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(54) **Title:** COMPOSITIONS AND METHODS OF USING SUBSTANCE P. ANALOGS

(57) **Abstract:** Provided herein are compositions and methods for use of Substance P analogs to enhance the appearance of human skin. The compositions can be administered as creams, ointments, liquids, lotions and the like.

COMPOSITIONS AND METHODS OF USING SUBSTANCE P ANALOGS

1. FIELD OF THE INVENTION

[0001] Provided herein are compositions and methods for use of Substance P analogs to enhance the appearance of human skin. The compositions can be administered as creams, ointments, liquids, lotions and the like.

2. BACKGROUND OF THE INVENTION

[0002] It is desirable to provide a composition and methods that enhance an individual's appearance. As an individual ages, the skin is prone to develop wrinkles or fine lines which are undesirable. Improvements are needed.

3. SUMMARY OF THE INVENTION

[0003] Provided herein are methods and compositions comprising substance P analogs useful for improving the texture or appearance of human skin. The compositions can be, for example, cosmetic or cosmeceutical compositions.

[0004] In certain embodiments, the substance P analog is of Formula (I):

$$Z_1\text{-}Xaa^1\text{-}Xaa^2\text{-}Xaa^3\text{-}Xaa^4\text{-}Xaa^5\text{-}Xaa^6\text{-}Xaa^7\text{-}Xaa^8\text{-}Xaa^9\text{-}Xaa^{10}\text{-}Xaa^{11}\text{-}Z_2 \quad (I)$$

wherein:

Xaa^1 is Arg, Lys, 6-N methyllysine, or (6-N, 6-N) dimethyllysine;

Xaa^2 is Pro or Ala;

Xaa^3 is Lys, Arg, 6-N-methyllysine, or (6-N, 6-N) dimethyllysine;

Xaa^4 is Pro or Ala;

Xaa^5 is Gln or Asn;

Xaa^6 is Gln or Asn;

Xaa^7 is Tyr, Phe or Phe substituted with chlorine at position 2, 3 or 4;

Xaa^8 is Tyr, Phe or Phe substituted with chlorine at position 2, 3 or 4;

Xaa^9 is Gly, Pro, Ala, or sarcosine (N-methylglycine);

Xaa^{10} is Leu, Val, Ile, Norleucine, Met, Met sulfoxide, Met sulfone, N-methylleucine, or N-methylvaline; and

Xaa^{11} is Met, Met sulfoxide, Met sulfone, or Norleucine;

Z_1 is R_2N– or RC(O)NR–;

Z_2 is –C(O)NR_2 or –C(O)OR or a salt thereof;

wherein each R is independently -H, (C_1 -C_6) alkyl, (C_1 -C_6) alkenyl, (C_1 -C_6) alkynyl, (C_5 -C_{20}) aryl, (C_6 -C_{26}) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl; and

each "—" between residues Xaa^1 through Xaa^{11} independently designates an amide linkage, a substitute amide linkage or an isostere of an amide.

[0005] In one embodiment, the substance P analog can be of Formula (I) as described herein, wherein Xaa^1 is Arg; Xaa^2 is Pro; Xaa^3 is Lys; Xaa^4 is Pro; Xaa^5 is Gln; Xaa^6 is Gln; Xaa^7 is Phe or Phe substituted with chlorine at position 4; Xaa^8 is Phe, or Phe substituted with chlorine at position 4; Xaa^9 is Gly, Pro or N-methylglycine; Xaa^{10} is Leu; and Xaa^{11} is Met, Met sulfoxide, Met sulfone, or Norleucine.

[0006] In certain embodiments, the substance P analog can be of Formula (I) as described herein wherein the "—" between residues Xaa^1 through Xaa^{11} designates -C(O)NH–; Z_1 is H_2N–; and Z_2 is –$C(O)NH_2$.

[0007] In certain embodiments, the substance P analog can be selected from the group consisting of:

RPKPQQFFGLM	(SEQ ID NO.: 1);
RPKPQQFFMeGlyLM(O_2)	(SEQ ID NO.: 2);
RPKPQQFFGLM(O_2)	(SEQ ID NO.: 3);
RPKPQQFFMeGlyLM(O)	(SEQ ID NO.: 4);
RPKPQQFFGLNle	(SEQ ID NO.: 5);
RPKPQQFFPLM	(SEQ ID NO.: 6);
RPKPQQFFMeGlyLM	(SEQ ID NO.: 7);
RPKPQQFTGLM	(SEQ ID NO.: 8);
RPKPQQF(4-Cl)F(4-Cl)GLM	(SEQ ID NO.: 9); and
RPKPQQFFGLM(O)	(SEQ ID NO.: 10);

[0008] In a preferred embodiment, the substance P analog can be Z_1—RPKPQQFFMeGlyLM(O_2)—Z_2; wherein Z_1 is NH_2 and Z_2 is $C(O)NH_2$.

[0009] As will be understood by those of skill in the art, substance P (SEQ ID NO. 1) refers to peptide sequence: Arg Pro Lys Pro Gln Gln Phe Phe Gly Leu Met, or the

single letter representation RPKPQQFFGLM (SEQ ID NO 1). In one embodiment, the peptide can be amidated at the carboxy terminus represented as RPKPQQFFGLM-NH_2.

[0010] In one embodiment, the methods and compositions provide a cosmetically effective amount of compounds of Formula I to improve the texture or appearance of human skin. The compositions are those which, when administered to the skin, render a benefit or an effect of ameliorating or improving the texture or appearance of the skin. The amelioration or improvement of the skin can be either short-term or long-term. The improvement or amelioration of the skin can be an amelioration of an abnormal skin condition. The abnormal skin condition to be ameliorated by administering a composition can be dry skin, severe dry skin, skin flakiness, wrinkles (both course and fine, caused by either intrinsic or extrinsic damage), blemished skin, inflammatory dermatoses, age-related skin changes, and/or the effects of skin atrophy. In one embodiment the compositions and methods provide for use of the substance P analogs as a rubefacient.

[0011] The cosmetic compositions are those which, when administered to the skin can be cosmetically effective, *i.e.*, the compositions can improve the texture or appearance thereof, without necessarily rendering a benefit, or mask the appearance of abnormal skin. In this context, improving the texture or appearance of the skin is meant to encompass enhancing the skin's natural look or feel so as to increase the beauty or smoothness of the skin from its pre-treated state, or to mask abnormal skin. This can include providing a temporary moisturizing effect to the epidermis of the skin or creating a rosy or red effect to the skin. Such abnormal skin conditions or diseases include, but are not limited to dry skin, severe dry skin, skin flakiness, wrinkles (both coarse and fine, caused by either intrinsic or extrinsic damage), blemished skin, inflammatory dermatoses, age-related changes, and/or the effects of skin atrophy.

[0012] In another embodiment, the methods provide for reducing the appearance of skin atrophy by administering to a subject an effective amount of a composition comprising one or more compounds of Formula I.

[0013] In yet another embodiment, the methods provide for ameliorating disorders including but not limited to dry skin, severe dry skin, skin flakiness, wrinkles (both coarse and fine, caused by intrinsic as well as extrinsic damage), blemished skin, inflammatory dermatoses, age-related skin changes and/or skin atrophy.

[0014] In one embodiment, the administration of the compositions can be to the skin, hair or nails of a human as a cosmetic composition. In another embodiment, the

administration of the composition can be by a personal care composition such as bathing compositions including, for example, bath beads, shower gel and the like.

[0015] In one embodiment, the compositions can be a substance P analog associated with a fat soluble compound. By 'associated' it is meant that the substance P analog and the fat soluble compound can be covalently bound, made into a complex (e.g. co-lyophilized without covalent bonds), or linked or adjoined in some fashion. In one embodiment the fat soluble compound can enhance skin penetration.

4. DEFINITIONS

[0016] The term "skin atrophy" refers to the thinning or general degradation of the dermis layer of human skin often characterized by a decrease in collagen or elastin as well as decreased number, size and doubling potential of fibroblast cells.

[0017] The term "cosmetically effective amount" refers to an amount of compound or composition sufficient to improve the texture or appearance of skin, without necessarily rendering a benefit thereto, or to mask the appearance of abnormal skin. In this context, improving the texture or appearance of the skin is meant to encompass enhancing the skin's natural look or feel so as to increase the beauty or smoothness of the skin from its pre-treated state, or to mask abnormal skin conditions. This can include providing a temporary moisturizing effect to the epidermis of the skin or creating a rosy or red effect to the skin.

[0018] The term "cosmetic" refers to a composition to be administered to the skin which improves the texture or appearance thereof, without necessarily rendering a benefit, or mask the appearance of abnormal skin. Such improvement includes providing a temporary moisturizing effect to the epidermis of mammalian skin.

[0019] The term "cosmeceutical" refers to a composition to be administered to the skin which improves the texture or appearance thereof and has biologically active ingredients that purportedly render a benefit to the user.

[0020] The term "alkyl" refers to a saturated branched, straight chain or cyclic hydrocarbon radical. Typical alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl, and the like. In preferred embodiments, the alkyl groups are (C_1 -C_6) alkyl.

[0021] The term "alkenyl" refers to an unsaturated branched, straight chain or cyclic hydrocarbon radical having at least one carbon-carbon double bond. The radical may be in either the cis or trans conformation about the double bond(s). Typical alkenyl

groups include, but are not limited to, ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, tert-butenyl, pentenyl, hexenyl and the like. In preferred embodiments, the alkenyl group is (C_1 -C_6) alkenyl.

[0022] The term "alkynyl" refers to an unsaturated branched, straight chain or cyclic hydrocarbon radical having at least one carbon-carbon triple bond. Typical alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, isobutynyl, pentynyl, hexynyl and the like. In preferred embodiments, the alkynyl group is (C_1 -C_6) alkynyl.

[0023] The term "aryl" refers to an unsaturated cyclic hydrocarbon radical having a conjugated π electron system. Typical aryl groups include, but are not limited to, penta-2,4-diene, phenyl, naphthyl, anthracyl, azulenyl, chrysenyl, coronenyl, fluoranthenyl, indacenyl, idenyl, ovalenyl, perylenyl, phenalenyl, phenanthrenyl, picenyl, pleiadenyl, pyrenyl, pyranthrenyl, rubicenyl, and the like. In preferred embodiments, the aryl group is (C_5 -C_{20}) aryl, with (C_5 -C_{10}) being particularly preferred.

