Title: Niacinamide Mononucleotide Formulations for Skin Aging

Abstract: Topical compositions comprising niacinamide mononucleotide to improve the appearance of aging skin and to prevent and treat skin aging; and methods of use of topical compositions comprising niacinamide mononucleotide to improve the appearance of aging skin and to prevent and treat skin aging.
TITLE OF INVENTION

NIACINAMIDE MONONUCLEOTIDE FORMULATIONS FOR SKIN AGING

FIELD OF THE INVENTION

[0001] The present invention relates to topical compositions comprising niacinamide mononucleotide and/or its derivative for skin aging and methods of use of the topical compositions to prevent and treat skin aging.

BACKGROUND OF THE INVENTION

[0002] Human skin is constantly directly exposed to the air, solar radiation, environmental pollutants, or other mechanical and chemical insults, which are capable of inducing the generation of free radicals as well as reactive oxygen species (ROS) of our own metabolism. Extrinsic skin damage develops due to several factors: ionizing radiation, severe physical and psychological stress, alcohol intake, poor nutrition, overeating, environmental pollution, and exposure to UV radiation (UVR). It is estimated that among all these environmental factors, UVR contributes up to 80%. UV-induced generation of ROS in the skin develops oxidative stress, when their formation exceeds the antioxidant defiance ability of the target cell. The primary mechanism by which UVR initiates molecular responses in human skin is via photochemical generation of ROS, mainly formation of superoxide anion (O(2) (-) (-)), hydrogen peroxide (H(2)O(2)), hydroxyl radical (OH(-)), and singlet oxygen ((1)O(2)). Over time, the presence of ROS will cause conditions of aging skin.

[0003] Niacinamide, also known as nicotinamide or nicotinic amide, is the amide of nicotinic acid (a.k.a. niacin) and a source of vitamin B₃. Niacinamide can be found in Vitamin B₃ containing foods including yeast, meat, fish, milk, eggs, green vegetables, beans, and cereal grains. Niacin and niacinamide are also found in many vitamin B complex supplements with other B vitamins. In cells, niacinamide is incorporated into coenzymes of nicotinamide adenine dinucleotide (NAD) and
nicotinamide adenine dinucleotide phosphate (NADP), which are responsible for a wide variety of enzymatic oxidation-reduction reactions ("redox reaction"). It is believed that niacinamide exerts antioxidant properties through the redox reaction; and that it can scavenge reactive oxygen species. Moreover, it is reported that nicotinamide has demonstrated anti-inflammatory activity.

[0004] U.S. Patent No. 7,179,477 to Gupta, S.K. discloses a three-step dermabrasion system for skin. Niacinamide salts such as niacinamide lactate, niacinamide glycolate, niacinamide malate, niacinamide mandelate, niacinamide ascorbate, niacinamide phytate, niacinamide citrate, niacinamide hydroxycitrate, niacinamide alevurate, niacinamide salicylate, and/or niacinamide hyaluronate are used as skin softening agents in the system.

[0005] U.S. Patent No. 7,320,797 to Gupta, S.K. discloses an anti-aging topical composition for skin comprising (i) a quaternary ammonium extra-cellular antioxidant agent, (ii) an intracellular antioxidant agent, (iii) an antiinflammatory agent, and (iv) a collagen boosting agent, and (v) a carrier base. The collagen boosting agent may include, among many other choices, niacinamide or a niacinamide salt selected from niacinamide lipoate and niacinamide ascorbate.

[0006] U.S. Application Publication No. 20150093346 to Burke-Colvin, D. discloses skin care formulations in which niacinamide lactate is used as a bleaching and lightening agent.

[0007] U.S. Patent No. 7,700,076 to Tamarkin, D. relates to a pharmaceutical foam composition having enhanced skin penetration for treatment of skin disorders, such as aging skin, wrinkles, hyperpigmentation, scaly skin and other undesirable skin properties. Niacinamide and niacinamide N-oxide can be included in the composition as anti-wrinkle actives and sources of vitamin B3.

[0008] U.S. Patent No. 8,106,184 to Sauve, A.A. is directed to methods of using nicotinoyl riboside and nicotinamide riboside to increase levels of NAD in cells and tissues for improving their lifespan. It proposes that skin aging can be prevented by
treating skin or epithelial cells in accordance with the methods. But no written
description of a nicotinoyl riboside or nicotinamide riboside formulation having the
proposed effect is disclosed.

[0009] WO2015066382 to Deren-Lewis, A., assigned to Chromadex Inc.,
discloses the use of nicotinoyl riboside or salts thereof for treating signs or symptoms of
aging or skin wrinkles in an individual. Chromadex Inc. has a commercial anti-aging
supplement sold under the trade name NIAGEN™, which is a chloride salt of
nicotinamide riboside supplied in vegetarian capsules for oral administration.

[0010] The prior art has disclosed specific nicotinamide derivatives for skin
care, namely, niacinamide salts, niacinamide N-oxide, and nicotinamide riboside. In
most cases, the nicotinamide derivatives, such as niacinamide salts and niacinamide N-
oxide, are merely used as optional adjunct supplements in topical cosmetic
compositions. Nicotinoyl riboside or nicotinamide riboside have been proposed, but
workable formulations containing nicotinoyl riboside or nicotinamide riboside for topical
treatment or prevention of skin aging have not been disclosed.

