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(54) Titre : METHODES ET COMPOSITIONS VISANT A FAVORISER LA SANTE OCLUAIRE

(54) Title: METHODS AND COMPOSITIONS TO PROMOTE OCULAR HEALTH

(57) **Abrégé/Abstract:**

A method and composition for promoting ocular health. The composition can include an effective amount of vitamin A, an effective amount of vitamin C, an effective amount of vitamin D, an effective amount of selenium, an effective amount of Omega-3 fatty acids, an effective amount of Taurine, an effective amount of alpha lipoic acid, and an effective amount of a non-vitamin A carotenoid. The composition is also effective without vitamin E or beta-carotene. The composition is operable to treat subjects for Age-Related Macular Degeneration, as well as to protect and strengthen their eyes, vision, lacrimal function, and/or support their dietary needs, particularly if they are at risk for increased oxidative stress in their retina (i.e. hyperglycemics and diabetics).

ABSTRACT

A method and composition for promoting ocular health. The composition can include an effective amount of vitamin A, an effective amount of vitamin C, an effective amount of vitamin D, an effective amount of selenium, an effective amount of Omega-3 fatty acids, an effective amount of Taurine, an effective amount of alpha lipoic acid, and an effective amount of a non-vitamin A carotenoid. The composition is also effective without vitamin E or beta-carotene. The composition is operable to treat subjects for Age-Related Macular Degeneration, as well as to protect and strengthen their eyes, vision, lacrimal function, and/or support their dietary needs, particularly if they are at risk for increased oxidative stress in their retina (i.e. hyperglycemics and diabetics).

METHODS AND COMPOSITIONS TO PROMOTE OCULAR HEALTH

Technical Field of the Invention

[0001] Embodiments of the present invention relates to methods and compositions to promote ocular health of a subject.

Background of the Invention

[0002] The eyes play an important role in mobility, function, and enjoyment of life. For this reason, it is important to maintain good ocular health. (The term "ocular" refers to the eye and its organ system.) Unfortunately, ocular health declines naturally with age. This natural decline can be attributable to many things, including ultraviolet light from the sun, wind, dust, chlorine fumes, other chemicals, automobile fumes, and physical injury.

[0003] Many of the compositions known heretofore have been focused solely on providing treatment for age-related visual decline. Many subjects, however, also suffer from poor ocular health due to other illnesses, such as dry eye, visual acuity, diabetes, hyperglycemia, and increased levels of visual stress due to long amounts of exposure to visual display terminals, such as computer monitors, smart phones, laptops, and tablet PCs.

[0004] Therefore, it would be advantageous to provide methods and compositions to promote ocular health that did not suffer from these shortcomings.

Summary of the Invention

[0005] Embodiments of the present invention are directed to methods and compositions that provide one or more of these benefits. In one embodiment, the invention provides for an orally digestible dose of a composition that is operable to promote ocular health of a subject.

[0006] In one embodiment, the composition for promoting ocular health of a subject can include an effective amount of vitamin A, an effective amount of vitamin C, an effective amount of vitamin D, an effective amount of selenium, an effective amount of Omega-3 fatty acids, an effective amount of Taurine, an effective amount of alpha lipoic acid, and an effective amount of a non-vitamin A carotenoid. Preferably, the effective amount of vitamin A is between 2,500 and 50,000 IU, more preferably about 2,500 IU. Preferably, the effective amount of vitamin C is within the range of 60 and 500 mg, more preferably about 250 mg. Preferably, the effective amount of vitamin D is within the range of 400 and 2,000 IU, more preferably about 800 IU. Preferably, the effective amount of selenium is within the range of 35 and 200 µg, more preferably about 70 µg. Preferably, the effective amount of Omega-3 fatty acids is no more than 5,0000 mg, more preferably about 500 mg. Preferably, the effective amount of taurine is within the range of 100 and 1,000 mg, more preferably about 500 mg. Preferably, the effective amount of alpha lipoic acid is no more than 1,000 mg, more preferably about 100 mg. Preferably, the effective amount of non-vitamin A carotenoid is no more than 62 mg, more preferably, about 12 mg.

[0007] In another embodiment of the present invention, the composition does not include vitamin E. In another embodiment of the present invention, the composition does not include

beta-carotene. In another embodiment, the composition can include an effective amount of pine bark extract, which is preferably in an amount not to exceed 500 mg, and more preferably in an amount of about 100 mg. In another embodiment, the composition can include an effective amount of astaxantin, which is preferably in an amount not to exceed about 5 mg, and more preferably in an amount of about 1 mg. In another embodiment, the composition can include an effective amount of piper spp. extract, which is preferably in an amount not to exceed about 5 mg, and more preferably in an amount of about 1 mg. In another embodiment, the composition can include an effective amount of zinc, which is preferably in an amount between about 15 mg and 80 mg, and more preferably in an amount of about 30 mg. In embodiments in which the amount of zinc exceeds 30 mg, it is preferable to include 1 to 2 mg of copper.

[0008] In another embodiment, the composition can include excipients. In one embodiment, the excipients are selected from the group consisting of soybean oil, white beeswax, soy lethicin, and combinations thereof. In another embodiment, the non-vitamin A carotenoid is selected from the group consisting of lutein, zeaxanthin, and combinations thereof. Lutein is preferably in an amount between 5 and 50 mg, and more preferably 10 mg. Zeaxanthin is preferably in an amount between 0.25 and 12 mg, and more preferably 2 mg. In another embodiment, the Omega-3 fatty acids are selected from the group consisting of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and combinations thereof. In another embodiment, the Omega-3 fatty acids are comprised of no more than 5,000 mg of eicosapentaenoic acid (EPA) and no more than 3,000 mg of docosahexaenoic acid (DHA).