[0024] The term "alkaryl" refers to a straight-chain alkyl, alkenyl or alkynyl group wherein one of the hydrogen atoms bonded to a terminal carbon is replaced with an aryl moiety. Typical alkaryl groups include, but are not limited to, benzyl, benzylidene, benzylidyne, benzenobenzyl, naphthenobenzyl and the like. In preferred embodiments, the alkaryl group is (C_6 -C_{26}) alkaryl, *i.e.*, the alkyl, alkenyl or alkynyl moiety of the alkaryl group is (C_1 -C_6) and the aryl moiety is (C_5 -C_{20}). In particularly preferred embodiments, the alkaryl group is (C_6 -C_{13}) alkaryl, *i.e.*, the alkyl, alkenyl or alkynyl moiety of the alkaryl group is (C_1 -C_3) and the aryl moiety is (C_5-C_{10}).

[0025] The term "alkheteroaryl" refers to a straight-chain alkyl, alkenyl or alkynyl group where one of the hydrogen atoms bonded to a terminal carbon atom is replaced with a heteroaryl moiety. In preferred embodiments, the alkheteroaryl group is 6-26 membered alkheteroaryl, *i.e.*, the alkyl, alkenyl or alkynyl moiety of the alkheteroaryl is (C_1 -C_6) and the heteroaryl is a 5-20-membered heteroaryl. In particularly preferred embodiments the alkheteroaryl is 6-13 membered alkheteroaryl, *i.e.*, the alkyl, alkenyl or alkynyl moiety is a 5-10 membered heteroaryl.

[0026] The term "heteroaryl" refers to an aryl moiety wherein one or more carbon atoms is replaced with another atom, such as N, P, O, S, As, Se, Si, Te, etc. Typical heteroaryl groups include, but are not limited to, acridarsine, acridine, arsanthridine, arsindole, arsindoline, carbazole, β-carboline, chromene, cinnoline, furan, imidazole, indazole, indole, indolizine, isoarsindole, isoarsinoline, isobenzofuran, isochromene,

isoindole, isophosphoindole, isophosphinoline, isoquinoline, isothiazole, isoxazole, naphthyridine, perimidine, phenanthridine, phenanthroline, phenazine, phosphoindole, phosphinoline, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, selenophene, tellurophene, thiophene and xanthene. In preferred embodiments, the heteroaryl group is a 5-20 membered heteroaryl, with 5-10 membered aryl being particularly preferred.

[0027] The term "substituted alkyl, alkenyl, alkynyl, aryl alkaryl, heteroaryl or alkheteroaryl" refers to an alkyl, alkenyl, alkynyl, aryl, alkaryl, heteroaryl or alkheteroaryl group in which one or more hydrogen atoms is replaced with another substituent. Preferred substituents include —OR, —SR, —NRR, —NO_2, —CN, halogen, —C(O)R, —C(O)OR and —C(O)NR, wherein each R is independently hydrogen, alkyl, alkenyl, alkynyl, aryl, alkaryl, heteroaryl or alkheteroaryl.

5. THE METHODS

[0028] The methods provided herein generally comprise administering a composition to the skin which renders a benefit or an effect of ameliorating or improving the texture or appearance of the skin. The amelioration or improvement of the skin can be either short-term or long-term. The improvement or amelioration of the skin can be an amelioration of an abnormal skin condition. The abnormal skin condition to be ameliorated by administering a composition include, but are not limited to, dry skin, severe dry skin, skin flakiness, wrinkles (both course and fine, caused by either intrinsic or extrinsic damage), blemished skin, inflammatory dermatoses, age-related skin changes, and/or the effects of skin atrophy. In one embodiment the compositions and methods provide for use of the substance P analogs as a rubefacient.

[0029] Generally recognized dermatological and cosmetic ingredients, including excipients, vehicles, emollients, suspending agents, wetting agents and the like, can be used in the compositions. *See*, for example, Barry, Dermatological Formulations, 1983, Informa Healthcare, 1st edition, Osborne and Amann, eds. Topical Drug Delivery Formulations, 1989, Informa Healthcare, 1st edition, Barel, Payne and Maibach, eds., Handbook of Cosmetic, Science and Technology, 2001, Informa Healthcare, 1st edition, Draelos and Thaman, eds. Cosmetic Formulation of Skin Care Products (Cosmetic Science and Technology Series Vol. 30), 2006, Informa Healthcare, 1st edition incorporated herein by reference in their entirety.

[0030] Native substance P has been shown to stimulate fibroblast production. Katayama and Nishioka demonstrated that fibroblast stimulatory activity was partially abrogated by substance P antagonists. (1997, *J. Dermatological Sci.* (15) 201-206). Substance P analogs such as those described herein have been shown to have greater binding affinity for the NK1 receptor than native substance P. While not wishing to be bound to any theory or mechanism of action, it is believed that cosmetically effective amounts of substance P analogs can ameliorate skin conditions and improve the texture or appearance of human skin through stimulation of fibroblasts.

[0031] In some embodiments, the methods and compositions can be used in conjunction with dermatological procedures such as dermabrasion (*e.g.* microderm abrasion), dermaplaning, chemical or acid peels, dermal fillers, (*e.g.* Restylane®, Medicis, Scottsdale, AZ), fibroblast injections (*e.g.* autologous fibroblasts, Isolagen Inc., Exton, PA), silicone injections, laser surgery and the like. In some embodiments, the procedures are surgical. In some embodiments, the procedures are cosmetic. For example, in one preferred embodiment, the compositions can be applied as a liquid spritz following dermabrasion or acid peel. In another embodiment, the compositions can be in a lotion or cream formulation for application following silicone or fibroblast injections.

[0032] In one embodiment, the number of wrinkles on the skin of a subject administered a composition as described herein is reduced. In one embodiment, the depth of a wrinkle on the skin of a subject administered a composition as described herein is reduced

[0033] In one embodiment, the compositions can be a substance P analog associated with a fat soluble compound. By 'associated' it is contemplated that the substance P analog and the fat soluble compound can be covalently bound, made into a complex (e.g. co-lyophilized without covalent bonds), linked or adjoined in some fashion. In one embodiment the fat soluble compound can enhance skin penetration.

[0034] In a preferred embodiment the substance P analog can be associated with a fat soluble compound, wherein the fat soluble compound is a lipid. In one embodiment, the fat soluble compound can be saturated, unsaturated, natural or synthetic lipid or combinations thereof. In one embodiment the lipid can be any of the eight categories of lipids: fatty acyls, glycerolipids, glycerophospholipids, sphingolipids, sterol lipids, prenol lipids, saccharolipids, and polyketides, as set forth by the Lipid Metabolites and Pathways Strategy established by the American Society of

Biochemistry and Molecular Biology. These categories are based on the functional backbone of the lipid molecule from a chemical standpoint. The categories are further subdivided into classes and subclasses to handle the existing and emerging arrays of lipid structures which are within the scope of the present invention. Fahy *et al.*, 2005, *J. Lipid Res.* 46: 839-62.

[0035] In one embodiment, the lipid can be a fatty acid or conjugate, octadecaoid, eicosanoid, docosanoid, fatty alcohol, fatty aldehyde, fatty ester, fatty amide, fatty nitrile, fatty ether, hydrocarbon, oxygenated hydrocarbon or combination thereof. In one embodiment the lipid can be a glycerolipids, including, but not limited to, monoradylglycerol, diradylflycerol, triradylglycerol, glycosylmonoradylglycerol, glycosyldiradylglycerol or combinations thereof. In one embodiment, the glycerophospholipids can be glycerophosphocholines, glycerophosphoethanolamine, glycerophosphoserine, glycerophosphoglycerol, glycerophosphoglycerophosphate, glycerophosphoinositol, glycerophosphoinositol monophosphate, glycerophosphoinositol bisphosphate, glycerophosphoinositol trisphosphate, glycerophosphate, glyceropyrophosphate, glycerophosphoglycerophosphoglycerol, cytidine-5'-diphosphate (CDP) glycerol, glycerophosphoglucose lipid, glycerophosphoinositolglycan, glycerophosphonocholine, glycerophosphonoethanolamine, di-glycerol tetraether phospholipid (caldarchaeols), glycerol-nonitol tetraether phospholipid, oxidized flycerophospholipid or combinations thereof. In one embodiment the sphingolipids can be sphingoid bases, ceramides, phosphophingolipids, phosphonosphingolipids, neutral glycosphingolipids, acidic glycosphingolipids, basic glycosphingolipids, amphoteric glycosphingolipids, arsenosphingolipids or combinations thereof. In one embodiment, the sterols can be steroids, secosteroids, bile acids and derivatives thereof, steroid conjugates or combinations thereof. In one embodiment, the prenol lipids can be isoprenoids, quinones, hydroquinones, polyprenols, hopanoids or combinations thereof. In one embodiment, the saccharolipids can be acylaminosugars, acylaminosugar glycans, acyltrehaloses, acyltrehalose glycans or combinations thereof. In one embodiment the polyketides can be macrolide polyketides, aromatic polyketides, non-ribosomal peptide/polyketide hybrids or combinations thereof.

6. THE COMPOSITIONS

[0036] The compositions can be formulated for topical application to keratin materials such as the skin, the hair, or the nails. The substance P analogs as described herein can be administered to human skin. In certain embodiments, the compositions can be applied topically. In certain embodiments, the topical compositions can be a solution (including collodions, liniments, aqueous and oleaginous solutions), suspension, gel, emulsion, lotion, ointment, cream, salve, lip balm, liquid, transdermal patch, tape, strip or gauze. In a preferred embodiment, the skin care composition can be a skin protectant treatment, body lotion, facial cream, moisturizing cream, facial cleansing emulsion, surfactant-based facial cleanser, facial exfoliating gel, facial toner, exfoliating cream, facial mask, or the like.

[0037] In one embodiment, the hair care composition can be a shampoo, conditioner, anti-dandruff treatment, styling aid, styling conditioner, hair repair or treatment serum, lotion, cream, pomade, and chemical treatments. In another embodiment, the styling aids can be a spray, mousse, rinse, gel, foam or the like. In another embodiment, the chemical treatments are selected from the group consisting of permanent waves, relaxers, and permanent, semi-permanent, and temporary color treatments and combinations thereof.

[0038] In another embodiment, the composition can be a sunscreen, skin protectant, anti-dandruff product, body wash, or bath composition. Moreover, the composition may be in the form of an emulsified vehicle, such as a nutrient cream or lotion, a stabilized gel or dispersioning system, such as skin softener, a nutrient emulsion, a nutrient cream, a massage cream, a treatment serum, a liposomal delivery system, a topical facial pack or mask, a surfactant-based cleansing system such as a shampoo or body wash, an aerosolized or sprayed dispersion or emulsion, a hair or skin conditioner or a styling aid.

[0039] The substance P analogs can be formulated into various compositions as described herein using generally recognized dermatological and cosmetic ingredients including excipients, carriers, vehicles, emollients, suspending agents, wetting agents and the like. Barry, Dermatological Formulations, 1983, Informa Healthcare, 1st edition, Osborne and Amann, eds. Topical Drug Delivery Formulations, 1989, Informa Healthcare, 1st edition, Barel, Payne and Maibach, eds., Handbook of Cosmetic, Science and Technology, 2001, Informa Healthcare, 1st edition, Draelos and Thaman,

eds. Cosmetic Formulation of Skin Care Products (Cosmetic Science and Technology Series Vol. 30), 2006, Informa Healthcare, 1st edition, each incorporated herein by reference in its entirety.