SUMMARY OF THE INVENTION

[0011] The present invention provides a topical composition for application to
aging skin, comprising an effective amount of β-niacinamide mononucleotide (in short,
"niacinamide mononucleotide" or "NMN") and/or its derivative, as shown in formula (I):

![Chemical Structure](image-url)
wherein each of $R_1$ and $R_2$ is individually selected from the group consisting of 
hydrogen, alkyl, cycloalkyl, alkenyl, alkaryl, hydroxy, alkoxy, and amino; each of $R_3$ and 
$R_4$ is individually selected from the group consisting of hydrogen, alkyl, aliphatic or 
aromatic acyl, and aliphatic or aromatic thioacyl; and $R_5$ is hydrogen, alkyl, or cation. 
When $R_5$ is hydrogen, the formula (I) may be in an ionic salt form when a sufficient 
amount of base is present (not shown). For example, the phosphate acid may be in a 
sodium salt form, wherein the covalent bond “O-R_5” may be replaced by an ionic bond, 
“O⁻ Na⁺”. In other words, $R_5$ is a sodium cation. In preferred embodiments, $R_1$ to $R_5$ are 
all hydrogen, in which case formula (I) represents niacinamide mononucleotide.

[0012] The topical composition further provides a pharmaceutically acceptable 
carrier. In some of these embodiments, the niacinamide mononucleotide or its 
derivative is present from about 0.005% to about 30.0% by weight. In certain of these 
embodiments, the niacinamide mononucleotide or its derivative is present from about 
0.1% to about 20.0% by weight. In certain embodiments, the niacinamide 
mononucleotide or its derivative is present from about 0.1% to about 5.0% by weight. In 
further embodiments, the niacinamide mononucleotide or its derivative is present from 
about 0.5% to about 1.5% by weight.

[0013] In some embodiments, the composition further comprises one or more 
adjunct active ingredients selected from the group consisting of fatty acid, fatty acid 
ester of ascorbic acid, and the mixture thereof. In some embodiments, the composition 
further comprises at least one adjunct active ingredient selected from the group 
consisting of salts of magnesium, zinc and copper, tocotrienols, tocotrienol derivatives, 
vitamin E compositions enriched with tocotrienols or tocotrienol derivatives (e.g., 
tocotrienol acetate, also known as vitamin E acetate), and mixtures thereof. In some 
embodiments, the adjunct active ingredient of the composition comprises a mixture of 
magnesium aspartate, zinc gluconate and copper gluconate. The adjunct active 
ingredients may be present from about 0.01% to about 20.0 % by weight.

[0014] In certain embodiments, the composition comprises an oil-in-water 
emulsion. In other embodiments, the composition comprises a cream. In the oil-in-
water emulsion embodiments, the composition comprises an emulsifier such as fatty acid derivatives of stearic acid or phosphatidylcholine.

[0015] As a non-limiting example, the invention provides a topical composition for application to aging skin in the form of a cream or lotion which comprises about 0.1% to about 5.0% by weight, preferably about 0.1% to about 5.0% by weight, and even more preferably about 0.5% to about 1.5% by weight of niacinamide mononucleotide or its derivative, about 2.0% to about 15.0% by weight of at least one emulsifier, and water. In a preferred embodiment, the above topical composition may have at least one adjunct active component in an amount of about 1.0% to about 5.0% by weight of the composition.

[0016] The topical composition for application to aging skin further comprises an emollient. One preferred emollient is isopropyl palmitate. In some of these embodiments, the composition comprises about 1.0% to about 3.0% by weight of niacinamide mononucleotide or its derivative, about 1.5% to about 5.0% by weight of at least one fatty acid derivative of stearic acid, about 1.0% to 5.0% by weight of an emollient, and water.

[0017] As another example, the invention provides a topical composition for application to aging skin in a gel form which comprises about 10.0% to about 30.0% by weight, preferably about 15.0% to about 25.0% by weight, and even more preferably about 15.0% to about 20.0% by weight of niacinamide mononucleotide or its derivative, about 30.0% to about 65.0% by weight of at least one emulsifier as a gel base. In a preferred embodiment, the gel form topical composition comprises about 15.0% to about 20.0% by weight of niacinamide mononucleotide or its derivative, about 75.0% to about 85.0% of emollients and/or emulsifiers, and no water.

[0018] The topical composition of the invention may contain additional ingredients commonly found in skin care compositions and cosmetics, such as, for example, tinting agents, skin conditioning agents, humectants, preservatives, antioxidants, perfumes, chelating agents.
[0019] The present invention further provides a method of topical use of compositions comprising niacinamide mononucleotide and/or its derivative of formula (I) to treat or prevent skin aging. The method comprises the step of topically applying the topical composition to the skin areas at predetermined intervals.

[0020] It is noticed that the use of the niacinamide mononucleotide and/or its derivative containing compositions improves the appearance of aging skin, including surface spots, brown spots, red areas, wrinkles and texture and other artifacts of aging skin, as well as conditions of skin dryness, dullness, loss of elasticity, lack of radiance, exaggerated lines and wrinkles, spider vessels or red blotchiness. The appearance of marionette lines, smile lines, deep nasolabial fold lines, crow’s feet, fine lines/wrinkles, vertical lines between the eyebrows, horizontal forehead lines, sagging thin/frail skin, skin redness and dullness are improved using the methods of the invention. Thus, the present invention also provides a method of treating aged skin.

DETAILED DESCRIPTION OF THE INVENTION

[0021] Aging skin is characterized histologically by cross-linking of collagen and elastin in the dermis. This results in loss of support seen clinically as sagging and wrinkling. The present invention recognizes these processes and provides compositions and methods to minimize both prospective and existing aging conditions. In particular, the present invention provides topical compositions comprising nicotinamide mononucleotide (NMN) and/or its derivative, when topically applied to skin, such that the rate of regeneration of skin cell tissues is predominant over the rate of degeneration, thereby preventing skin aging conditions.