[0009] In one embodiment, the composition is in a deliverable state to the subject such that the composition may be taken orally by the subject, wherein the deliverable state is selected from the group consisting of a tablet, a hard capsule, a liquid-filled capsule, hard gelatin capsule, hard vegetable-based capsule, elixir, soft-chew, lozenge, chewable bar, juice suspension and combinations thereof.

[0010] In another embodiment, the composition can include the following active components: an effective amount of vitamin A, an effective amount of vitamin C, an effective amount of vitamin D, an effective amount of selenium, an effective amount of Omega-3 fatty acids, an effective amount of Taurine, an effective amount of alpha lipoic acid, and an effective amount of a non-vitamin A carotenoid. In one embodiment, the effective amounts of each component are as described above.

Detailed Description

[0011] Although the invention will be described in connection with several embodiments, it will be understood that it is not intended to limit the invention to those embodiments. On the contrary, it is intended to cover all the alternatives, modifications and equivalents as may be included within the spirit and scope of the invention defined by the appended claims. Like numbers refer to like elements throughout.

[0012] Embodiments of the present invention can help to promote ocular health for a subject. Exemplary subjects include, without limitation, mammals, with homo sapiens being the most preferred mammal. In certain embodiments of the present invention, beta-carotene and Vitamin E can be excluded. In certain embodiments of the present invention, the composition can be effective for subjects exposed to visually stressful situations, such as working with visual display terminals for extended periods of time. In yet another embodiment of the present invention, the composition can provide vasoprotective effects, anti-inflammatory properties, and improvement in capillary function. In another embodiment of the present invention, the composition can do more than treat Age-Related Macular Degeneration. For example, the composition can be a multi-factorial nutritional adjuvant for subjects seeking to protect and strengthen their eyes, vision, lacrimal function, and/or support their dietary needs, particularly if they are at risk for increased oxidative stress in their retina (i.e. hyperglycemics and diabetics).

[0013] In certain embodiments of the present invention, the composition can include lutein, zeaxanthin, alpha lipoic acid, vitamin D, astaxanthin, an absence of beta-carotene, and an

absence of pro-vitamin A (PVA) carotenoids. In one embodiment, the composition is operable to provide support of polyphenolics.

[0014] In another embodiment of the present invention, the composition can include fatty acids, such as omega-3 fatty acids. Fatty acids, specifically fatty acids obtained from fish oil, have been found to have a number of beneficial health effects. It is understood that oil from fish contains eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These are classified as omega-3 fatty acids. These omega-3 fatty acids derived from fish oil are known to keep blood triglycerides in check and may inhibit the progression of atherosclerosis. EPA and DHA are believed to have anti-inflammatory activity and are sometimes used as dietary supplements with inflammatory conditions, such as Crohn's disease and rheumatoid arthritis. It is believed that the omega-3 fish oil fatty acids may balance other fatty acids. When fatty acids are out of balance in the body, the body may release chemicals that promote inflammation. Omega-3 fatty acids are needed for prostaglandin. Prostaglandin are hormone-like substances that regulate dilation of blood vessels, inflammatory responses, and other critical body processes. DHA and EPA are also believed important for nerve and eye functions. DHA comprises about 60 percent of the outer rod segments of photoreceptor cells that are used to see with by humans. Brain tissue has a substantial component of fat composed of DHA. It is believed that fish oil omega-3 fatty acids and, specifically, DHA and EPA, are useful in wet macular degeneration since these fatty acids help heal and support blood vessel walls. Studies show that eating fish several times a month may reduce the risk of developing AMD.

[0015] It is believed that omega-3 fatty acids may slow the progression of vision loss and reverse the signs of dry eye syndrome. It is also believed that there is a relationship between essential fatty acid (EFA) supplementation and improvement in dry eyes and dry eye symptoms. For these reasons, it is believed that no more than 5,000 mgs of omega-3 fatty acids in a nutritional supplement with any other ingredients will perform vital functions in terms protecting against loss of visual acuity due to various eye diseases including AMD. The preferred composition is 500 mgs of omega-3 fatty acids on a daily basis. This may be provided in one capsule to be taken daily or may be split into two or more doses provided in a dosage, which can be one or more capsules. The actual capsules themselves may contain slightly more than the recommended dosages in order to guard against degradation over the shelf life of the nutritional supplement.

Preferred Embodiment

[0016] In the preferred embodiment, the composition is provided for in an easy-to-swallow, oblong soft gelatin capsule with an opaque caramel color to shield the active ingredients from light.

[0017] Table I shows a composition of a daily supplement constituting an embodiment of the present invention.