[0040] The composition provides a means whereby the substance P analog can be diluted, dispersed, conveyed to and distributed on the skin surface, hair or nails at an appropriate concentration. The compositions can be a form used for this type of application including, oil-in-water emulsion, water-in-oil emulsion, silicone emulsion, microemulsion, nanoemulsion, or an aqueous or oily gel or liquid.

[0041] In one embodiment the composition is an aqueous emulsion that can be a water-in-oil emulsion, or an oil-in-water emulsion. In another embodiment, the composition is an aqueous fat emulsion in which the aqueous phase of the emulsion acts as a carrier.

[0042] Surfactants can be used in the compositions. Preferred surfactants are those which make it possible to obtain an oil-in-water or wax-in-water emulsion. In one embodiment the surfactants are nonionic surfactants: fatty acids, fatty alcohols, polyethoxylated or polyglycerolated fatty alcohols such as polyethoxylated stearyl or cetylstearyl alcohol, fatty acid esters of sucrose, alkyl glucose esters, in particular polyoxyethylenated fatty esters of C_1-C_6 alkyl glucose and mixtures thereof; anionic surfactants: C_{16}-C_{30} fatty acids neutralized with amines, aqueous ammonia or alkaline salts, and mixtures thereof.

[0043] When the composition is an emulsion, the proportion of the fatty phase ranges from about 2% to about 80% by weights and preferably from about 5% to about 50% by weight relative to the total weight of the composition. The fatty substances, emulsifiers and co-emulsifiers included in the composition in emulsion form are those conventionally formulated in the art. The emulsifier and co-emulsifier are preferably present in the composition in a proportion ranging from about 0.3% to about 30% by weight and preferably from about 0.5% to about 20% by weight relative to the total weight of the composition.

[0044] Emulsifiers and co-emulsifiers include fatty acid esters of polyethylene glycol, such as PEG-100 stearate, PEG-50 stearate and PEG-40 stearate, fatty acid esters of polyols, such as glyceryl stearate, sorbitan tristearate and oxyethylenated sorbitan stearates commercially available under the trademark Tween®20 (Uniqema, Chicago, IL), or Tween®60 (Uniqema, Chicago, IL), for example, or mixtures thereof.

[0045] Fatty substances that can be used in the compositions include, but are not limited to, oils and mineral oils (liquid petroleum jelly), oils of plant origin, oils of animal origin (lanolin), synthetic oils (perhydrosqualene), silicone oils (cyclomethicone) and fluoro oil (perfluoro polyethers). Fatty alcohols such as cetyl alcohol, fatty acids, waxes and gums (including silicone gums) can be fatty substances in the compositions described herein.

[0046] In one embodiment the compositions comprise one or more aqueous gel or hydrogel or hydrophilic gelling agents. Examples of thickening agents include, but are not limited to, carbomers, cellulose base materials, gums, algin, agar, pectins, clays, carrageenan, gelatin, mineral or modified mineral thickeners, polyethylene glycol and polyalcohols, polyacrylamide and iother polymeric thickeners. The thickening agents that give the stability and optimal flow characteristics of the composition are preferably used. Lipophilic gelling agents include, for example, modified clays uschy as bentones, metal salts of fatty acids and hydrophobic silica.

[0047] In certain embodiments, the compositions can further comprise an effective amount of a physiologically acceptable antioxidant selected from the group consisting of butylated p-cresol, butylated hydroxyquinone monomethyl ether, or a tocopherol.

[0048] In certain embodiments the compositions can further comprise one or more natural or modified sterol compounds such as cholesterol and plant sterol (phytosterol), including stigmasterol, campesterol, β-sitosterol, chalinosterol, clionasterol, brassicasterol, α-spinasterol, dancosterol, desmosterol or poriferasterol.

[0049] In one embodiment, the compositions can be comprised of one or more moisturizers or emollients (*e.g.* a compound that has occlusive, humectants or lubricating properties) wherein the emollient can be glycerin, aminobenzoic acid, octinoxate, betacarotine, stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, isopropyl isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, dimethylpolysiloxane, di-n-butyl sebacate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl or myristate. Examples of moistures include, but are not limited to, ceramides, sphingoid-based compounds, lecithins, glycosphingolipids, phospholipids, cholesterol

and derivatives thereof, phytosterols (stigmaterol, β-sitosterol, or campersterol), essentially fatty acids, 1, 2-diaculglycerol, 4-chromanone, pentacyclic triterpenes, petroleum jelly and lanolin, threalose and derivatives thereof, hyaluronic acid and derivatives thereof, glycerol, pentanediol pidolates, amino acids (for examples) serine, proline, flutamates, arginine), xylitol, urea, creatine, flucosamines, lactic acid, lactates, polyglyceryl acrylate, ectoin and derivatives thereof, pyrrolidone-carboxylic acid and derivatives thereof, N-lauroyl-pyrrlidonecarboxylic acid, N-lauroyl-lysine and N-alpha-benzoyl-L-arginine.

[0050] In certain embodiments, the composition can be comprised of one or more herbal or botanical extracts or oils. Exemplary botanicals can be algae, aloe vera, menthol, glucosamine, chondroitin, a capsaicinoid, arnica, coriander oil, chamomile, Roman chamomile, *Epilobium angustifolium* (willowherb), feverfew, St. John's wort, *Helianthus annus* (sunflower), kava kava, nettle leaf, acetylsalicylic acid, Bala, black cohosh, black snakeroot, bugbane, squawroot, *Orbignya oleifera* (babassu), bupleurum, calendula, camphor, cayenne, devil's claw root, evening primrose, ginger, gotu kola, juniper, lavender, *Glycyrrhiza glabra* (licorice), marjoram, meadow sweet, passion flower, quercetin, salicinum, wild yam, wintergreen, wood betony, wormwood, grape seed, grape seed proanthocyanidin extract (GSPE), marigold, nettle leaf, blue-bottle, witch hazel extract, barley grass, Boswellia, borage, bromelain, cayenne, dandelion, dehydroepiandosterone (DHEA), echinacea, essential fatty acids such as omega-3 and omega-6 fatty acids including linoleic acid and alpha-linolenic acid, elderflower, flaxseed, ginkgo, ginseng, Hawthorne, kaempferol, life root, *Simmondsia chinensis* (jojoba), golden Senecio, squaw weed, golden groundsel, cocash weed, coughweed, ragwort, golden ragwort, grundy swallow, linden, marjoram, meadow sweet, neem, Padma 28, quercetin, turmeric, yucca, bilberry, *Prunus amygdalus dulcis* (sweet almond), garlic, green tea, lemon balm, milk thistle, oregano, peppermint, pomegranate juice, purslane, pycnogenol, red wine, rosemary, *Persea americana* (avocado), schizandra, wuweizi, wurenchun, trilinolein, sanchi, turmeric,arnica extract, Roman chamomile, nettle, lime tree extract, arjuna, benzoin, black pepper, blue gum eucalyptus, blue vervain, borneol, butcher's broom, cypress, geranium, L-arginine, lemon, lemon grass, niaouli, *Avena sativa* (oat) kernel flour, oat straw, *Triticum vulgare* (wheat) germ protein, orange blossom, Peru balsam, pine, prickly ash bark, rose oils, Spanish sage, spruce, Tien Chi ginseng, thyme, violet, white birch, yohimbe, bee pollen, bergamot, black horehound, bugleweed, California poppy, clary sage, cowslip,

damiana, grapefruit, hyssop, Jamaican dogwood, lady's slipper, lobelia, apricot, calendula, coconut (coconut milk), extra virgin olive oil, grapeseed, macadamia, neem, peach, rice bran, rosehip seed, sesame seed, soybean, mate, mistletoe, motherwort, mugwort, skullcap, valerian root, vervain, wild lettuce and oils and extracts thereof and combinations thereof.

[0051] Preferred embodiments include the arnica plant or oils or extracts thereof. The arnica plant has a bright yellow, daisy-like flower, and preparations made from the flowering heads have been used in homeopathic medicine for hundreds of years. The active components in arnica are sesquiterpene lactones, which reduce inflammation and decrease pain. Arnica extract also stimulates the activity of white blood cells that perform much of the digestion of congested blood and disperse trapped, disorganized fluids from bumped and bruised tissue, joints and muscles. Arnica extract is known to stimulate blood circulation. Furthermore, it has antibacterial and antiinflammatory qualities that can reduce swelling or edema.

[0052] Arnica extract can comprise from about 1% to about 10% of the composition. Preferably, Arnica extract comprises from about 3% to about 5% of the composition. An particularly preferred concentration of arnica extract is about 4% of the composition.

[0053] In one embodiment, the compositions can be formulated with emu oil. Emu oil is generally comprised of myristic acid, palmitic acid, palmitoleic acid, margaric acid, stearic acid, elaidic acid, oleic acid, vaccenic acid, linoleic acid, linolenic acid, arachidic acid and eicosenoic acid. The preparation of emu oil from an emu has been described in U.S. Patent No. 6,103,246. Also disclosed therein are preparations comprising emu oil and at least one medically active component, such as lactic acid or some other alpha-hydroxy acid. The composition provides for increased penetrability due to the emu oil. In addition, U.S. Patent Nos. 5,698,227, and 5,849,334 describe compositions comprising emu oil and a local anesthetic such as lidocaine for topical application to achieve anesthesia of skin to which it is applied.

[0054] Emu oil can comprise from about 1% to about 10% of the composition. Preferably, emu oil comprises from about 4% to about 6% of the composition. A particularly preferred concentration of emu oil is about 5% of the composition.

[0055] In one embodiment, the compositions can be comprised of one or more vitamins wherein the vitamins can be tocopheryl acetate (vitamin E), retinyl palmitate (vitamin A), ascorbyl palmitate (vitamin C) or ergocalciferol (vitamine D). In one

embodiment, the vitamin can be from the vitamin B family including thiamin (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folic acid (B9) or cobalamin (B12) or combinations thereof. Cobalamin can be any form of a cobalt containing vitamer compound including, cyanocobalamin, hydroxocobalamin, methylcobalamin or 5-deoxyadenosylcobalamin (adenosylcobalamin).

[0056] In one embodiment, the compositions can be comprised of one or more skin protectants or therapeutic agents wherein the skin protectants or therapeutic agents can be octinoxate, urea, niacinamide, salicylic acid, farnesol, alpha-hydroxy acids, sulfur containing compounds, retinoids, peptides, amino acids, zinc oxide, iron oxide or lanolin. In a preferred embodiment, the peptides can be pentapeptides. *See*, U.S. Patent No. 6,493,326. In one embodiment, the therapeutic agents can be antimicrobial or antifungal agents.