[0022] The term “topical composition” as used herein shall mean the complete product including the niacinamide mononucleotide or its derivative active ingredient, the carrier, and any adjuvants, thickeners, excipients, etc. as described herein which is applied to a person’s skin.
[0023] The term "skin" means the keratinous surfaces skin, hair and nails. The term "skin" when used herein is in the broad sense meaning the skin of the face, body, and neck as well as the lips.

[0024] In one aspect, the present invention provides a topical compositions comprising niacinamide mononucleotide and/or its derivative of formula (I) for improving the appearance of aging skin and/or treating or preventing skin aging. The compositions are expected to help address severe skin dryness, dullness, loss of elasticity, lack of radiance, exaggerated lines and wrinkles, spider vessels or red blotchiness. Particularly, marionette lines, smile lines, deep nasolabial fold lines, crow’s feet, fine lines/wrinkles, vertical lines between the eyebrows, horizontal forehead lines, sagging thin/frail skin, skin redness and dullness may be improved using the compositions of the invention. When applied to skin, compositions of the present invention are expected to show improvement in surface spots, brown spots, red areas, wrinkles and texture and other artifacts of aging skin.

[0025] The term “surface spots” refers to brown or red spots which include freckles, acne marks or scars, hyperpigmentation and vascular lesions.

[0026] The term “brown spots” refers to those caused by an excess of melanin on and within the skin, these lesions include freckles, melasma, hyperpigmentation and lentigines.

[0027] The term “red areas” refers to various skin conditions such as acne, rosacea, inflammation and spider veins that have apparent red structures due to the blood vessels and hemoglobin contained in the papillary dermis.

[0028] The term “wrinkles” refers to fine lines, furrows, folds and creases in the skin. Wrinkles are associated with decreased skin elasticity.

[0029] The term “texture” refers to gradations in the skin’s color and tone and surface peaks and valleys that are analyzed to measure smoothness.

[0030] Formula (I) has the following structure:
wherein each of R₁ and R₂ is individually selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkaryl, hydroxy, alkoxy, and amino; each of R₃ and R₄ is individually selected from the group consisting of hydrogen, alkyl, aliphatic or aromatic acyl, and aliphatic or aromatic thioacyl; and R₅ is hydrogen, cation, or alkyl. When R₅ is hydrogen, the formula (I) may be in an ionic salt form when a sufficient amount of base is present (not shown). For example, the phosphate acid may be in a sodium salt form, wherein the covalent bond “O-R₅” may be replaced by an ionic bond, “O⁻ Na⁺”. In a preferred embodiment, R₁, R₂, R₃, and R₄ are hydrogen, and R₅ is a sodium cation or hydrogen.

[0031] "Alkyl" refers to an alkyl group and substituted alkyl group wherein the alkyl group preferably has from 1 to about 12 carbon atoms, more preferably 1 to 8 carbon atoms and still more preferably 1 to 6 carbon atoms, wherein the alkyl group may be substituted with to 1 to 3 substituents selected from the group consisting of alkoxy, amino, mono- and dialkylamino, aminoacyl, aminocarbonyl, alkoxy carbonyl, aryl, carboxyl, cyano, halo, heterocyclic, hydroxy, nitro, thioalkoxy and the like.

[0032] "Cycloalkyl" refers to cyclic alkyl groups of from 3 to 10 carbon atoms having a single cyclic ring or multiple condensed rings which can be optionally substituted with from 1 to 3 alkyl groups. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, 1-methylcyclopropyl, 2-methylcyclopentyl, 2-methylcyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like.
"Alkenyl" refers to alkenyl groups preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkenyl unsaturation. Preferred alkenyl groups include ethenyl, n-propenyl, isopropenyl, and the like.

"Alkaryl" refers to alkylene-aryl groups preferably having from 1 to 10 carbon atoms in the alkylene moiety and from 6 to 14 carbon atoms in the aryl moiety. Such alkaryl groups are exemplified by benzyl, phenethyl, and the like.

"Alkoxy" refers to the group "alkyl-O-". Preferred alkoxy groups include, by way of example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, 1,2-dimethylbutoxy, and the like.

"Amino" refers to primary, secondary and tertiary alkyl substituted amino groups and the like.

"Acyl" refers to a monovalent group with a carbon atom of a carbonyl group as the point of attachment, further having a linear or branched, cyclo, cyclic or acyclic structure which may contain a heteroatom.

"Thioacyl" refers to a monovalent group with a carbon atom of a thiocarbonyl group as the point of attachment, further having a linear or branched, cyclo, cyclic or acyclic structure which may contain a heteroatom.

Nicotinamide mononucleotide is a naturally occurring compound in the body that plays a vital role in how cells use energy. Samarista-Giron, A. reported in 2011 that nicotinamide mononucleotide is able to reduce high blood sugar levels and elevated levels of cholesterol, triglycerides and free fatty acids during in vitro animal studies by with mice. Samhita, L. reported in 2013 that nicotinamide mononucleotide may rejuvenate mice’s muscle tissues via intramuscular injection of nicotinamide mononucleotide. U.S. Application Publication No. 20160022712 to Imai et al. discloses the use of nicotinamide mononucleotide compositions for treating aged-related diseases and conditions, such as age-related obesity, age-related increases in blood lipid levels, age-related decreases in insulin sensitivity, age-related decreases in memory function,
and age-related changes in eye function such as macular degeneration. U.S. Application Publication No. 20160024527 to Tilly et al. discloses the use of nicotinamide mononucleotide compositions for improving female fertility.

