade.

[00154] The nutraceutical compositions can also be administered in a form suitable for injecting or for providing as an intravenous drip. Formulations suitable for injection or intravenous administraion are known in the art and can be used to formulate the nutraceutical compositions described herein accordingly.

[00155] All patents, patent publications, and other publications referred to herein are hereby incorporated by reference, to the same extent as if each individual publication, patent, or patent publication was specifically and individually indicated to be incorporated by reference.

[00156] Certain modifications and improvements will occur to those skilled in the art upon a reading of the foregoing description. It should be understood that all such modifications and improvements have been deleted herein for the sake of conciseness and readability. Nonetheless, all such modifications and improvements are contemplated as within the scope of the instant invention and are properly within the scope of the following claims.

We Claim:

1. A nutraceutical composition for treating and/or preventing Alzheimer's, comprising an aluminum-blocking component, a calcium supplement, and a calcium-enhancing component.

2. The nutraceutical composition according to claim 1, wherein said aluminum-blocking component comprises boron.

3. The nutraceutical composition according to claim 1, wherein said aluminum-blocking component comprises a mixture of silica and boron.

4. The nutraceutical composition according to claim 1, wherein said calcium-enhancing component comprises cholecalciferol.

5. The nutraceutical composition according to claim 1, further comprising a brain-repairing component.

6. The nutraceutical composition according to claim 5, wherein said brain-repairing component further comprises at least one compound selected from the group consisting of niacinamide, acetyl-l-carnitine, alpha lipoic acid, vitamin B12, SAM-e, and extra virgin coconut oil.

7. The nutraceutical composition according to claim 6, wherein said brain-repairing component further comprises at least one compound selected from the group consisting of selenium, hyperzine A, grape seed extract, vitamin B1, folate, vitamin E, and phosphatidyl serine.

8. A method for treating and/or preventing Alzheimer's in a patient in need thereof, comprising administering to said patient a nutraceutical composition according to any one of claims 1 to 7.

9. A nutraceutical composition for treating and/or preventing Alzheimer's, consisting essentially of an aluminum-blocking component, a calcium supplement, and a calcium-enhancing component.

10. The nutraceutical composition according to claim 9, wherein said aluminum-blocking component comprises boron.

11. The nutraceutical composition according to claim 9, wherein said aluminum-blocking component comprises a mixture of silica and boron.

12. The nutraceutical composition according to claim 9, wherein said calcium-enhancing component comprises cholecalciferol.

13. The nutraceutical composition according to claim 9, further comprising a brain-repairing component.

14. The nutraceutical composition according to claim 13, wherein said brain-repairing component further comprises at least one compound selected from the group consisting of niacinamide, acetyl-l-carnitine, alpha lipoic acid, vitamin B12, SAM-e, and extra virgin coconut oil.

15. The nutraceutical composition according to claim 14, wherein said brain-repairing component further comprises at least one compound selected from the group consisting of selenium, hyperzine A, grape seed extract, vitamin B1, folate, vitamin E, and phosphatidyl serine.

16. A method for treating and/or preventing Alzheimer's in a patient in need thereof, comprising administering to said patient a nutraceutical composition according to any one of claims 9 to 15.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2010/000032

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***A61K 33/22*** (2006.01) , ***A61K 31/59*** (2006.01) , ***A61K 33/00*** (2006.01) , ***A61P 25/28*** (2006.01) , ***A61P 3/02*** (2006.01)

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)

IPC: ***A61K 33/22*** (2006.01) , ***A61K 31/59*** (2006.01) , ***A61K 33/00*** (2006.01) , ***A61P 25/28*** (2006.01) , ***A61P 3/02*** (2006.01)

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

Epoque, Pubmed Search terms: boron, silica, cholecalciferol D3, niacinamide, acetyl-L-carnitine, alpha lipoic acid, vitamin B12, SAM-e, S adenosylmethionine-amino acid, extra virgin coconut oil, selenium, huperazine A-alkaloid, grape seed extract, vitamin B1, folate,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 7 217 701 B2 (MIKOSHIBA ET AL.) 15 May 2007 (15-05-2007) abstract	1-16
Y	US 5 523 295 (FASMAN) 04 June 1996 (04-06-1996) the whole document	1-16
Y	Oudshoorn et al. Higher serum vitamin D3 levels are associated with better cognitive test performance in patients with Alzheimer's disease. Dement Geriatr Cogn Disord. 2008; 25(6):539-43. Epub 2008 May 26.	1-16
Y	Green et al. Nicotinamide restores cognition in Alzheimer's Disease Transgenic Mice via a mechanism involving sirtuin inhibition and selective reduction of Thr231-Phosphatau, J. Neuroscience, 2008 Nov 5, vol. 28, no. 5, pp. 11500-11510.	1-16