[0057] In one embodiment, the compositions can comprise a substance P analog and one or more sunscreen ingredients. In certain embodiments the compositions can further comprise one or more ultra-violet (UV) screening agents capable of screening out UVA or UVB radiation, or both UVA and UVB radiation. Exemplary UV screening agents can be: (a) Benzophenone derivatives: 2,4-dihydroxybenzophenone (benzophenone-1); 2,2'4,4'-tetrahydroxybenzophenone (benzophenone-2); (b) 2-hydroxy-4-methoxybenzophenone (benzophenone-3), (Uvinul M40®, BASF, Florham Park, NJ) 2,2'-dihydroxy-4,4'-dimethoxybenzophenone (benzopheonone-6), 5-chloro-2-hydroxybenzophenone (benzophenone-7); 2,2'-dihydroxy-4-methoxybenzophenone (benzophenone-8); the disodium salt of 2,2'-dihydroxy-4,4'-dimethoxybenzophenone-5,5'-disulfonic acid (benzophenone-9); 2-hydroxy-4-methoxy-4'-methylbenzophenone (benzophenone-10); benzophenone-11; 2-hydroxy-4-(octyloxy)benzophenone (benzophenone-12); (c) Triazine derivatives: 2,4-bis {[4-(2-ethylhexyloxy)-2-hydroxy]phenyl}-6-(4-methoxy-phenyl)-1,3,5-triazine (Tinosorb S® Ciba Specialty Chemicals, Basel Switzerland) and 2,2'-methylenebis[6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol] (Tinosorb M®, Ciba Specialty Chemicals, Basel Switzerland); (d) benzene-1,4-bis(3-methylidene-10-camphorsulfonic acid), optionally in partially or totally neutralized form, and mixtures thereof.

[0058] Exemplary compounds for screening out UVB radiation include: (a) salicylic acid derivatives, in particular homomenthyl salicylate and octyl salicylate; (b) cinnamic acid derivatives, in particular 2-ethylhexyl p-methoxycinnamate, (Parsol MCX®, Givaudan, Vernier, Switzerland); (c) liquid β,β'-diphenylacrylate

derivatives, in particular 2-ethylhexyl α-cyano-α,β'-diphenylacrylate, or octocrylene (Uvinul N539®, BASF, Florham Park, NJ); (d) p-aminobenzoic acid derivatives; (e) 4-methylbenzylidenecamphor (Eusolex 6300®, Merck, Whitehouse Station, NJ); (f) 2-phenylbenzimidazole-5-sulfonic acid (Eusolex 232®, Merck, Whitehouse Station, NJ); (g) 1,3,5-triazine derivatives; or (h) 2,4,6-tris[p-(2'-ethylhexyl-1'-oxycarbonyl)anilino]-1,3,5-triazine (Uvinul T150®, BASF, Florham Park, NJ) or combinations thereof.

[0059] Other compounds for screening out UVA and UVB radiation can be plant extracts, such as rosemary (rosmarinic acid) and extracts of the genus *Leontopodium*, in particular *Leontopodium alpinum* or *Leontopodium stracheyi*; and benzotriazole silicone, as described in FR-A-2,642,968.

[0060] In preferred embodiments, the sunscreen can be homomenthyl salicylate (homosalate), 2-ethylhexyl salicylate (octyl salicylate), p-aminobenzoic acid (PABA), octyl dimethyl p-aminobenzoate (octyl dimethyl PABA or padimate O), 2-hydroxy-4-methoxy benzophenone (benzophenone-3, oxybenzone), 2-hydroxy-4-methoxy benzophenone-5-sulfonic acid (benzophenone-4-sulisobenzone), 2-ethylhexyl-p-methoxycinnamate (octyl methoxycinnamate) or butyl methoxydibenzoylmethane (avobenzone).

[0061] The composition can also comprise a vehicle to enable the active ingredient to be conveyed to the skin in an appropriate dilution. The composition can be in a form of liquid, suspension, emulsion, lotion or cream.

[0062] The selection of a vehicle for the active ingredient(s) in compositions of the invention presents a wide range of possibilities depending on the required product from of the composition. Suitable vehicles can be classified as described hereinafter.

[0063] Cosmetic vehicles are substances which can act as diluents, dispersants, or solvents for the substance P analogs that can promote the application and distribution of the composition on the skin at an appropriate concentration; the vehicle is preferably one which can aid penetration of the active ingredient into the skin, thus ensuring that the effectiveness of the active ingredient is prolonged because of improved properties. Compositions can include water is a vehicle, and/or at least one cosmetically acceptable vehicle other than water.

[0064] Vehicles other than water that can be used in the compositions can include solids or liquids such as propellants, solvents, humectants, thickeners and powders. Examples of each of these types of vehicles, which can be used singly or as mixtures of one or more carriers, are as follows: (a) Propellants, such as trichlorofluoromethane,

dichlorodifluoromethane, dichlorotetrafluorethane, monochlorodigluoromethane, trichlorotrifluorethane, propane, butane, isobutane, dimethyl ether, carbon dioxide, nitrous oxide; (b) Solvents, such as ethyl alcohol, methylene chloride, isopropanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethyl sulphoxide, tetrahydrofuran; (c) Humectants, such as glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, gelatin; and (d) Powders, such as chalk, talc, fullers, earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl and/or trialkyl aryl ammonium smectites, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminium silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, ethylene glycol monostearate.

[0065] The amount of vehicle in the composition, including water if present, should preferably be sufficient to carry at least a portion of the active ingredient to the skin in an amount which is sufficient effectively to provide skin benefit. The amount of the vehicle can comprise the major portion of the composition, particularly where little or no other ingredients are present in the composition.

[0066] The composition will accordingly comprise from 15% to 99.989% and preferably from 50% to 99.5% by weight of the vehicle or vehicles.

[0067] The compositions can further comprise additives and excipients that are common in cosmetics such as preservatives, solvents, fragrances, fillers, pigments, odor absorbers and dyestuffs. The amounts of these additives and excipients are those conventionally employed in the field under consideration and range for example, from about 0.01% to about 20% of the total weight of the composition. Depending on their nature, these additives and excipients can be introduced into the fatty phase or into the aqueous phase.

[0068] Examples of such excipients are, steric acid, caprylic/capric triglyceride, glyceryl stearate, PEG-100, PEG-400, PEG-600, dimethicone, distarch phosphate, cetearyl alcohol, ceteareth-20, phenoxyethanol, squalane, EDTA, methylparaben, triethanolamine, propylparaben, allantoin, benzyl alcohol, cetyl alcohol, distearyldimonium chloride, isopropyl palmitate, petrolatum, sodium chloride, water, mineral oil, stearic acid, carbomer, sodium lauryl sulfate, propylene glycol, polysorbate 20, panthenol, xanthan gum or fragrance.

[0069] The composition can also be in a formulation as a mask for the face or the body. The mask can comprise a backing sheet impregnated with the substance P

analogs to exert a cosmetic effect on the skin. The backing sheet can be in a dry or web state, preferably stretchable at least in the wet state, in order to enable the mask to be adapted to fit the shape of the face or of the portion of the body to be covered. The backing sheet can be made of paper, fabric, cloth, or a polymeric material.

[0070] Also provided is a process for the preparation of a cosmetic composition for topical application to skin which comprises mixing a substance P analog of Formula (I) with a suitable vehicle to provide a concentration of from 0.001% to about 40%. In preferred embodiments, the substance P analog can be at a concentration of about 0.1% to about 0.5%. In more preferred embodiments the substance be analog can be at a concentration of about 0.1% to about 5%.

[0071] The compositions can be formulated as liquids, for example as a lotion or milk for use in conjunction with an applicator such as a roll-ball applicator, or a spray device such as an aerosol can containing propellant, or a container fitted with a pump to dispense the liquid product. Alternatively, the compositions can be solid or semi-solid, for example sticks, creams or gels, for use in conjunction with a suitable applicator or simply a tube, bottle or lidded jar, or as a liquid-impregnated fabric, such as a tissue wipe.

[0072] In one embodiment, the compositions can be a bathing composition such as bath beads comprising substance P analogs. In another embodiment, the compositions can be used in the shower. In one embodiment the compositions can be bath beads comprising a cosmetically effective amount of the substance P analogs. In a preferred embodiment, the bath beads are also perfumed.

[0073] The bath beads can be made by techniques known in the art. Compositions in which an active ingredient is tumbled with a mixture of about 0.2% to about 2.0% of an oily perfume and about 0.3% to about 2.0% of a water soluble polyalkylene ether emollient to cause the perfume and the emollient to be distributed over the beads. Other bath bead compositions and methods of making bath beads are disclosed in U.S. Patent Numbers 4,183,959 and 4,294,855 and incorporated herein by reference in their entirety.

[0074] In view of the above, a non-limiting object of the bath beads is to help create an aura of body comfort with a scented, premeasured, moisturizing and muscle soothing bath product which also improves the texture of the skin.

[0075] The emollient or moisturizing oils which can be utilized in or to form moisturizing beads and generally known and referred to in the art as bath oils. Suitable

bath or emollient oils include, for example, mink oil, lanolin, liquid lanolin esters and other lanolin derivaties, cocoa butter, lower alkanol esters of saturated fatty acids such as isopropyl palmitate, ispropyl myristate, isopropyl stearate, isopropyl linoleate, methyl laurate, ethyl stearate, and the like. Also suitable are the glycerol esters of saturated fatty acids, *e.g.*, glyceryl monostearate, glyceryl monolaurate, glyceryl tripalmitate, the cholesterol esters of saturated fatty acids, polyethers such as polymers of propylene oxide, C_{12}-C_{18} alcohols, *e.g.*, oleyl alcohol, cetyl alcohol, stearyl alcohol, lauryl alcohol, and adducts of C_{12}-C_{18} alcohols with 1 to 4 moles of ethylene oxide, *e.g.*, ethoxylated lauryl alcohol containing about 1 mole of ethylene oxide per mole of lauryl alcohol, glycols such as dipropylene glycol, oily liquids, *e.g.*, the vegetable oils such as olive oil, cottonseed oil, corn oil, almond oil, peanut oil, and the like, hydrocarbons such as mineral oils, light liquid petrolatum and the like, and similar absorbable substances which soften, moisturize or give the effect of softening or moisturizing the skin.

[0076] In one embodiment, the compositions can further include a coloring agent. Coloring agents are included in preferred embodiments of the personal care bath products. The coloring agents provide a pleasing color to the bath water, and can be suggestive of the fragrant agent used. For example, a coloring agent which imparts a pink color to the water can be used in conjunction with a rose fragrant agent. Similarly, a blue agent can be used to suggest hyacinth, and a green agent for mimosa. *See*, U.S. Patent Number 4,659,495.