[0040] However, there is no disclosure in the art regarding topical administration of nicotinamide mononucleotide for anti-aging skin treatment or improving the appearance of aging skin. In particular, none of the prior art discloses suitable formulations that are sufficiently stable, have good bioavailability via topical administration on an affected skin, and effectively lead to anti-aging effects.

[0041] Niacinamide mononucleotide may be purchased commercially from Sigma-Aldrich. Niacinamide mononucleotide and its derivative compounds may also be prepared by various means known to those of skill in the art. For example, Leder I.G. discloses an in vitro synthesis of nitcotinamide mononucleotide. See Lder I.G., "Synthesis of nicotinamide mononucleotide by human erythrocytes in vitro", J. Biol. Chem. 1951, 189:889-899.

[0042] The compositions may further comprise a dermatologically acceptable carrier, and particularly one in which the niacinamide mononucleotide or its derivative is soluble per se or is effectively solubilized (e.g., as an emulsion or microemulsion). If a dermatologically acceptable carrier is employed, the carrier should be inert in the sense of not bringing about a deactivation or oxidation of the glutathione derived active ingredient(s), and in the sense of not bringing about any adverse effect on the skin areas to which it is applied.

[0043] In one preferred practice of the invention, one or more niacinamide mononucleotides and/or their derivatives are applied in admixture with the dermatologically acceptable carrier or vehicle (e.g., a solution, a dispersion, a lotion, a cream, an ointment, a soap, a solid stick, a gel, and the like) so as to facilitate topical application. In some cases, the carrier may provide additional therapeutic effects as might be brought about, e.g., by moisturizing of the affected skin areas. While the carrier for the topical composition can consist of a relatively simple solvent or dispersant
such as water, it is generally preferred that the carrier comprise a composition more
conducive to topical application, and particularly one which will form a film or layer on
the skin to which it is applied so as to localize the application and provide some resis-
tance to washing off by immersion in water or by perspiration and/or aid in the
percutaneous delivery of the active agent(s).

[0044] Many preparations are known in the art, and include lotions containing
oils and/or alcohols and emollients vegetable oils, hydrocarbon oils and waxes, silicone
oils, animal or marine fats or oils, glyceride derivatives, fatty acids or fatty acid esters, or
alcohols (e.g., ethanol, propanediol, etc.) or alcohol ethers, lecithin, lanolin and
derivatives, polyhydric alcohols or esters, wax esters, sterols, phospholipids and the
like, and generally also emulsifiers (nonionic, cationic or anionic), although some of the
emollients inherently possess emulsifying properties. In the preferred embodiment, the
carrier is an oil-in-water emulsion. It is noticed that an oil-in-water emulsion system
stabilizes the active ingredient therein. Without wishing to be bound by theory, the
niacinamide mononucleotide and/or its derivatives have hydrophilic and hydrophobic
moieties in each molecule, which are more compatible and thus more stable in an oil-in-
water emulsion system. Moreover, depending on the substituents of R1 to Rs, the
overall hydrophilicity of niacinamide mononucleotide and/or its derivatives may cover a
large spectrum. An oil-in-water emulsion system is suitable for dissolving and
stabilizing this class of active ingredients.

[0045] The quantity of niacinamide mononucleotide or its derivative active
ingredient in the carrier may be varied or adjusted widely depending upon the particular
application, the potency of the particular compound or the desired concentration.
Generally, the quantity of niacinamide mononucleotide or its derivative active ingredient
will range between about 0.05% to about 30% by weight, more preferably, about 0.1%
to about 20.0% by weight. In some embodiments, niacinamide mononucleotide is
present in an amount of about 0.1% to about 5.0% by weight. In further preferred
embodiments, niacinamide mononucleotide is present from about 0.5% to about 1.5%
by weight. Generally, lower concentrations of niacinamide mononucleotide or its
derivative active ingredients in a carrier are suitable, depending upon the application regimen and the active and adjunct active ingredients employed. The term “by weight” shall mean by weight of the total composition, unless otherwise specified.

[0046] In some embodiments, the compositions of this invention contain at least one other active adjunct ingredient in addition to niacinamide mononucleotide or its derivative. The active adjunct ingredients may present in an amount ranging from 0.01% to about 20% by weight of the composition. They include, but are not limited to one or more of: isothiocyanates, caffeine, vitamin D3, lipoic acid; α-hydroxy acids such as glycolic acid or lactic acid; ascorbic acid and its derivatives, especially fatty acid esters of ascorbic acid; polyenylphosphatidylcholine; or tocotrienols and tocotrienol derivatives and vitamin E compositions enriched with tocotrienols or tocotrienol derivatives (e.g., tocotrienol acetate, also known as vitamin E acetate); and neuropeptides. Preferred adjunct agents include glycolic acid, citric acid, ascorbyl palmitate, a Septonic™ M3 by Seppic product (which contains magnesium aspartate, zinc gluconate and copper gluconate), a Tocomin® 50 product (which comprises palm oil, tocotrienols, tocopherol), and Oligopeptide-17 (which is a synthetic 35 amino acid peptide consisting of alanine, arginine, asparagine, aspartic acid, glutamine, glutamic acid, glycine, isoleucine, leucine, lysine, threonine and proline), and Oligopeptide-49 (which is a synthetic 35 amino acid peptide consisting of alanine, arginine, asparagine, aspartic acid, glutamine, glutamic acid, glycine, isoleucine, lysine, threonine, and proline).