Table I: Composition of an Embodiment of the Present Invention

Component	Preferred Range	Preferred Amount
Vitamin A (pre-formed)	2,500 - 50,000 IU	2,500 IU

Beta-Carotene (pro-vitamin A)	<50,000 IU	0
Vitamin C	60 - 500 mg	250 mg
Vitamin D	400 - 2,000 IU	800 IU
Vitamin E (natural or synthetic)	0 - 400 IU	0
Zinc	15 - 80 mg	30 mg
Copper	1 - 2 mg (if zinc is above 30 mg)	0
Selenium	35 - 200 µg	70 µg
Non-Vitamin A Carotenoids - TOTAL	0-12 mg	12 mg
Non-Vitamin A Carotenoid - Lutein	5 - 50 mg	10 mg
Non-Vitamin A Carotenoid - Zeaxanthin	0.25 - 12 mg	2 mg
Omega-3 Fatty Acid - EPA	0 - 5,000 mg	300 mg
Omega-3 Fatty Acid - DHA	0 - 3,000 mg	200 mg
Omega-3 Fatty Acids - TOTAL	≤ 5,000 mg	500 mg
Taurine	100 - 1,000 mg	500 mg
Anthocyanosides (from Grape Skin)	0	0
Alpha Lipoic Acid	≤ 1,000 mg	100 mg
Pine Bark Extract	0 - 500 mg	10 mg
Astaxanthin	≤ 5 mg	1 mg
Piper spp. Extract	0 - 5 mg	1 mg

[0018] The active ingredients of the above supplement may be presented in a variety of forms. The chemistry is well known to one of art. Additionally, the method of manufacturing may take a variety of forms and a number of inactive ingredients may be added to provide longer shelf life, to make the capsule more palatable or presentable, and to aid in the ease of manufacturing process. The capsules may be blended with any desired inactive ingredients, so long as the blend is uniform and the appropriate composition is reached for each capsule. The tablets may be coated or they can be placed in a caplet or capsule and contained in a carrier, such as mineral oil, to produce a soft gel.

[0019] Consequently, the above composition is preferably provided for oral administration in a variety of forms, including lacquered tablets, unlacquered tablets, caplets, or capsules. For simplicity, during the remaining portion of this description, the form of administration, whether lacquered tablets, unlacquered tablets, caplets, or capsules, will be referred to as "capsules" without distinguishing among the various forms. The daily dosage of a subject composition, as specified above, may be administered in the form of one or more capsules. The formulation of an individual capsule is determined based on the amount of the active ingredients that are required to be present in each capsule to total the amount of active ingredients as outlined in Table I. The preferred form of administration is one capsule taken three times a day for a total of three capsules per day.

[0020] The actual capsules sold for consumption may contain somewhat more than the total amounts specified in Table I. The active ingredients may degrade over time. Consequently, in order to assure that the active ingredients are presented in the minimum amounts required at the time the capsules are actually ingested, may require increasing the dosage beyond the minimum amounts required in order to account for and compensate for degradation over time. Some of the active ingredients degrade faster than others, which can result in different percentages of excess in each capsule for one active ingredient as compared to a different active ingredient. Although it is believed that oral ingestion through the form of a capsule is the preferred administration, there are variations in administration which could be appropriate in some circumstances. These could include time-release capsules, orally ingested liquid,

intraperitoneal, intravenous, subcutaneous, sublingual, transcutaneous, intramuscular, or other forms of administration.

[0021] For each of the ingredients specified, there may be more than one source for the ingredients. For Vitamin C, ascorbic acid may be the preferred source of Vitamin C, but other forms of Vitamin C, such as sodium ascorbate, could alternatively be used in lieu of the ascorbic acid. For Zinc, zinc oxide may be used and provides the most concentrated form of elemental Zinc. Other forms, such as zinc gluconate are alternative forms that are also acceptable. For Copper, copper oxide is a form that is frequently used in dietary supplements, but also alternative forms such as copper gluconate may be alternatively used.

[0022] The preferred dose for an adult subject is three (3) capsules daily, preferably with a meal, or as recommended by an eye care practitioner. The dosage can be taken all at once, or split throughout the day. Research suggests that fat soluble antioxidants such as carotenoid lutein are best absorbed when combined with fat (e.g. oil). Advantageously, in this embodiment, the composition contains molecularly distilled fish oil as a source of omega-3 fatty acids, which also acts as a carrier and solubilizer for these carotenoids, thereby reducing the need to take the capsules with a fatty meal. Nevertheless, it is believed that combining the dose with the intake of a small meal containing a healthy portion of fat (i.e. olive oil, salmon, etc) may further help in the proper assimilation of the active components. It is preferable to avoid taking at the same time as foods rich in oxalic or phytic acid (e.g. raw beans, seeds, grains, soy, spinach, rhubarb), as they may depress the absorption of minerals like zinc; however, it is not necessary to avoid these foods for the composition to still be effective.

Pharmacology

[0023] Oxidative stress to the retina may be involved in the pathogenesis of several conditions leading to visual decline, both in normal as well as diseased individuals. Dietary antioxidants play a role in neutralizing free radicals caused by physiological factors such as excessive mitochondrial activity and hyperglycemia, as well as environmental factors such as exposure to ultraviolet light.

[0024] It is well documented that vitamin A deficiency can result in night blindness and blindness due to the erosion of the cornea, but recent evidence suggests that preformed vitamin A may positively impact vision in individuals who are not vitamin A-deficient, possibly by virtue of its antioxidant and immunomodulatory properties. Furthermore, vitamin A is known to modulate retinal pigment epithelial (RPE) cellular function and behavior by helping to restore visual pigment and function.