[0077] Lotions can be either suspensions or emulsions but generally are fluid liquids that are typically used for their lubricating effect. Creams are emulsions and are typically opaque, thick liquids or soft solids. Creams also have the added feature that they tend to "vanish" or disappear with rubbing.

[0078] In certain embodiments, the topical compositions can be an aerosol or powder. In another embodiment, the topical compositions can be impregnated in an apparatus such as a transdermal patch, tape, strip or gauze.

[0079] In one embodiment, the compositions can be a spritz, *i.e.* a liquid composition for spraying or atomization. In a preferred embodiment, the compositions can be sprayed onto the skin or scalp. Apparatuses for atomizing a liquid composition are known in the art including U.S. Patent Numbers 6,569,458, 3,584,792 and WO 2007/002048. As will be understood by those in the art, the particle size of the liquid composition will be larger with a spraying apparatus than with an atomizer. The

method of application and other characteristics and qualities of the composition and use thereof is to be considered when using a liquid composition.

[0080] In one embodiment, the compositions can be a cosmetic cloths, tape or bandage comprising the substance P analog. Examples known in the art are Bioré® Cleansing Cloths and Bioré® Pore Strips (Kao Corporation, Cincinnati, Ohio) as well as Cosmetic Tapes and sheets for pore-cleansing (Nitto Denko Corporation, Osaka, Japan)

[0081] In one embodiment provided herein are kits for administering a cosmetically effective amount of a substance P analog. For example, such a kit can comprise more than one composition for improving the appearance of human skin.

[0082] In one embodiment, the substance P analogs can have a modified methionine residue. In a preferred embodiment, the methionine residue side chain S can be oxidated. In one embodiment the methionine is methionine sulfoxide (-NH-CHα(CO)-CH_2-CH_2-S(O)CH_3). In one embodiment the methionine is methionine sulfone or methionine S, S, dioxide, (-NH-CHα (CO)-CH_2-$CH\alpha_2$-S(O_2)CH_3) , also referred to herein as Met(O_2).

[0083] In one embodiment, the substance P analog can be of Formula (I):

$$Z_1\text{-}Xaa^1\text{-}Xaa^2\text{-}Xaa^3\text{-}Xaa^4\text{-}Xaa^5\text{-}Xaa^6\text{-}Xaa^7\text{-}Xaa^8\text{-}Xaa^9\text{-}Xaa^{10}\text{-}Xaa^{11}\text{-}Z_2 \quad (I)$$

or a pharmaceutically acceptable salt thereof, wherein:

Xaa^1 is Arg, Lys, 6-N methyllysine, or (6-N, 6-N) dimethyllysine;

Xaa^2 is Pro or Ala;

Xaa^3 is Lys, Arg, 6-N-methyllysine, or (6-N, 6-N) dimethyllysine;

Xaa^4 is Pro or Ala;

Xaa^5 is Gln or Asn;

Xaa^6 is Gln or Asn;

Xaa^7 is Tyr, Phe or Phe substituted with chlorine at position 2, 3 or 4;

Xaa^8 is Tyr, Phe, or Phe substituted with chlorine at position 2, 3 or 4;

Xaa^9 is Gly, Pro, Ala, or N-methylglycine;

Xaa^{10} is Leu, Val, Ile, Norleucine, Met, Met sulfoxide, Met sulfone, N-methylleucine, or N-methylvaline;

Xaa^{11} is Met, Met sulfoxide, Met sulfone, or Norleucine;

Z_1 is R_2N– or RC(O)NR–;

Z_2 is –C(O)NR_2 or –C(O)OR or a salt thereof;

each R is independently H, (C_1 -C_6) alkyl, (C_1 -C_6) alkenyl, (C_1 -C_6) alkynyl, (C_5 -C_{20}) aryl, (C_6 -C_{26}) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl; and

each "—" between residues Xaa^1 through Xaa^{11} independently designates an amide linkage, a substitute amide linkage or an isostere of an amide.

[0084] In a preferred embodiment the substance P analogs can be of Formula (I) wherein

Xaa^1 is Arg; Xaa^2 is Pro; Xaa^3 is Lys; Xaa^4 is Pro; Xaa^5 is Gln; Xaa^6 is Gln; Xaa^7 is Phe or Phe substituted with chlorine at position 4; Xaa^8 is Phe, or Phe substituted with chlorine at position 4; Xaa^9 is Gly, Pro or N-methylglycine; Xaa^{10} is Leu; and Xaa^{11} is Met, Met sulfoxide, Met sulfone, or Norleucine. In a more preferred embodiment, the "—" between residues Xaa^1 through Xaa^{11} of the substance P analogs can be –C(O)NH–; and Z_1 is H_2N–; and Z_2 is –C(O)NH_2.

[0085] In yet another preferred embodiment the substance P analogs can be selected from the group consisting of:

RPKPQQFFGLM (SEQ ID NO.: 1);

RPKPQQFFMeGlyLM(O_2) (SEQ ID NO.: 2);

RPKPQQFFGLM(O_2) (SEQ ID NO.: 3);

RPKPQQFFMeGlyLM(O) (SEQ ID NO.: 4);

RPKPQQFFGLNle (SEQ ID NO.: 5);

RPKPQQFFPLM (SEQ ID NO.: 6);

RPKPQQFFMeGlyLM (SEQ ID NO.: 7);

RPKPQQFTGLM (SEQ ID NO.: 8);

RPKPQQF(4-Cl)F(4-Cl)GLM (SEQ ID NO.: 9); or

RPKPQQFFGLM(O) (SEQ ID NO.: 10).

[0086] In another preferred embodiment, the substance P analog can be Z_1—RPKPQQFFMeGlyLM(O_2)—Z_2; wherein Z_1 is NH_2 and Z_2 is $C(O)NH_2$.

[0087] It will be apparent to one skilled in the art that the amino (designated herein as Z_1) or carboxy terminus (designated herein as Z_2) of the substance P analogs can be modified. Included are "blocked" forms of the substance P analogs, *i.e.*, forms of the substance P analogs in which the N- and/or C-terminus is blocked with a moiety capable of reacting with the N-terminal —NH_2 or C-terminal —C(O)OH. In some embodiments, the N- and/or C-terminal charges of the substance P analogs can be an N-acylated peptide amide, ester, hydrazide, alcohol and substitutions thereof. In a preferred embodiment, either the N- and/or C-terminus (preferably both termini) of the substance P analogs are blocked. Typical N-terminal blocking groups include RC(O)—, where R is —H, (C_1 -C_6) alkyl, (C_1 -C_6) alkenyl, (C_1 -C_6) alkynyl, (C_5 -C_{20}) aryl, (C_6 -C_{26}) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl. Preferred N-terminal blocking groups include acetyl, formyl and dansyl. Typical C-terminal blocking groups include —C(O)NRR and —C(O)OR, where each R is independently defined as above. Preferred C-terminal blocking groups include those where each R is independently methyl. In another preferred embodiment the C-terminal group is amidated.

[0088] Substituted amides generally include, but are not limited to, groups of the formula —C(O)NR—, where R is (C_1 -C_6) alkyl, substituted (C_1 -C_6) alkyl, (C_1 -C_6) alkenyl, substituted (C_1 -C_6) alkenyl, (C_1 -C_6) alkynyl, substituted (C_1 -C_6) alkynyl, (C_5 -C_{20}) aryl, substituted (C_5 -C_{20}) aryl, (C_6 -C_{26}) alkaryl, substituted (C_6 -C_{26}) alkaryl, 5-20 membered heteroaryl, substituted 5-20 membered heteroaryl, 6-26 membered alkheteroaryl and substituted 6-26 membered alkheteroaryl.

[0089] Amide isosteres generally include, but are not limited to, —CH_2 NH—, —CH_2 S—, —CH_2CH_2 —, —CH=CH— (cis and trans), —C(O)CH_2 —, —CH(OH)CH_2 — and —CH_2 SO—. Compounds having such non-amide linkages and methods for preparing such compounds are well-known in the art (see, *e.g.*, Spatola, March 1983, Vega Data Vol. 1, Issue 3; Spatola, 1983, "Peptide Backbone Modifications" In: Chemistry and Biochemistry of Amino Acids Peptides and Proteins, Weinstein, ed., Marcel Dekker, New York, p. 267 (general review); Morley, 1980, *Trends Pharm. Sci.* 1:463-468; Hudson *et al.*, 1979, *Int. J. Prot. Res.* 14:177-185 (—CH_2 NH—, —CH_2 CH_2 —); Spatola *et al.*, 1986, *Life Sci.* 38:1243-1249 (—CH_2 —S); Hann, 1982, *J. Chem. Soc. Perkin Trans.* I. 1:307-314 (—CH=CH—, cis and trans); Almquist *et al.*, 1980, *J. Med.*

Chem. 23:1392-1398 (—$COCH_2$ —); Jennings-White *et al.*, *Tetrahedron. Lett.* 23:2533 (—$COCH_2$—); European Patent Application EP 45665 (1982) CA 97:39405 (—$CH(OH)CH_2$ —); Holladay *et al.*, 1983, *Tetrahedron Lett.* 24:4401-4404 (—$C(OH)CH_2$ —); and Hruby, 1982, *Life Sci.* 31:189-199 (—CH_2 —S—).

[0090] Additionally, one or more amide linkages can be replaced with peptidomimetic or amide mimetic moieties which do not significantly interfere with the structure or activity of the peptides. Suitable amide mimetic moieties are described, for example, in Olson *et al.*, 1993, *J. Med. Chem.* 36:3039-3049.

[0091] The kit can further comprise tapes, bandages or gauzes for use with the substance P analog and can be in separate, or divided or undivided containers. The components of the kit can be in liquid, dried, lyophilized, or frozen form, as is convenient for the end user and good for shelf life.

7. EXAMPLES

[0092] Various embodiments have been described. The descriptions and examples are intended to be illustrative and not limiting. Indeed, it will be apparent to those of skill in the art that modifications may be made to the various embodiments described without departing from the spirit of the invention or scope of the appended claims set forth below.

[0093] All references cited herein are incorporated herein by reference in their entireties for all purposes.

7.1 Example 1. Firm Lotion

[0094] The following presents an exemplary firm lotion formulation that can be used in accordance with the methods and compositions described herein.

Deionized water	45 %
Olive oil	30 %
Sweet almond oil	5 %
Wheat germ oil	2.5 %
Jojoba oil	4 %
Shea butter	2 %
Beeswax	7.5 %
Glycerin	1 %
Homspera	3 %

7.2 Example 2. Light Lotion

[0095] The following presents an exemplary light lotion formulation that can be used in accordance with the methods and compositions described herein.