[0047] The topical composition of the invention can contain additional ingredients commonly found in skin care compositions and cosmetics, such as, for example, tinting agents, emollients, skin conditioning agents, emulsifying agents, humectants, preservatives, antioxidants, perfumes, chelating agents, etc., provided that they are physically and chemically compatible with other components of the composition.

[0048] Emollients, typically present in amounts ranging from about 0.01% to about 20% of the total composition include, but are not limited to, fatty esters, fatty
alcohols, mineral oils, polyether siloxane copolymers, docosahexanoic acid (DHA) and mixtures thereof. Preferred emollients are Actiglow® (hydrolyzed glycosaminoglycans, propylene glycol, water, phenoxyethanol) by Active Organics, CCTG (carpric caprylic triglyceride), squalane, shae butter, meadowfoam seed oil, IPP (isopropyl palmitate), and DHA.

[0049] Humectants, typically present in amounts ranging from about 0.1% to about 5% by weight of the total composition include, but are not limited to, polyhydric alcohols such as glycerol, polyalkylene glycols (e.g., butylene glycol, propylene glycol, dipropylene glycol, polypropylene glycol, and polyethylene glycol) and derivatives thereof, alkylene polyols and their derivatives, sorbitol, hydroxy sorbitol, hexylene glycol, 1,3-dibutylene glycol, 1,2,6-hexanetriol, ethoxylated glycerol, propoxylated glycerol, L-tyrosine, and mixtures thereof. A preferred humectant is shae butter.

[0050] Emulsifiers, which are also called emulsifying agents, typically present in amounts from about 0.1% to about 70% by weight of the composition, include, but are not limited to, stearic acid, cetyl alcohol (as known as C-95 alcohol, or Crodacoil C95, as sold by Croda Inc.), stearyl alcohol, steareth 2, steareth 20, acrylates/C10-30 alkyl acrylate cross polymers, silicones, dimethyl ethanolamine (DMEA), phosphatidylcholine (PPC), docosahexanoic acid (DHA) and mixtures thereof. Preferred emulsifiers are sodium hyaluronate, Promulgen-D® (a mixture of 75% cetostearyl alcohol and 25% ethoxylate cetostearyl alcohol sold by Amerchol Corp.), Polawax NF (cetostearyl alcohol and polysorbate 60 sold by a company called Coop Coco), Arlacel™ 165 (glyceryl stearate and PEG-100 Stearate sold by Croda Inc.), Crodesta™ F10 (sucrose distearate sold by Croda Inc.), silicone (Dow Corning® 200 Fluid, 350 CST), dimethylaminoethanol, also known as DMAE, and Phospholipon® 90 G (phosphatidylcholine with 0.1% ascorbyl palmitate sold by Phospholipid GmbH). Noticeably, some ingredients can have multiple functions. For example, some ingredients, such as PPC can be both an emulsifier as well as an active adjunct ingredient.
One preferred emulsifier is PPC. By "polyenylphosphatidylcholine (PPC)" it meant any phosphatidylcholine (PC) bearing two fatty acid substituents, wherein at least one is an unsaturated fatty acid with at least two double bonds. In some embodiments, dilinoleoylphosphatidylcholine is the most abundant phosphatidylcholine species in polyenylphosphatidylcholine. Preferred PPCs contain at least one linoleic (18:2) group, most preferably two, in a cis geometrical configuration typical of natural products, for example, dilinoleoylphosphatidylcholine, which presents in the preparation at levels of at least about 25%, preferably at least about 40% by weight. Other forms of PPC can also be used as those set out in U.S. Pat. No. 6,797,459 at column 3 lines 34 to 52. PPC itself is an active antioxidant that has been shown to protect against lipid peroxidation and liver damage, including fibrosis and cirrhosis. Moreover, because PC itself is a major constituent of cell membranes, PPC greatly enhances the antioxidant activity of the composition because it facilitates the niacinamide nucleotide to penetrate and disperse in cell membranes in quantities sufficient to reach therapeutic levels.

Chelating agents, typically present in amounts ranging from about 0.01% to about 2% by weight, include, but are not limited to, ethylenediamine tetraacetic acid (EDTA) and derivatives and salts (e.g., sodium salt) thereof, dihydroxyethyl glycine, tartaric acid, and mixtures thereof.

Antioxidants, typically present in an amount ranging from about 0.01% to about 0.75% by weight of the composition, include, but are not limited to, butylated hydroxy toluene (BHT); vitamin C and/or vitamin C derivatives, such as fatty acid esters of ascorbic acid, particularly ascorbyl palmitate; butylated hydroanisole (BHA); phenyl-α-naphthylamine; hydroquinone; propyl gallate; nordihydroguaiaretic acid; vitamin E and/or derivatives of vitamin E, including tocotrienol and/or tocotrienol derivatives (such as tocotrienol acetate, also known as vitamin E acetate); calcium pantothenates; green tea extracts; mixed polyphenols; and mixtures of any of these. Particularly preferred antioxidants are those that provide additional benefits to the skin such as ascorbyl
palmitate, sesame seed oil, alpha-lipoic acid, and Tocomin® 50 (which comprises palm oil, tocotrienols, tocopherol).

[0054] Preservatives include, but are not limited to, C₁-C₃ alkyl parabens and phenoxyethanol (e.g., benzyl alcohol), typically present in an amount ranging from about 0.1% to about 2.0% by weight percent, based on the total composition. A preferred preservative is ISP’s Optiphen™ Plus, a liquid preservative formulation featuring a blend of phenoxyethanol, sorbic acid, and an emollient base.