[0025] Vitamin C is arguably the most important water-soluble biological antioxidant. It can scavenge both reactive oxygen species (ROS) and reactive nitrogen species thought to play roles in tissue injury associated with the pathogenesis of various conditions. By virtue of this activity, it inhibits lipid peroxidation, oxidative DNA damage and oxidative protein damage. It helps preserve intracellular reduced glutathione concentrations, which in turn helps maintain nitric oxide levels and potentiates its vasoactive effects. In addition, vitamin C may modulate prostaglandin synthesis to favor the production of eicosanoids with antithrombotic and vasodilatory activity. Some studies suggest a protective effect against cataracts. Age-related lens opacities are thought to be due to oxidative stress. Ocular tissue concentrates

vitamin C, and its antioxidant action could account for its possible effect in protection against visual decline.

[0026] Vitamin D has immunomodulatory activity. It is known that serum levels of vitamin D are inversely associated with age-related visual decline and early stages of macular structural damage. Though the pharmacodynamics are not fully understood, it is believed that vitamin D offers a protective effect against retinal oxidative damage. Furthermore, vitamin D acts as an inhibitor of retinal neovascularization in animal models.

[0027] The mechanisms underlying the immune effects of zinc are not fully understood, though some of them may be accounted for by its membrane-stabilization effect. Zinc is also believed to have secondary antioxidant activity. Although zinc does not have any direct redox activity under physiological conditions, it nevertheless may influence membrane structure by its ability to stabilize thiol groups and phospholipids. It may also occupy sites that might otherwise contain redox active metals such as iron. These effects may protect membranes against oxidative damage. Zinc also comprises the structure of copper/zinc superoxide dismutase (Cu/Zn SOD), a very powerful antioxidant. Additionally, it may have secondary antioxidant activity via the copper-binding protein metallothionein.

[0028] The carotenoids lutein and zeaxanthin are naturally present in the macula. They filter out potentially phototoxic blue light and near-ultraviolet radiation from the retina. The protective effect is due in part, to the reactive oxygen species (ROS) quenching ability of these carotenoids. Zeaxanthin is the predominant pigment in the fovea, the region at the center of the macula. The quantity of zeaxanthin gradually decreases and the quantity of

lutein gradually increases in the region surrounding the fovea, and lutein is the predominant pigment at the outermost periphery of the macula. Lutein and zeaxanthin also are the only two carotenoids that have been identified in the human lens. They may offer some protection against age-related increases in lens density and possibly cataract formation. Unlike lutein and zeaxanthin, astaxanthin, another xanthophyll carotenoid, is not a retinal pigment. Astaxanthin has both lipo- and hydrophilic antioxidant activity, working both inside as well as outside cell membranes. Astaxanthin is known to cross the blood-brain barrier and effectively work inside retinal tissues. Evidence suggests it inhibits the neurotoxicity induced by peroxide radicals or serum deprivation; reduces the intracellular oxidation induced by various reactive oxygen species (ROS); decreases the radical generation induced by serum deprivation in RGC-5 (retinal ganglion cells); and ameliorates the retinal damage (a decrease in retinal ganglion cells and in thickness of inner plexiform layer) induced by chemical and environmental factors. Furthermore, astaxanthin reduced the expressions of 4-hydroxy-2-nonenal (4-HNE)-modified protein (indicator of lipid peroxidation) and 8-hydroxy-deoxyguanosine (8-OHdG; indicator of oxidative DNA damage) in animal models. These findings indicate that astaxanthin has neuroprotective effects against retinal damage in-vivo, and that its protective effects may be partly mediated via its antioxidant effects. Moreover, astaxanthin has been shown to increase muscular fiber endurance through improved muscle lipid metabolism via inhibitory effect of oxidative CPT I (carnitine palmitoyl transferase - type 1) modification, which may account for documented improvements in eye strain and accommodation in visual display terminal workers, as well as visual acuity and endurance.

[0029] Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are essential omega-3 fatty acids and both play a role in the formation of anti-inflammatory and immunemodulating eicosanoids. As such, they have several actions in a number of body systems. Both play an important role in the maintenance of normal blood flow as they lower fibrinogen levels. DHA is vital for normal neurological function throughout life. Several mechanisms are believed to account for the anti-inflammatory activity of EPA and DHA. Most notably, the two competitively inhibit the conversion of arachidonic acid to the pro-inflammatory prostaglandin E2 (PGE2), and leukotriene B4 (LKB4), thus reducing their synthesis. EPA and DHA also inhibit the synthesis of the inflammatory cytokines Tumor Necrosis Factor-alpha (TNF-a), Interleukin-1 (IL-1) beta. EPA and DHA inhibit the 5-LOX (lipoxygenase) pathway responsible for the conversion of arachidonic acid to inflammatory leukotrienes in neutrophils and monocytes and can suppress phospholipase C-mediated signal transduction, also involved in inflammatory events. EPA is the precursor to series-3 prostaglandins, series-5 leukotrienes (LTB5) and series-3 thromboxanes (TXA3). This could account in part for its microvascular and anti-inflammatory role. Furthermore, EPA is a precursor of resolvins (Rv) such as RvE1 and RvD1 which may help reduce tear gland inflammation, increase tear volume and ocular lubrication.

[0030] EPA and DHA have both similar and dissimilar physiologic roles. EPA appears to be more important in those roles where the eicosanoids are involved such as inflammation as well as tear gland function and tear production, whereas DHA seems to play its most

important role in offering structural protection to the retina and other neurovascular structures such as corneal nerves.