Water	44.4 %
Olive oil	32 %
Sweet almond oil	5 %
Wheat germ oil	2.5 %
Jojoba oil	3.5 %
Shea butter	1.5 %
Castor oil	1.5 %
Beeswax	7.5 %
Glycerin	1.5 %
Homspera	0.6 %

7.3 Example 3. Body Lotion

[0096] The following presents an exemplary body lotion formulation that can be used in accordance with the methods and compositions described herein.

Water	QS
Glycerine	8%
Isohexadecane	3%
Isopropyl isostearate	3%
Polyacrylamide	3%
Isoparaffin	3%
Laureth-7	3%
Petrolatum	4%
Dimethicone	2%
Stearyl alcohol 97%	1%
cetyl alcohol 95%	0.5%
Behenyl alcohol	1%
Stearic acid	0.15%
PEG-100 Stearate (MYRJ 59)	0.15%
Homspera	3%

7.4 Example 4. Moisturizing Cream

[0097] The following presents an exemplary moisturizing cream formulation that can be used in accordance with the methods and compositions described herein.

Water	QS
Glycerine	3%
Petrolatum	3%
Cetyl alcohol 95%	1.5%
Dimethicone copolyol	2%
Isopropyl palmitate	1%
Carbopolmer 954	0.7%
Dimethicone	1%
Stearly alcohol 97%	0.5%
Stearic acid	0.1%

PEG-100 stearate	0.1%
Titanium dioxide	0.3%
Homspera	2%
Preservative	0.1%
Fragrance & color	0.1%

7.5 Example 5. Ultra Moisturizing Facial Cream

[0098] The following presents an exemplary ultra-moisturizing facial cream formulation that can be used in accordance with the methods and compositions described herein.

Water	QS
Glycerin	5%
PEG 400	10%
Niacinamide	7%
Isohexadecane	5%
Dimethicone	2%
Polyacrylamide, isoparaffin, Laureth-7	3%
Isopropyl isostearate	25
Polymethylsilsequioxane	2%
Cetyl alcohol 95%	1%
Sucrose polycottonseed oil	1%
D-panthenol	1%
tocopherol acetate	1%
Stearyl alcohol 95%	0.5%
Cetearyl glucoside	0.5%
Titanium dioxide	0.3%
Stearic acid	0.15%
PEG-100 stearate	0.15%
Homspera	8%
Fragrance & color	0.01%

7.6 Example 6. Moisturizing Body Wash

[0099] The following presents an exemplary moisturizing body wash formulation that can be used in accordance with the methods and compositions described herein.

Water	QS
Glycerin	4%
PEG-6 Caprylic/Capric Glycerides	4%
Palm Kernel Fatty acids	3%
Sodium Laureth-3 sulfate	45%
Cocamide MEA	3%
Sodium Lauroamphoacetate	25%
Soyabean Oil	10%
Polyquaternium-10	1%
Homspera	1%
Preservative	0.5%

Fragrance & color	0.01%

7.7 Example 7. Body Wash

[00100] The following presents an exemplary body wash formulation that can be used in accordance with the methods and compositions described herein.

Water	QS
Sodium laureth sulfate	15%
Cocamidopropyl betaine	10%
decylAPG Glucoside (Plantacare 2000 1)	2%
Homspera	1%
Preservative	0.5%
Fragrance & color	0.02%

7.8 Example 8. Shampoo

[00101] The following presents an exemplary shampoo formulation that can be used in accordance with the methods and compositions described herein.

Water	QS
Sodium laureth sulfate 30%	27%
Cocamidopropyl betaine	3.7%
Coco-glucoside and glyceryl oleate	5%
Coco-glucoside and glycol distearate/glycerine	3%
Guar hydroxypropyl trimonium chloride	0.1%
Laureth-2	1.55%
Homspera	2%
Preservative	0.2%
Fragrance & color	QS

7.9 Example 9. Cream Rinse

[0100] The following presents an exemplary cream rinse formulation that can be used in accordance with the methods and compositions described herein.

Water	QS
Behentrimonium chloride	2%
Trilaureth-4 phosphate	1.5%
Cetyl alcohol	2%
Citric acid	0.5%
Homspera	1-2%
Preservative	0.2%
Fragrance & color	0.01%

7.10 Example 10. Leave on Hair Conditioner

[0101] The following presents an exemplary leave-in hair conditioner formulation that can be used in accordance with the methods and compositions described herein.

Water	QS
Isostearamidopropyl morpholine lactate	6%
Hydroxyethylcellulose	1%
Homspera	1%
Preservative	0.1%
Fragrance & color	QS

7.11 Example 11. Facial Cleaning Emulsion

[0102] The following presents an exemplary facial cleaning emulsion formulation that can be used in accordance with the methods and compositions described herein.

Water	QS
Disodium EDTA	0.1%
Glycerol polymethacrylate and propylene glycol	1%
Glycerin	2
Xanthan gym	0.5
Hydroxyethyl cellulose	0.5
Tridecyl neopentanoate	4%
Isocetyl stearate	6%
Octyl paolmitate	8%
Glyceryl dilaurate	4%
PEG-20 stearate	2%
Glyceryl stearate and Laureth-23	2%
Lauryl pyrrolidone	0.5%
Chamomile extract	0.2%
Aloe vera	0.05%
Homspera	0.05%
Preservative	0.1%
Fragrance & color	0.02%

7.12 Example 12. Exfoliant Gel

[0103] The following presents an exemplary exfoliant gel formulation that can be used in accordance with the methods and compositions described herein.

Water	QS
Disodium EDTA	0.05%
Aloe vera	0.01%
Benzophenone-4	0.25%
Propylene glycol	1%
Acrylates/C10-30 alkyl acrylate crosspolymer (2%)	20%
Glyceryl polymethacrylate and propylene glycol	10%
Glyceryl polymethacrylate and propylene glycol and PVM/MA copolymer	1%
Hydrogenated jojoba oil	1.5%

Homspera	0.25%
Preservative	0.1%
Fragrance & color	QS

7.13 Example 13. Facial toner

[0104] The following presents an exemplary facial toner formulation that can be used in accordance with the methods and compositions described herein.

Water	QS
Disoium EDTA	0.1%
Butylenes glycol	2%
Aloe vera	0.1%
Allantoin	0.1%
Benophenone-4	0.5%
Witch hazel extract	0.3%
Propylene glycol	0.05%
euphrasia extract and green tea extract	0.01%
PEG-40 hydrogrenated castor oil	0.5%
Sandlewood oil	0.02%
Homspera	0.05%

7.14 Example 14. Sunscreen

[0105] The following presents an exemplary sunscreen formulation that can be used in accordance with the methods and compositions described herein.

	SPF ~25	SPF~15
Water	53%	71%
PVM/MA decadiene crosspolymer	0.5%	0.5%
Butylenes glycol	3.0%	3.0%
Disodium EDTA	0.1%	0.1%
PEG-20 stearate	1.5%	1.5%
Glyceryl stearate and laureth-23	2.0%	2.0%
Isostearyl neopentanoate	1.0%	1.0%
Ethylhexyl palmitate	0.5%	0.5%
Octinoxate	7.5%	7.5%
Oxybenzone	2.0%	2.0%
Ethylhexyl salicylate	3.0%	3.0%
Sodium hydroxide (10%)	1.3%	1.3%
Glyceryl polymethacrylate/ propylene glycol	3.0%	3.0%
Glyceryl polymethacrylate/ propylene glycol/PVM/MA copolymer	0.5%	0.5%
Styrene/acrylates copolymer	18.5%	0
Homspera	0.05%	0.05%

7.15 Example 15. Skin Irritation

[0106] An ISO 10993-10 Primary Skin Irritation Test was performed to determine the dermal irritation potential of Homspera®. ISO 10993-10: 2002 Standard, "Biological Evaluation of Medical Devices, Part 10-Tests for Irritation and Sensitization" pp.6-10, 21.

7.15.1. Materials and Methods

[0107] Three New Zealand White Strain albino rabbits were obtained from Bakkrom Rabbitry (Viroqua, WI) and monitored for signs of disease and injury prior to study. The fur of each animal was clipped on both sides of the spinal column to expose a sufficient sized area for patch application. Loose fur was removed from the skin.

[0108] Homspera® (16 mg; a substance P analog having the structure Z_1—RPKPQQFFMeGlyLM(O_2)—Z_2; wherein Z_1 is NH_2 and Z_2 is C(O)NH_2) was dissolved in 114.3 ml of saline. The test article was placed onto a one-inch square gauze patch and applied to the shaved skin of the rabbits. Negative control patches were wet with tap water and applied to the same three rabbits. The patches were held in place by wrapping the trunk of the animals with an elastic bandage and securing with hypoallergenic tape.

[0109] Detailed dermal observations were recorded at 30 to 60 minutes after unwrapping and at 24, 48, and 72 (± 2) hours and scored according to Table 1. The tissue reactions were rated for gross evidence of erythema, edema and necrosis using diluted alcohol to lightly swab the skin.

Table 1. Dermal Observation Scoring

Erythema	**Edema**
0 = no erythema	0 = no edema
1 = very slight erythema (barely perceptible)	1 = very slight edema (barely perceptible)
2 = well defined erythema	2 = slight edema (raised edges)
3 = moderate to severe erythema	3 = moderate edema (raised ~1 mm)
4 = Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4 = Severe edema (raised > 1 mm and extending beyond area)

[0110] The sum of the erythema and edema scores for the test article and control sites were calculated for only the 24, 48 and 72 hour observation periods for each rabbit. The total scores were divided by 6 (2 observation sites x 3 observation periods) to determine the Primary Irritation Score observation average. The response of the test article is categorized based on the Primary Irritation Index shown in Table 2. The Primary Irritation Index (PII) is determined by adding the Primary Irritation Score for each animal and dividing the total score by the number of animals. *See*, Handbook of Toxicology, 2nd ed. Derelanko and Hollinger eds., CRC Press, Dermatotoxicology, 4th ed. Marzuli and Maibach eds. Hemisphere Publishing Corp., New York, NY 1991, United States Environmental Protection Administration, Office of Prevention, Pesticides and Toxic Substances (OPPTS), Health Effects Test Guidelines, OPPTS 870. 1200 Acute Dermal Toxicity.

Table 2. Primary Irritation Response Categories in the Rabbit

Response Category	Comparative Mean Score (PII)
Negligible	0 to 0.4
Slight	0.5 to 1.9
Moderate	2 to 4.9
Severe	5 to 8

7.15.2. Results

[0111] There were no significant dermal reactions observed at the test sites on the rabbits at 0.5, 24, 48 and 72 hour observation periods. None of the animals showed abnormal clinical signs during the 72 hour test period. The Primary Irritation Scores for each rabbit was 0 and the PII for the group of subjects was 0. The Irritation Response Category was thus 0 and negligible. Homspera® is a non-irritant.