[0055] Buffering agents are employed in many compositions. Preferably, the amount of buffering agent is one that results in compositions having a pH ranging from about 4.0 to about 8.5, more preferably from about 4.5 to about 7.0, most preferably from about 5.0 to about 6.0. Typical buffering agents are chemically and physically stable agents commonly found in cosmetics, and can include compounds that are also adjunct ingredients such as citric acid, malic acid, and glycolic acid buffers.

[0056] NMN and its derivatives are stable in the compositions of the present invention. No significant degradation, precipitation, or uneven distribution of the ingredients has been observed at room temperature. It is believed that the formulations as described above stabilize NMN and its derivatives and the adjunct active ingredients. Depending on the substituents of R₁ to R₅, the overall hydrophilicity of niacinamide mononucleotide and/or its derivatives may cover a large spectrum, from hydrophilic to hydrophobic. Likewise, the adjunct active ingredients also range from hydrophilic to hydrophobic. The formulations of the present invention are compatible to and thus stabilize this type of the actives and adjunct actives.

[0057] In some embodiments, the compositions comprise of about 0.1% to about 5.0% by weight, preferably about 0.1% to about 5.0% by weight, and even more preferably about 0.5% to about 1.5% by weight of niacinamide mononucleotide and its derivative of formula (I), about 2.0% to about 15% by weight of at least one emulsifier, and water. In some of these embodiments, the at least one emulsifier is PPC.
In some other embodiments, the compositions comprises about 1.0% to about 3.0%, preferably about 0.1% to about 3.0% by weight, and even more preferably about 0.5% to about 1.5% by weight of niacinamide mononucleotide and its derivative of formula (I), about 1.5% to about 5.0% by weight of at least one fatty acid derivative of stearic acid, about 1% to 5% by weight an emollient, and water. In some of these embodiments, the emollient is isopropyl palmitate ("IPP").

In another aspect, the present invention provides a method of treating aging skin by topically applying the compositions containing niacinamide mononucleotide or its derivative to an affected skin. After treatment for the recommended period of time, decreased inflammation, irritation, and erythema of the skin are observed, along with an increased skin elasticity and suppleness. Particularly, marionette lines, smile lines, deep nasolabial fold lines, crow’s feet, fine lines/wrinkles, vertical lines between the eyebrows, horizontal forehead lines, sagging thin/frail skin, skin redness and dullness are reduced.

Only effective amounts of topical compositions containing niacinamide mononucleotide or its derivative are needed to achieve the aforementioned benefits and prevent typical menopausal and aging effects on the skin. One advantage of the present invention is the use of very small amount of the active ingredient topically to achieve the anti-aging effect.

In the practice of methods of the invention, the topical composition is topically applied to the skin areas, such as that of the face, at predetermined intervals often as a moisturizer, lotion, or cream, it generally being the case that gradual improvement is noted with each successive application. Although immediate effects can be observed, enhanced results are observed when the topical composition is applied twice daily, preferably in the morning and evening, for an extended period of time. Insofar as has been determined based upon clinical studies to date, no adverse side effects are encountered. The composition may also be applied three, four, or more times a day.
[0062] In a further aspect, the present invention provides methods to improve the appearance of skin, prevent and treat skin aging, dryness, dullness, loss of elasticity and lack of radiance. Particularly, the present invention may be used to prevent or retard the appearance of spider vessels or red blotchiness associated with menopausal skin. In another embodiment, the present invention may be used to prevent or treat exaggerated lines and wrinkles. It is an advantage of the invention that compositions of the invention do not require a pharmaceutical prescription.

[0063] While not wishing to be bound by any theory, it is believed that niacinamide mononucleotide and/or derivatives composition, when administrated into a human body, increases intracellular levels of the two codehydrogenases, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) in a body, which in turn activate a protein called SIRT1 to invigorate mitochondria inside living cells and inhibit NADPH, thereby improving metabolism throughout the body. It is further believed that as a result of the improved metabolism, the skin cell generation rate speeds up, leading to improvement of the appearance of wrinkles and fine lines, dryness, dullness or lack of radiance of skin, sagging, discoloration, or redness and blotchiness of skin. It is also proposed that niacinamide mononucleotide and/or derivatives exert antioxidant properties; thus, it may scavenge reactive oxygen species which is the key etiology of skin aging such as wrinkles, sag, poor texture, hyperpigmentation, and skin yellowness.

[0064] It is known that NAD and NADP have the following structures:
[0065] Compared to niacinamide or its derivatives known in the art, niacinamide mononucleotide contains a phosphate functional group on its molecules, which advantageously makes it more prone to be converted to NAD or NADP. The phosphate functional group may contribute to the high efficiency of niacinamide mononucleotide in increasing intracellular levels of NDA and NADP, thereby improving the anti-aging effects observed after topical administration of niacinamide mononucleotide on an affected skin.

[0066] Additional ingredients and methods as disclosed in Inventor’s U.S. Patent Nos. 5,376,361; 5,409,693; 5,545,398; 5,554,647; 5,574,063; 5,643,586; 5,709,868; 5,879,690; 6,191,121; 6,296,861; 6,437,004; 6,979,459; 8,609,604; 8,609,618, 9,023,801; and 9,029,317 which are hereby incorporated by reference, may also be used.