[0031] Taurine has antioxidant activity derived from its ability to scavenge the reactive oxygen species (ROS) hypochlorite to form the relatively harmless N-chlorotaurine, which is then reduced to taurine and chloride. This activity may protect against collateral tissue damage that can occur from the respiratory burst of neutrophils in the retina. Taurine also appears to modulate the activation of cGMP gated channels, which control the influx of calcium into the rod outer segments, the function of which is critical in the phototransduction process. Taurine may also suppress peroxidation of membrane lipoproteins by other ROS. It is thought that this effect is not due to taurine's scavenging of these ROS, but rather to taurine's membrane-stabilizing activity, which confers greater resistance to the membrane lipoproteins against lipid peroxidation.

[0032] Alpha-lipoic acid (ALA) forms a redox couple with its metabolite, dihydrolipoic acid (DHLA) and may scavenge a wide range of reactive oxygen species. Both ALA and DHLA can scavenge hydroxyl radicals, nitric oxide radicals, peroxynitrite, hydrogen peroxide and hypochlorite. ALA, but not DHLA, may scavenge singlet oxygen, and DHLA, but not ALA, may scavenge superoxide and peroxy reactive oxygen species.

[0033] ALA has been found to decrease urinary isoprostanes, O-LDL and plasma protein carbonyls, markers of oxidative stress. Furthermore, ALA and DHLA have been found to have antioxidant activity in aqueous as well as lipophilic regions, and in both extracellular as well as intracellular environments. ALA is also involved in the recycling of other biological

antioxidants such as vitamins C and E, as well as glutathione. Finally, preliminary scientific evidence suggests a protective effect in the retina against ischemia and elevated blood sugar levels, such as is commonly seen in diabetic patients.

[0034] Pine bark bioflavonoids have demonstrated a number of antioxidant and vasoprotective activities, including scavenging of the superoxide radical anion, hydroxyl radical, lipid peroxy radical, peroxynitrite radical, and singlet oxygen. Pharmacological studies employing in vitro, animal, and human models have found that pine bark and its bioflavonoids have potent anti-inflammatory actions, improve endothelial function (produce vasodilatation), reduce platelet aggregation, reduce alpha-glucosidase activity and blood glucose levels, and promote wound healing through mechanisms not yet fully understood. They have also been shown to protect low-density lipoprotein (LDL) from oxidation. It has been suggested that pine bark flavonoids may bind to the blood vessel wall proteins and mucopolysaccharides, and produce a capillary sealing effect, leading to a reduced permeability and edema formation, which may account for their protective effect in the eye.

[0035] Piperine, a chemical constituent of the black pepper (*Piper* spp.) has bioavailability enhancing activity of certain nutrients, including antioxidants of the carotenoid family (i.e. lutein, zeaxanthin, etc) as well as several vitamins and minerals. The mechanism of action is not completely understood, but experiments done both in-vitro and in-vivo suggest that it may operate by increasing either membrane fluidity and affinity of nutrients to the cell membrane, or solubilization of the intracellular lipid moiety in the epithelial gastrointestinal tissues due to its lipophilic nature, making it more permeable to the applied nutrient.

Pharmacokinetics

[0036] Vitamin A (retinyl palmitate ester) is hydrolyzed by a pancreatic hydrolase and combined with bile acids and other fats prior to its uptake by enterocytes in the form of micelles. It is then re-esterified and secreted by the enterocytes into the lymphatic system in the form of chylomicrons. These chylomicrons enter the circulation via the thoracic duct and undergo metabolism via lipoprotein lipase. Most of the retinyl esters are then rapidly taken up into liver parenchymal cells and again hydrolyzed to all-trans retinol and fatty acids (e.g. palmitate). All-trans retinol may be then stored by the liver as retinyl esters or transported in the circulation bound to serum retinol binding protein (RBP). Serum RBP is the principal carrier of retinol, which comprises greater than 90% of serum vitamin A. It is believed that RBP in association with transthyretin or prealbumin co-transport proteins are responsible for the transport of retinol into target cells. All-trans retinol is delivered to the cornea via the tears and by diffusion through eye tissue. Retinol is oxidized to retinal via retinol dehydrogenase. Retinal is metabolized to retinoic acid via retinal dehydrogenase. The metabolites of retinol and retinoic acid undergo glucuronidation, glucosylation and amino acylation. They are excreted mainly via the biliary route, though some excretion of retinol and its metabolites also occurs via the kidneys.

[0037] Intestinal absorption of vitamin C occurs primarily via a sodium-dependent active transport process, although some diffusion may also come into play. The major intestinal transporter is SVCT1 (sodium-dependent vitamin C transporter 1). Some ascorbic acid may be oxidized to dehydroascorbic (DHAA) acid and transported into enterocytes via glucose

transporters. Within the enterocytes, all DHAA is reduced to ascorbic acid via reduced glutathione, and ascorbic acid leaves the enterocytes to enter the portal and systemic circulation for distribution throughout the body. The transporter SVCT2 appears to aid in the transport of vitamin C into the aqueous humor of the eyes. Though it cannot itself cross the blood-brain barrier, ascorbic acid may be oxidized to DHAA and be transported to the brain tissues via GLUT1 (glucose transporter 1), where it can then be reduced back to ascorbic acid for utilization. Metabolism and excretion of vitamin C occurs primarily via oxidation to DHAA and hydrolyzation to diketogulonate, though other metabolites such as oxalic acid, threonic acid, L-xylose and ascorbate-2-sulfate can also result. The principal route of excretion is via the kidneys.