7.16 Example 16. Dermal Sensitization

[0112] An ISO 10993-10 Buehler Dermal Sensitization Test was performed to determine the potential of Homspera® to elicit a dermal sensitization reaction.

7.16.1. Materials and Methods

[0113] Ten female Hartley strain albino guinea pigs were obtained from Willow River Acres (Maiden Rock WI) and monitored for signs of disease and injury prior to study. The application sites were prepared by removed a 5 x 7 cm area of fur with an electric clipper. The left flank of the animals was shaved the day before the induction dosing on day 0, day 7, and day 14. The right flank was shaved for the challenge on day 27.

[0114] A test sample was prepared by mixing 16 mg of Homspera® with 114.3 ml of saline. An induction procedure was initiated using a 0.4 ml sample of test article applied to the left flank site of the test group animals. Prepared control patches were applied to the negative control animals. The animals were wrapped with an elastic bandage and secured with hypoallergenic tape. The bandaging and patches were removed after 6 to 8 hours of exposure. At 24 hours (± 2 hours) after topical application, the sites were assessed for erythema and edema using the grading scale provided in Table 1. This procedure was repeated once per week for three weeks for a total of three inductions.

[0115] A challenge procedure was initiated, following a two week rest period. The animals were topically patched on the opposite flank with the appropriate test article on the test animals and the control on the control animals. The patches were removed after 6 to 8 hours of exposure. The dermal patch sites were observed for erythema and edema at 24, 48 and 72 (± 2) hours after patch removal. Each animal was assessed for a sensitization response based upon the dermal scores.

[0116] Individual animal challenge scores of one or greater in the test group generally indicate sensitization, provided scores of less than one are observed on the negative control animals. If scores of one or greater are noted on the negative control animals, then the reactions of the test animals which exceeded the most severe negative control reaction are presumed to be due to desitization. Background or artifactual reactions from fur clipping or patch edge were not considered as evidence of sensitization. An effect interpreted as "irritation" is generally observed at 24 hours, but diminished thereafter. Closed patches typically show maximal sensitization response 48 hours after patch removal in test conditions.

7.16.2. Results

[0117] The results were based upon incidence and severity of the sensitization reaction.

[0118] The dermal responses to the repeated patching of the test article during the induction phase were all scored as 0. There was no irritation observed on the test article and control blank animals during the induction phase. None of the negative control animals were observed with a response at any time point, indicated a 0% incidence.

[0119] None of the test animals challenged with the test article were observed with a sensitization response at any time point, indicating a 0% incidence. None of the control animals challenged with the control article were observed with a sensitization response at any time point, indicating a 0% incidence. The severity was calculated as 0 at each time point.

7.16.3. Conclusion

[0120] The negative control material had a 0% incidence and a grade of 0 for severity. None of the animals tested demonstrated signs of edema or erythema in response to a secondary challenge with following a 14-day recovery period. Homspera® does not cause dermal sensitization.

7.17 Example 17. Clinical Trial to Evaluate Sensitivity

[0121] The following experiment is performed to determine if human subjects experience sensitivity to various topical compositions of Homspera. This study is used to evaluate the effect of a cosmetic cream comprising Homspera on skin laxity and the appearance of facial wrinkles.

7.17.1. Methods and Materials

[0122] A topical test composition is formulated into a commercially available base such as a PEG base such as polyethylene glycol 400 (60% by weight) and polyethylene glycol 3350 (40% by weight). The control composition containing no Homspera®, the second composition containing 100 nM Homspera®. The test compositions are mixed thoroughly, placed in small jars and stored at 4°C until ready for use.

[0123] Each jar is labeled with a blinded ID indicator and area to be applied. The trial optimally includes at least 20 or as many as 100 subjects. Each subject receives 2 jars of composition, one test composition and one control. Each subject is instructed to apply the composition on either their right or left inner elbow as indicated by the label on the jar. Test subject exclusion criteria could include recent (within 6 months) microdermabrasion, chemical peels, skin resurfacing, facial plastic surgery, facial skin cancer, acne outbreak within the facial area to be studied; electrolysis or depilatory

used to remove facial hair in the region around the mouth, chin, and philltrum (area between the nose and upper lip); renal dysfunction; allergies to products containing polyethylene glycol; recent history (last 6 months) of atopic dermatitis or other skin condition that results in redness, rash, in area to be tested; recent (within one month) history of facial sunburn; recent (within one month) use of Retin-A® or other prescription strength anti-acne medication or topical bleaches used in area to be treated or other medications that induce facial skin irritation or the presence of scars within the test area.

[0124] The subjects are instructed to cease the use of any other treatment products upon distribution of the test compositions.

[0125] After a seven day phase, subjects are acclimated to ambient temperature and humidity of the research facility for 30 minutes. Baseline measurements of skin color, viscoelasticity, hydration level and wrinkle depth are obtained from the periorbital, nasolabia, cheek and forehead of each participant. Skin color is assessed by use of a chromameter (Model CR300, Minolta). Viscoelasticity is measured by use of Cutometer® MPA 580 (Courage and Khazaka, Germany). Skin hydration levels are measured by a Corneometer®-CM825 (Courage and Khazaka, Germany) and wrinkle depth is assessed by a Skinvisiometer®-SV600 (Courage and Khazaka, Germany). *See*, Kerchove, *et al.*, 2008, *Skin Res. Tech.* 7(1): 56-59 and Chardon, *et al.*, 1991, *Int. J. Cosm. Science* 13: 191-208. Each measurement is performed in triplicate.

[0126] After baseline control data is collected, subjects are given two facial creams (one placebo and one cream containing Homspera). The subjects are directed to apply one cream to the left side of the face and the second cream to the right side of the face. Subjects are blinded as to which cream is placebo and which contains Homspera.

[0127] Homspera creams are manufactured in 5 concentrations: 0.1%, 0.5%, 1%, 2% and 5% creams as described in Examples 1-5. Twenty subjects receive cosmetic creams of each of these concentrations.

[0128] Subjects are instructed to apply a dime sized amount of cream each to the periorbital, nasoliabia, cheek and forehead region each night for 30 nights. Measurements are taken weekly.

[0129] In addition to objective measurements, subjective scoring and comments are collected.

7.18 Example 18: The effect of an exemplary substance P analog, Homspera® on fibroblast proliferation

7.18.1. Material and Methods

[0130] Homspera® (as the acetate salt) was obtained by ImmuneRegen from CS Bio. The peptide was shipped under refrigerated conditions and stored at -20°C until reconstitution. Reconstitution of Homspera® was performed by dissolving compound to 1 mg/ml final concentration in sterile phosphate buffer saline (PBS) pH 7.4, then storing reconstituted Homspera® at 4°C in polypropylene enclosure. Appropriate dilutions were made from this 1mg/ml working stock by diluting with sterile PBS. Spantide I (CAS 91224-37-2) was obtained from Sigma Aldrich and was added at a concentration of 10 μM. Normal human fibroblasts were obtained from ATCC (passage 2-3) and grown in IMDM-Glutamax media (Invitrogen #31980-030) containing 10% Fetal Bovine Serum (FBS) (Invitrogen #10437-028) and penicillin-streptomycin-amphotericin B (Invitrogen #15240-104). These cells were cultivated up to passage 40. Cells were trypsinized using 0.05% Trypsin (Invitrogen #15400-054) in calcium and magnesium-free Hanks solution (Invitrogen #14170), followed by neutralization in Iscoves medium containing 10% FBS. Cells were maintained in a cell incubator at 37°C and 5% CO_2.

[0131] To quantify proliferation, MTT assay (Invitrogen Molecular Probes M6494) was performed. *See*, Mosman, 1983, *J. Immunol. Methods* 65: 55. Briefly, cells were plated into 96-well tissue culture plates at 2,000 cells per well. Cultures were then treated with Homspera®; total well volume was kept to 0.1mL. MTT was weighed (5mg) and dissolved in distilled water, filtered using a 200 micron syringe filter and stored in the dark at 4°C. Ten μL MTT was added to each well and mixed. Cultures were incubated for 4 hours with MTT. Then medium was removed and 200μL DMSO was added to each well and the absorbance was measured on an ELISA plate reader with a test wavelength of 570 nm and a reference wavelength of 630 nm to obtain sample signal.

[0132] To test whether Homspera® may induce proliferation directly or act to facilitate growth-factor driven proliferation, Homspera® was tested at various concentrations (within the range of 0.01-10μM) under varying growth conditions (serum-free or serum containing) for defined periods of time (24, 48 or 72 hrs) under serum-starved (0.5% FBS) or serum containing conditions (2.5% vs. 5% vs. 10% FBS), respectively. To determine the optimal concentration of serum, MTT assays were performed on fibroblasts grown in media containing 0.5%, 2.5%, 5% or 10% FBS.

These studies showed that normal foreskin fibroblasts survive in serum-starved conditions (containing 0.5% FBS) for 5 days and can be propagated in media containing 5% FBS while achieving maximal growth in 4 days. In each of these experiments, the mean optical density (OD) was representative of eight replicates.

[0133] To establish the relationship between the number of viable cells and OD (derived from the MTT assay), cells were seeded in various amounts (2,000-200,000 cells/well) and subjected to an MTT assay. Mean OD was calculated from eight replicates. Graphical analysis (OD vs. number of viable cells) revealed that saturation occurs between 0.7-0.8 OD units at a cell density between 30,000- 40,000 cells/well. Growth curves generated by seeding 2000 cells/well indicate this occurs within 4-5 days of growth. Hence, all further experiments were performed within this time frame, so as to expose cells to Homspera® within their proliferative phase of growth.

[0134] One group of 10μM Homspera®-treated fibroblasts, was also exposed to 10 μM Spantide I, a neurokinin-1 receptor antagonist. *See*, Hazlett *et al.*, 2007, *Investigative Ophthalmology Visual Sci.* 48: 797-807.

[0135] Experiments were conducted with Homspera® as follows: normal foreskin fibroblasts were seeded in a 96 well plate using IMDM (media) containing 0.5% FBS. The following day, these serum-starved cells were treated with various amounts of Homspera® or Homspera® + antagonist-(Spantide I) for a period of 1 or 3 days. Cells were pretreated with Homspera® in serum free media (0.5% FBS) for 3 hours. Spantide I was added 1-hour prior to the addition of Homspera® in the 10μM-Homspera®-treated group treated with Spantide I. Cells were then re-stimulated with serum (5% FBS) or not (0.5% FBS) while maintaining the presence of Homspera® and/or Spantide I. MTT assays were performed after 1 and 3 days of treatment with Homspera® . Three independent experiments (n=3) were performed and mean OD was represented as average of eight replicates. One experiment had a lower starting number of cells and was excluded from the analysis. Hence, the following analysis is representative of two independent experiments (n=2) done in replicates of eight. Results are represented as % growth where mean OD of each sample is normalized to its control (Table 3).