[0067] EXAMPLES:

[0068] Example 1. A cream formulation in accordance with the present invention is shown below:

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMN</td>
<td>0.05 to 1.5</td>
</tr>
</tbody>
</table>
Sepitonic M3 0.5 to 5.0
Vitamin E Acetate 0.5 to 3.0
Emulsifier(s) 4.5 to 20.0
Emollient(s) 5.0 to 15.0
Chelating agent(s) 0.05 to 0.5
Preservative(s) 0.5 to 3.0
Water q.s. to 100

Example 2. A gel cream formulation in accordance with the present invention is shown below:

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMN</td>
<td>10.0 to 25.0</td>
</tr>
<tr>
<td>A second alcohol</td>
<td>1.0 to 5.0</td>
</tr>
<tr>
<td>Gel matrix</td>
<td>70.0 to 89.0</td>
</tr>
</tbody>
</table>

Wherein the gel matrix has the following formulation:

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emulsifier(s)</td>
<td>55.0 to 75.0</td>
</tr>
<tr>
<td>Emollient(s)</td>
<td>16.0 to 36.0</td>
</tr>
<tr>
<td>A first alcohol</td>
<td>4.0 to 14.0</td>
</tr>
</tbody>
</table>

The above description is for the purpose of teaching the person of ordinary skill in the art how to practice the present invention, and it is not intended to detail all those obvious modifications and variations of it which will become apparent to the skilled worker upon reading the description. It is intended, however, that all such obvious modifications and variations be included within the scope of the present invention.
We claim:

1. A topical composition for topical application to skin for prevention and treatment of skin aging, comprising:

   from about 0.05% to about 30% by weight of β-niacinamide mononucleotide and its derivative of formula (I):

   ![Chemical Structure](image)

   wherein each of R₁ and R₂ is individually selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkaryl, hydroxy, alkoxy, and amino; each of R₃ and R₄ is individually selected from the group consisting of hydrogen, alkyl, aliphatic or aromatic acyl, and aliphatic or aromatic thioacyl; and R₅ is hydrogen, cation, or alkyl; and

   a dermatologically acceptable carrier.

2. The method according to claim 1, wherein R₁ to R₄ are hydrogen, and wherein R₅ is a sodium cation or hydrogen.

3. The topical composition of claim 1 or 2, wherein the composition comprises:

   about 0.1% to about 5% by weight of niacinamide mononucleotide and its derivative of formula (I), about 2.0% to about 15% by weight of at least one emulsifier, and water.
4. The topical composition of claim 1 or 2, wherein the composition comprises: about 10.0% to about 30.0% by weight of niacinamide mononucleotide and its derivative of formula (I), about 30.0% to about 65.0% by weight of at least one emulsifier.

5. The topical composition of claim 1, 2, 3, or 4, wherein the emulsifier is a polyenylphosphatidylcholine.

6. A method for the prevention and treatment of skin aging comprising: topically applying to affected skin areas a topical composition comprising: \( \beta \)-niacinamide mononucleotide and/or its derivative of formula (I):

\[
\text{(I)}
\]

wherein each of \( R_1 \) and \( R_2 \) is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkaryl, hydroxy, alkoxy, and amino; each of \( R_3 \) and \( R_4 \) is selected from the group consisting of hydrogen, alkyl, aliphatic or aromatic acyl, and aliphatic or aromatic thioacyl; and \( R_5 \) is hydrogen, alkyl, or a cation; and a dermatologically acceptable carrier.

7. The method according to claim 6, wherein \( R_1, R_2, R_3, \) and \( R_4 \) are hydrogen, and wherein \( R_5 \) is a sodium cation or hydrogen.

8. The method according to claim 6 or 7, wherein said topical composition contains from about 0.05% to about 30% of said \( \beta \)-niacinamide mononucleotide and/or its derivative of formula (I) by weight of the composition.
9. The method according to claim 8, wherein said topical composition contains from about 15.0% to about 20.0% of said β-niacinamide mononucleotide and/or its derivative of formula (I) by weight of the composition.

10. The method according to claim 8, wherein said topical composition contains from about 0.5% to about 1.5% of said β-niacinamide mononucleotide and/or its derivative of formula (I) by weight of the composition.

11. The method according to claim 6, 7, 8, 9, or 10, wherein said carrier is a solution, dispersion, cream, lotion, gel, or solid stick.

12. The method according to claim 6, 7, 8, 9, 10, or 11, wherein the affected skin areas are skin areas having surface spots, brown spots, red areas, wrinkles, texture, skin dryness, dullness, loss of elasticity, lack of radiance, exaggerated lines and wrinkles, spider vessels, and/or red blotchiness.

13. The method according to claim 6, 7, 8, 9, 10, 11, or 12, wherein said topical composition further comprises an adjunct ingredient selecting from the group consisting of isothiocyanates, caffeine, vitamin D3, lipoic acid, α-hydroxy acids, glycolic acid, lactic acid, ascorbic acid and its derivatives, fatty acid esters of ascorbic acid, polyenylphosphatidylcholine; tocotrienols, tocotrienol derivatives, vitamin E compositions enriched with tocotrienols or tocotrienol derivatives, neuropeptides, magnesium aspartate, zinc gluconate, copper gluconate, and a combination thereof.

14. The method according to claim 13, wherein said adjunct ingredient is in an amount of about 0.01% to about 20% by weight of the composition.
15. The method according to claim 13, wherein said adjunct ingredient is selected from the group consisting of lipoic acid, α-hydroxy acids, glycolic acid, lactic acid, ascorbic acid, ester of ascorbic acid, and a mixture thereof.

16. The method according to claim 13, wherein said adjunct ingredient is polyenylphosphatidylcholine.

17. The method according to claim 13, wherein said adjunct ingredient is selected from the group consisting of magnesium aspartate, zinc gluconate, copper gluconate, and a mixture thereof.

18. The method according to claim 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16, wherein said topical composition further comprises an emollient in an amount ranging from about 0.01% to 20% of the composition.

19. The method according to claim 18, wherein said emollient is isopropyl palmitate, caprylic caprylic triglyceride, or a combination thereof.