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 April 2010 (26-04-2010)	3 May 2010 (03-05-2010)

Name and mailing address of the ISA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Charles Greenough (819) 994-0243

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2010/000032

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

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

1. [X] Claim Nos. : 8, 16
because they relate to subject matter not required to be searched by this Authority, namely :

Although claims 8 and 16 are directed to a method of treatment of the human/animal body, the search has been carried out based on the alleged effects of the product.

2. [X] Claim Nos. : 1-16(part)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

SEE ADDITIONAL SHEET

3. [ ] Claim Nos. :
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

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

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

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

Remark on Protest

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

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

[ ] No protest accompanied the payment of additional search fees.

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Pettegrew et al. Acetyl-L-carnitine physical-chemical, metabolic, and therapeutic properties: relevance for its mode of action in Alzheimer's disease and geriatric depression. Mol Psychiatry. 2000 Nov; 5(6):616-32.	1-16
Y	Holmquist et al. Lipoic acid as a novel treatment for Alzheimer's disease and related dementias, Pharmacol Theor. 2007 Jan; 113(1):154-64. Epub 2006 Sep 20.	1-16
P, Y	Siuda et al., From mild cognitive impairment to Alzheimer's disease - influence of homocysteine, vitamin B12, and folate on cognition over time: results from one year follow-up, Neurol. Neurochir. Pol. 2009 Jul-Aug, 43(4): 321-9.	1-16
Y	Shea et al. S-adenosyl methionine: a natural therapeutic agent effective against multiple hallmarks and risk factors associated with Alzheimer's disease. J. Alzheimers Dis. 2008 Feb; 13(1): 67-70.	1-16
Y	Mary Newport, What if there was a cure for Alzheimer's disease and no one knew? Case study, July 22, 2008 http://www.coconutketones.com/whatifcure.pdf	1-16
Y	Benton, Selenium intake, mood and other aspects of psychological functioning, Nutr Neurosci. 2002 Dec; 5(6):363-74.	1-16
Y	Little et al. An update on huperazine A as a treatment for Alzheimer's disease. Expert Opin Investig Drugs. 2008 Feb; 17(2):209-15.	1-16
Y	Wang et al. Grape-derived polyphenolics prevent Abeta oligomerization and attenuate cognitive deterioration in a mouse model of Alzheimer's disease. J. Neurosci. 2008 Jun 18; 28(25): 6388-92.	1-16
Y	Morris et al. Thoughts on B-vitamins and dementia, J. Alzheimers Dis. 2006 Aug; 9(4):429-33.	1-16
Y	Luchsinger JA, et al, Relation of higher folate intake to lower risk of Alzheimer's disease in the elderly, Arch Neurol. 2007 Jan; 64: 86-92.	1-16
P, Y	Pavlik et al. Vitamin E use is associated with improved survival in an Alzheimer's disease cohort. Dement Geriatr Cogn Disord. 2009; 28(6): 536-40. Epub 2009 Dec 10.	1-16
Y	Crook et al. Effects of phosphatidylserine in Alzheimers's disease. Psychopharmacol Bull. 1992; 28(1):61-6	1-16

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
US7217701	15-05-2007	EP1444981 A1	11-08-2004
		WO03033002 A1	24-04-2003
US5523295	04-06-1996	WO9601114 A1	18-01-1996

Continuation of Box No. II, Part 2.

Claims 1-16 relate to an extremely large number of possible compounds and compositions. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found however for only a very small proportion of the defined materials, compounds, compositions and uses thereof. In the present application, the claims so lack support and the specification so lacks disclosure that a meaningful search over the whole of the claimed scope is not possible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts that relate to the materials and uses thereof disclosed in the description.