[0038] Vitamin D is principally absorbed in the small intestine via passive diffusion. It is delivered to the enterocytes in micelles formed from bile acids, fats, and other substances. Like vitamin A, vitamin D is secreted by the enterocytes into the lymphatic system in the form of chylomicrons and enters the circulation via the thoracic duct. It is also transported in the blood bound to an alpha globulin known as Vitamin D-Binding Protein (DBP) and the group-specific component (Gc) protein. Much of the circulating vitamin D is extracted by the hepatocytes to be metabolized to 25-hydroxyvitamin D [25(OH)D] or calcidiol via the enzyme vitamin D 25-hydroxylase. 25(OH)D is then metabolized in the kidney to the biologically active hormone form of vitamin D, calcitrol [1,25(OH)₂D], via the enzyme 25-hydroxyvitamin D-1-alpha-hydroxylase. Calcitrol may undergo further hydroxylation and metabolism into 24,25(OH)₂D and 1,24,25(OH)₃D. These metabolites, as well as vitamin D

are excreted primarily via the biliary route. The final degradation product of 1,25(OH)₂D is calcitroic acid, which is excreted by the kidney.

[0039] Much of the pharmacokinetics of zinc in humans remains unknown. Zinc is absorbed all along the small intestine, though most appears to be assimilated from the jejunum. Zinc uptake across the brush border appears to occur by both a saturable barrier-mediated mechanism and a non-saturable non-mediated mechanism. The exact mechanism of zinc amino-acid chelates (such as the zinc-methionine used in AmeriSciences OS2) transport into the enterocytes remains unclear, but evidence demonstrates greater bioavailability than other supplemental forms. Zinc transporters have been identified in animal models. Once the mineral is within the enterocytes, it can be used for zinc-dependent processes, become bound to metallothionein and held within the enterocytes or pass through the cell. Transport of zinc across the serosal membrane is carrier-mediated and energy-dependent. Zinc is transported to the liver via the portal circulation. A fraction of zinc is extracted by the hepatocytes, and the remaining zinc is transported to the various cells of the body via the systemic circulation. It is transported bound to albumin (about 80%), alpha-3-macroglobulin (about 18%), and to such proteins as transferrin and ceruloplasmin. The major route of zinc excretion appears to be the gastrointestinal tract via biliary, pancreatic or other gastrointestinal secretions. Fecal zinc is also comprised of unabsorbed dietary zinc as well as the sloughing of mucosal cells. Carotenoids such as lutein and zeaxanthin appear to be more efficiently absorbed when administered with high-fat meals. They are hydrolyzed in the small intestine via esterases and lipases, and solubilized in the lipid core of micelles formed from bile acids and other lipids.

They can also form clathrate complexes with conjugated bile salts. Both of these complexes can deliver carotenoids to the enterocytes, where they are then released into the lymphatics in the form of chylomicrons. From there, they are transported to the general circulation via the thoracic duct. Lipoprotein lipases hydrolyze much of the triglyceride content in the chylomicrons found in the circulation, resulting in the formation of chylomicrons remnants, which in turn retain apolipoproteins E and B48 on their surfaces and are mainly taken up by the hepatocytes. Within the liver, carotenoids are incorporated into lipoproteins and they appear to be released into the blood mainly in the form of HDL and – to a much lesser extent – VLDL. Lutein and zeaxanthin are mainly accumulated in the macula of the retina, where they bind to the retinal protein tuberlin. Zeaxanthin is specifically concentrated in the fovea. Lutein is distributed throughout the retina. Astaxanthin, on the other hand, is distributed throughout the body, with muscle tissue seemingly receiving larger concentrations based on tissue/plasma ratio at 8 and 24 hours after oral ingestion. Lutein appears to undergo some metabolism in-situ to meso-zeaxanthin. Xanthophylls as well as their metabolites are believed to be excreted via the bile and, to a lesser extent, the kidney.

[0040] Following ingestion, EPA and DHA undergo hydrolysis via lipases to form monoglycerides and free fatty acids. In the enterocytes, reacylation takes place and this results in the formation of triacylglycerols, which are then assembled with phospholipids, cholesterol and apoproteins into chylomicrons. These are then released into the lymphatic system from whence they are transported to the systemic circulation. Here, the chylomicrons are degraded by lipoprotein lipase, and EPA & DHA are transported to various tissues of the

body via blood vessels, where they are used mainly for the synthesis of phospholipids. Phospholipids are incorporated into the cell membranes of red blood cells, platelets, neurons and others. EPA and DHA are mainly found in the phospholipid components of cell membranes. DHA is taken up by the brain and retina in preference to other fatty acids. DHA can be partially and conditionally re-converted into EPA, and vice-versa, although the process is thought to be less-than-efficient and may be adversely affected by age.

[0041] Although not an amino-acid in the true sense of the word, taurine is absorbed from the small intestine via the beta-amino acid transport system: a carrier system dependent on sodium and chloride that serves gamma-aminobutyric acid and beta-alanine, as well as taurine. It is transported to the liver via the portal circulation, where much of it forms conjugates with bile acids. Taurocholate (the bile salt conjugate of taurine and cholic acid) is the principal conjugate formed via the enzyme choloyl-CoA N-acyltransferase. Taurine conjugates are excreted through the bile. Remaining taurine that is not conjugated or used in the biliary process is distributed via the systemic circulation to various tissues in the body, including the retina and other eye tissues. Taurine is not usually completely reabsorbed from the kidneys, and fractions of ingested taurine are excreted in the urine.