20. The method according to claim 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19, wherein said topical composition has a pH range from about 4.0 to about 8.5.
INFORMATION SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/455; A61K 31/708; A61K 45/06; C07H 19/02; C07H 19/04; C07H 19/048 (2016.01)
CPC - A61K 31/44; A61K 31/455; A61K 45/06; C07H 19/02; C07H 19/04; C07H 19/048 (2016.08)

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(8) - A61K 31/455; A61K 31/708; A61K 45/06; C07H 19/02; C07H 19/04; C07H 19/048 (2016.01)
CPC - A61K 31/44; A61K 31/455; A61K 45/06; C07H 19/02; C07H 19/04; C07H 19/048 (2016.08)

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

USPC - 5144/2; 51443; 51445; 51446; IPC(8) - A61K 31/455; A61K 31/708; A61K 45/06; C07H 19/02; C07H 19/04; C07H 19/048 (2016.01); CPC - A61K 31/44; A61K 31/455; A61K 45/06; C07H 19/02; C07H 19/04; C07H 19/048 (2016.08) (keyword delimited)

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

PatBase, PubChem, STN, Google Patents, Google Scholar
Search terms used: nicotinamide riboside o-phosphate topical

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>US 2014/0275057 A1 (BAIR et al) 18 September 2014 (18.09.2014) entire document</td>
<td>1-3, 6-8, 10</td>
</tr>
<tr>
<td>A</td>
<td>W0 2015/063832 A1 (CHROMADEX INC) 07 May 2015 (07.05.2015) entire document</td>
<td>1-3, 6-8, 10</td>
</tr>
<tr>
<td>A</td>
<td>W0 2014/074715 A1 (GENETECH INC) 15 May 2014 (15.05.2014) entire document</td>
<td>1-3, 6-8, 10</td>
</tr>
</tbody>
</table>

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

** Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search
30 September 2016

Date of mailing of the international search report
28 OCT 2016

Name and mailing address of the ISA/
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450
Facsimile No. 571-273-8300

Authorized officer
Blaine R. Copenhaver
PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)
## INTERNATIONAL SEARCH REPORT

**Box No. II. Observations where certain claims were found unsearchable (Continuation of item 2 of 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. ☐ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.: 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:

3. ☒ Claims Nos.: 5, 11-20 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:

See Extra Sheet

Claims 1-3, 6-8, and 10 have been analyzed subject to the restriction that the claims read on a topical composition for topical application to skin for preventing and treatment of skin aging, comprising: from about 0.1% to 5% by weight of beta-niacinamide mononucleotide and its derivative of formula (I): wherein each of R1 and R2 is individually hydrogen; each R3 and R4 is individually hydrogen; R5 is hydrogen; and a dermatologically acceptable carrier.

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 claims 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 claims Nos.: 1-3, 6-8, 10

**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.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2015)
Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I*: claims 1-4 and 8-10 are drawn to topical compositions and methods thereof.

The first invention of Group I* is restricted to a topical composition for topical application to skin for preventing and treatment of skin aging, comprising: from about 0.1% to 5% by weight of beta-niacinamide mononucleotide and its derivative of formula (I): wherein each of R1 and R2 is individually hydrogen; each R3 and R4 is individually hydrogen; R5 is hydrogen; and a dermatologically acceptable carrier; and methods thereof. It is believed that claims 1-3, 8-6, and 10 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would a topical composition for topical application to skin for preventing and treatment of skin aging, comprising: from about 0.1% to 5% by weight of beta-niacinamide mononucleotide and its derivative of formula (I): wherein each of R1 and R2 is individually amino; each R3 and R4 is individually hydrogen; R5 is alkyl; and a dermatologically acceptable carrier; and methods thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the * group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I* do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I* formulae do not share a significant structural element requiring the selection of alternatives for the compound variables R1, R2, R3, R4, and R5.

The Groups I* share the technical features of a topical composition for topical application to skin for prevention and treatment of skin aging, comprising: from about 0.05 to about 30% by weight beta-niacinamide mononucleotide and its derivative of formula (I); and a dermatologically acceptable carrier; and a method for the prevention and treatment of skin aging comprising topically applying to affected skin areas a topical composition comprising: beta-niacinamide mononucleotide and/or its derivative of formula (I); and a dermatologically acceptable carrier. However, these shared technical features do not represent a contribution over the prior art.

Specifically, WO 2014/074715 A1 to Genentech Inc. teaches a topical composition for topical application to skin for prevention and treatment of skin aging (Claim 33; Paras. [0004] and [0005]; and Para. [0133]), comprising: beta-niacinamide mononucleotide and its derivative of formula (I); and a dermatologically acceptable carrier (Para. [0133]; Para. [0091]).

Additionally, WO 2015/006382 A1 to ChromaDex Inc. teaches a topical composition for topical application to skin for prevention and treatment of skin aging (Claims 1 and 7; Para. [0011]; Para. [0061]), comprising: from about 0.05 to about 30% by weight of a niacinamide ribose (Claim 15; Para. [0011]; Paras. [0031] and [0032],...see shown structure...); and a dermatologically acceptable carrier (Para. [0050]); and a method for the prevention and treatment of skin aging (Abstract; Paras. [0027] and [0013]) comprising: topically applying to affected skin areas a topical composition (Paras. [0053] and [0056]; Para. [0063]) comprising: a niacinamide ribose (Claim 15; Para. [0011]; Paras. [0031] and [0032],...see shown structure...); and a dermatologically acceptably carrier (Para. [0050]).

The inventions listed in Groups I* therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.