[0042] Alpha lipoic acid pharmacokinetic data demonstrate that its absorption takes place from the small intestine, followed by portal circulation delivery to the liver, and to various tissues in the body via systemic circulation. Alpha lipoic acid readily crosses the bloodbrain barrier, and is readily found (following distribution to the various tissues) extracellularly, intracellularly and intramitochondrially. It is metabolized to its reduced form, dihydrolipoic

acid (DHLA) by mitochondrial lipoamide dehydrogenase, which can in turn form a redox couple with lipoic acid. ALA is also metabolized to lipoamide, which forms an important cofactor in the multienzyme complexes that catalyze pyruvate and alpha-ketoglutarate, both important aspects of cellular respiration and energy production via the Krebs cycle. ALA can also be metabolized to dithiol octanoic acid, which can undergo catabolism.

[0043] The pharmacokinetics of bioflavonoids such as those found in pine bark and piperine found in *Piper* species are not fully understood in humans. It is known, however, that pine bark flavonoids undergo extensive glucuronidation and sulfation during and following absorption from the small intestine. Both glucuronides and sulfates, as well as other metabolites are primarily excreted through the urine. In animals, piperine is absorbed following ingestion, and some metabolites have been identified, such as piperonylic acid, piperonyl alcohol, piperonal and vanillic acid are found in the urine. One metabolite, piperic acid, is found in the bile. Most publications conclude that further pharmacokinetic studies are needed to fully understand if this data is applicable to humans as well.

[0044] Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications, and variations will be apparent to those skilled in the art in light of the foregoing description. Accordingly, it is intended to embrace all such alternatives, modifications, and variations as fall within the spirit and broad scope of the appended claims. The present invention may suitably comprise, consist or consist essentially of the elements disclosed and may be practiced in the absence of an element not disclosed.

CLAIMS

What is claimed is:

1. A composition for promoting ocular health of a subject, the composition comprising:

vitamin A in an amount of less than about 50,000 IU, wherein the vitamin A is not in the form of beta-carotene;

vitamin C in an amount between about 60 mg to about 500 mg;

vitamin D in an amount between about 400 IU and about 2,000 IU;

selenium in an amount between about 35 µg and about 200 µg;

omega-3 fatty acid in an amount of less than about 5,000 mg;

taurine in an amount between about 100 and about 1,000 mg;

alpha lipoic acid in an amount of less than about 1000 mg; and

non-vitamin A carotenoid in an amount between about 5 mg and about 50 mg,

wherein the composition is free of vitamin E and beta-carotene.
2. The composition of claim 1, wherein the composition is formulated for administration to the subject over one, or more than one, administrations.
3. The composition of either one of claims 1 and 2, wherein the composition is for administration to the subject daily.

4. The composition of any one of claims 1-3, wherein the vitamin A is in an amount of about 2,500 IU.
5. The composition of any one of claims 1-4, wherein the vitamin C is in an amount of about 250 mg.
6. The composition of any one of claims 1-5, wherein the vitamin D is in an amount of about 800 IU.
7. The composition of any one of claims 1-6, wherein the selenium is in an amount of about 70 μg .
8. The composition of any one of claims 1-7, wherein the omega-3 fatty acid is in an amount of about 500 mg.
9. The composition of any one of claims 1-8, wherein the taurine is in an amount of about 500 mg.

10. The composition of any one of claims 1-9, wherein the alpha lipoic acid is in an amount of about 100 mg.

11. The composition of any one of claims 1-10, wherein the non-vitamin A carotenoid is in an amount of about 12 mg.

12. The composition of claim 1, wherein the vitamin A is in an effective amount of about 2,500 IU, the vitamin C is in an effective amount of about 250 mg, the vitamin D is in an effective amount of about 800 IU, the selenium is in an effective amount of about 70 µg, the omega-3 fatty acid is in an effective amount of about 500 mg, the taurine is in an effective amount of about 500 mg, the alpha lipoic acid is in an effective amount of about 100 mg, and the non-vitamin A carotenoid is in an effective amount of about 12 mg.

13. The composition of any one of claims 1-12, wherein the vitamin A comprises pre-formed vitamin A.

14. The composition of any one of claims 1-13, wherein at least a portion of the Vitamin A is in the form of Vitamin A palmitate.

15. The composition of any one of claims 1-14, further comprising pine bark extract.

16. The composition according to any one of claims 1-15, further comprising astaxanthin.
17. The composition according to any one of claims 1-16, further comprising piper spp. extract.
18. The composition of any one of claims 1-17, further comprising zinc in an amount between about 15 mg to about 80 mg.
19. The composition of claim 18, further comprising copper in an amount of about 1 mg to about 2 mg when the zinc is in an amount above 30 mg.
20. The composition of any one of claims 1-19, further comprising one or more excipients.
21. The composition of claim 20, where the one or more excipients are one or more of soybean oil, white beeswax, soy lethicin, or any combination thereof.
22. The composition of any one of claims 1-21, wherein the non-vitamin A carotenoid is lutein, zeaxanthin, or a combination thereof.

23. The composition of any one of claims 1-22, wherein the omega-3 fatty acid comprises eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), or a combination thereof.

24. The composition of any one of claims 1-7, wherein the omega-3 fatty acid comprises no more than 5,000 mg of EPA, and no more than 3,000 mg of DHA.

25. The composition of any one of claims 1-10, wherein the non-vitamin A carotenoid comprises about 5 to about 50 mg of lutein, and about 0.25 to about 12 mg zeaxanthin, and wherein the amount of the non-vitamin A carotenoid is between about 5 mg and about 50 mg.

26. The composition of any one of claims 1-25, wherein the composition is in a deliverable state to the subject such that the composition is for oral administration to the subject, wherein the deliverable state is a coated or uncoated tablet, a hard capsule, a liquid-filled capsule, hard gelatin capsule, hard vegetable-based capsule, elixir, soft-chew, lozenge, chewable bar, juice suspension, time-release formulation, formulation for intramuscular administration, or any combination thereof.

27. The composition of any one of claims 1-26, wherein the composition is for administration over one or more administrations per day, wherein the sum of all administrations per day amounts to the composition as defined in any one of claims 1-26.
28. The composition of any one of claims 1-27, wherein the composition is formulated into one or more dosages, each having an approximately equal portion of the composition.
29. The composition of any one of claims 1-28, wherein the composition is formulated as a single dosage comprising approximately 100% of the composition, as two dosages comprising approximately 50% of the composition per dosage, or as three dosages comprising approximately one-third of the composition per dosage.
30. The composition of any one of claims 1-29, wherein the composition is divided into 3 soft gels or capsules for administration to the subject daily.
31. Use of the composition as defined in any one of claims 1-30, for promoting ocular health in a subject in need thereof.
32. The use of claim 31, wherein the subject is a mammal.

33. The use of claim 31, wherein the subject is a dog, a cat, or a homo sapiens.
34. The use of claim 31, wherein the subject is a human.
35. The use of any one of claims 31-34, wherein the composition is for oral administration to the subject.
36. The use of any one of claims 31-35, wherein the composition is in a deliverable state to the subject, wherein the deliverable state is a coated or uncoated tablet, a hard capsule, a liquid-filled capsule, hard gelatin capsule, hard vegetable-based capsule, elixir, soft-chew, lozenge, chewable bar, juice suspension, time-release formulation, formulation for intramuscular administration, or any combination thereof.
37. The use of any one of claims 31-36, wherein the subject is a human having an increased risk of oxidative stress in its retinas.
38. The use of any one of claims 31-37, wherein the subject suffers from hyperglycemia or diabetes.

39. The use of any one of claims 31-36, wherein the composition comprises astaxanthin, and wherein the subject is a human that interacts with a visual display terminal for a sustained period of time.

40. The use of claim 39, wherein the sustained period of time typically exceeds about 6 hours per day.

41. The use of any one of claims 31-40, wherein the composition is for administration over one or more administrations per day, wherein the sum of all administrations per day amounts to the composition as defined in any one of claims 1-26.

42. The use of any one of claims 31-41, wherein the composition is formulated into one or more dosages, each having an approximately equal portion of the composition.

43. The use of any one of claims 31-42, wherein the composition is formulated as a single dosage comprising approximately 100% of the composition, as two dosages comprising approximately 50% of the composition per dosage, or as three dosages comprising approximately one-third of the composition per dosage.

44. The use of any one of claims 31-43, wherein the composition is divided into 3 soft gels or capsules for administration to the subject daily.

45. A dosage form of a composition for promoting ocular health of a subject, the dosage form comprising:

vitamin A in an amount of about 833 IU, wherein the vitamin A is not in the form of beta-carotene;

vitamin C in an amount of about 83 mg;

vitamin D in an amount of about 267 IU;

selenium in an amount of about 23 µg;

omega-3 fatty acid in an amount of about 167 mg;

taurine in an amount of about 167 mg;

alpha lipoic acid in an amount of about 33 mg; and

non-vitamin A carotenoid in an amount of about 4 mg,

wherein the composition is free of vitamin E and beta-carotene.

46. The dosage form of claim 45, wherein three of the dosage forms are for administration to the subject daily.

47. The dosage form of claim 45 or 46, wherein the dosage form is formulated as a soft-gel for oral administration to the subject.
48. The dosage form of any one of claims 45-47, wherein the vitamin A comprises pre-formed vitamin A.
49. The dosage form of any one of claims 45-48, wherein at least a portion of the Vitamin A is in the form of Vitamin A palmitate.
50. The dosage form of any one of claims 45-49, further comprising pine bark extract.
51. The dosage form according to any one of claims 45-50, further comprising astaxanthin.
52. The dosage form according to any one of claims 45-51, further comprising piper spp. extract.
53. The dosage form of any one of claims 45-52, wherein the dosage form further comprises zinc in an amount of about 10 mg.

54. The dosage form of any one of claims 45-53, further comprising one or more excipients.
55. The dosage form of claim 54, where the one or more excipients are one or more of soybean oil, white beeswax, soy lethicin, or any combination thereof.
56. The dosage form of any one of claims 45-55, wherein the non-vitamin A carotenoid is lutein, zeaxanthin, or a combination thereof.
57. The dosage form of any one of claims 45-56, wherein the omega-3 fatty acid comprises eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), or a combination thereof.
58. The dosage form of any one of claims 45-57, wherein the non-vitamin A carotenoid of the dosage form comprises about 3 mg of lutein, and about 0.67 mg zeaxanthin.