7.18.2. Results

[0136] In cultures exposed to 5% FBS, Homspera® trends toward increasing proliferation after 1 day of exposure. Peak percentage growth (almost 143%) was seen

at 10 μM Homspera®, with 1μM Homspera® providing proliferation about 135% of control. At concentrations of 0.1 μM and less, growth was increased to about 115% of control (114.8% at 0.01 μM Homspera® concentration and 115.5% at 0.1 μM Homspera® concentration). Homspera® increased proliferation at 1-day post-treatment in a dose-dependent manner when cultures were exposed to 5% FBS.

[0137] In cultures exposed to 0.5% FBS, treatment with increasing concentrations of Homspera® trends toward increasing proliferation after 3 days of treatment. No effect on proliferation was observed at 1-day post-exposure for cultures exposed to 0.5% FBS.

Table 3. Percentage growth of fibroblasts normalized to control.

Sample	Days of treatment	0.5% FBS		5% FBS	
		% growth	Std dev	% growth	Std dev
Vehicle control	1 day	100.0	0.0	100.0	0.0
0.01 μM Homspera®		86.1	12.8	114.8	3.6[1]
0.1 μM Homspera®		86.0	3.4	115.5	10.9[2]
1 μM Homspera®		85.0	5.9	134.7	19.9[3]
10 μM Homspera®		82.2	8.8	142.8	34.4[4]
1 μM Homspera® + 10 μM Spantide I		79.4	12.9	120.4	20.6[5]
Vehicle control	3 days	100.0	0.0	100.0	0.0
0.01 μM Homspera®		107.4	6.3	106.4	6.8
0.1 μM Homspera®		103.4	10.1	105.4	3.2
1 μM Homspera®		106.7	4.6	102.6	0.6
10 μM Homspera®		118.3	7.8	97.3	1.5
1 μM Homspera® + 10 μM Spantide		114.5	2.6	87.2	6.1

[1] 1-tail P-value compared to vehicle control = 0.177497
[2] 1-tail P-value compared to vehicle control = 0.261254
[3] 1-tail P-value compared to vehicle control = 0.028291
[4] 1-tail P-value compared to vehicle control = 0.118126
[5] 1-tail P-value compared to vehicle control = 0.08662

7.18.3. Conclusion

[0138] The effects of Homspera® on human dermal fibroblasts were evaluated in both "serum-starved" (0.5% FBS) and serum-exposed (5% FBS) conditions. An increasing proliferative effect was observed in cultures treated with Homspera® and exposed to 5% FBS at 1-day post-treatment. At 1-day post treatment, cultures exposed to 1μM Homspera® and 5% FBS had statistically significant ($P<0.05$) increases in proliferation as determined by MTT assay. Other groups in this series (5% FBS at 1 day of exposure) exhibited an increase in proliferation as well (Table 3). This proliferative effect was less pronounced in cultures exposed to 5% FBS and treated with Homspera® for 3 days. An increasing proliferative effect was also observed in cultures treated with Homspera® and exposed to serum-started (0.5% FBS) conditions at 3-days post-treatment. Thus, Homspera® could have a short-term (about 1-day) effect on the proliferation of human dermal fibroblasts cultured in 5% FBS and a longer-term (about 3 day) effect on the proliferation of human dermal fibroblasts cultured in 0.5% FBS as determined by MTT assay.

CLAIMS:

1. A topical composition comprising a substance P analog in a cosmetically effective amount wherein said substance P analog is according to Formula (I):

$$Z_1\text{-}Xaa^1\text{-}Xaa^2\text{-}Xaa^3\text{-}Xaa^4\text{-}Xaa^5\text{-}Xaa^6\text{-}Xaa^7\text{-}Xaa^8\text{-}Xaa^9\text{-}Xaa^{10}\text{-}Xaa^{11}\text{-}Z_2 \quad (I)$$

or a pharmaceutically acceptable salt thereof, wherein:

Xaa^1 is Arg, Lys, 6-N methyllysine, or (6-N, 6-N) dimethyllysine;

Xaa^2 is Pro or Ala;

Xaa^3 is Lys, Arg, 6-N-methyllysine, or (6-N, 6-N) dimethyllysine;

Xaa^4 is Pro or Ala;

Xaa^5 is Gln or Asn;

Xaa^6 is Gln or Asn;

Xaa^7 is Tyr, Phe or Phe substituted with chlorine at position 2, 3 or 4;

Xaa^8 is Tyr, Phe, or Phe substituted with chlorine at position 2, 3 or 4;

Xaa^9 is Gly, Pro, Ala or N-methylglycine;

Xaa^{10} is Leu, Val, Ile, Norleucine, Met, Met sulfoxide, Met sulfone, N-methylleucine, or N-methylvaline;

Xaa^{11} is Met, Met sulfoxide, Met sulfone or Norleucine;

Z_1 is R_2N– or RC(O)NR–;

Z_2 is –C(O)NR_2 or –C(O)OR or a salt thereof;

each R is independently R is ——H, (C_1 -C_6) alkyl, (C_1 -C_6) alkenyl, (C_1 -C_6) alkynyl, (C_5 -C_{20}) aryl, (C_6 -C_{26}) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl; and

each "—" between residues Xaa^1 through Xaa^{11} independently designates an amide linkage, a substitute amide linkage or an isostere of an amide.

2. The composition of claim 1 wherein

Xaa^1 is Arg;

Xaa^2 is Pro;

Xaa^3 is Lys;

Xaa^4 is Pro;

Xaa^5 is Gln;

Xaa^6 is Gln;

Xaa^7 is Phe or Phe substituted with chlorine at position 4;

Xaa^8 is Phe, or Phe substituted with chlorine at position 4;

Xaa^9 is Gly, Pro or N-methylglycine;

Xaa^{10} is Leu; and

Xaa^{11} is Met, Met sulfoxide, Met sulfone or Norleucine.

3. The composition of claim 1 wherein the "—" between residues Xaa^1 through Xaa^{11} designates

–C(O)NH–;

Z_1 is H_2N–; and Z_2 is $–C(O)NH_2$.

4. The composition of claim 1 wherein the substance P analog is selected from the group consisting of:

RPKPQQFFGLM	(SEQ ID NO.: 1);
RPKPQQFFMeGlyLM(O_2)	(SEQ ID NO.: 2);
RPKPQQFFGLM(O_2)	(SEQ ID NO.: 3);
RPKPQQFFMeGlyLM(O)	(SEQ ID NO.: 4);
RPKPQQFFGLNle	(SEQ ID NO.: 5);

RPKPQQFFPLM (SEQ ID NO.: 6);

RPKPQQFFMeGlyLM (SEQ ID NO.: 7);

RPKPQQFTGLM (SEQ ID NO.: 8);

RPKPQQF(4-Cl)F(4-Cl)GLM (SEQ ID NO.: 9); or

RPKPQQFFGLM(O) (SEQ ID NO.: 10).

5. The composition of claim 1 wherein the substance P analog is

Z_1—RPKPQQFFMeGlyLM(O_2)—Z_2;

wherein

Z_1 is NH_2 and Z_2 is $C(O)NH_2$.

6. The composition of claim 1 wherein the substance P analog is of about 0.001% to about 5%.

7. The composition of claim 1 further comprising water, caprylic/capric triglyceride, coco-caprylate/caprate, hexadecyl D-glucoside, octadecyl D-glucose, glycerin, xanthan gum and benzyl alcohol.

8. The composition of claim 1 that is a cream.

9. The composition of claim 1 that is an ointment.

10. The composition of claim 1 that is a lotion.

11. The composition of claim 1 that is a gel.

12. The composition of claim1 that is a salve or balm.

13. The composition of claim 1 that is a liquid.

14. The composition of claim 1 that is an emulsion.

15. The composition of claim 1 that is an aerosol.

16. The composition of claim 1 that is atomized.

17. The composition of claim 1 that is a bandage.

18. The composition of claim 1 that is a tape.

19. The composition of claim 1 that is a patch.

20. The composition of claim1 that is bath beads.

21. The composition of claim 1 that is shower gel.

22. The composition of claim 1 further comprising alpha hydroxyl acid.

23. The composition of claim 1 further comprising sulfur compounds.

24. The composition of claim 1 further comprising sun block.

25. The composition of claim 1 that ameliorates or improves the appearance of dry skin, severe dry skin, skin flakiness, wrinkles, blemished skin, inflammatory dermatosies or skin atrophy.

26. The composition of claim 1 that is a rubefacient.

27. A method of improving the texture or appearance of skin in a human, said method comprising applying a composition comprising a cosmetically effective amount of a substance P analog according to formula (I):

Z_1-Xaa^1-Xaa^2-Xaa^3-Xaa^4-Xaa^5-Xaa^6-Xaa^7-Xaa^8-Xaa^9-Xaa^{10}-Xaa^{11}-Z_2 (I)

or a pharmaceutically acceptable salt thereof, wherein:

Xaa^1 is Arg, Lys, 6-N methyllysine, or (6-N, 6-N) dimethyllysine;

Xaa^2 is Pro or Ala;

Xaa^3 is Lys, Arg, 6-N-methyllysine, or (6-N, 6-N) dimethyllysine;

Xaa^4 is Pro or Ala;

Xaa^5 is Gln or Asn;

Xaa^6 is Gln or Asn;

Xaa^7 is Tyr, Phe or Phe substituted with chlorine at position 2, 3 or 4;

Xaa^8 is Tyr, Phe, or Phe substituted with chlorine at position 2, 3 or 4;

Xaa^9 is Gly, Pro, Ala or N-methylglycine;

Xaa^{10} is Leu, Val, Ile, Norleucine, Met, Met sulfoxide, Met sulfone, N-methylleucine, or N-methylvaline;

Xaa^{11} is Met, Met sulfoxide, Met sulfone, or Norleucine;

Z_1 is R_2N- or $RC(O)NR-$;

Z_2 is $-C(O)NR_2$ or $-C(O)OR$ or a salt thereof;

each R is independently R is —H, (C_1 -C_6) alkyl, (C_1 -C_6) alkenyl, (C_1 -C_6) alkynyl, (C_5 -C_{20}) aryl, (C_6 -C_{26}) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl; and

each "—" between residues Xaa^1 through Xaa^{11} independently designates an amide linkage, a substitute amide linkage or an isostere of an amide.

28. The method of claim 27 wherein:

Xaa^1 is Arg;

Xaa^2 is Pro;

Xaa^3 is Lys;

Xaa^4 is Pro;

Xaa^5 is Gln;

Xaa^6 is Gln;

Xaa^7 is Phe or Phe substituted with chlorine at position 4;

Xaa^8 is Phe, or Phe substituted with chlorine at position 4;

Xaa^9 is Gly, Pro or N-methylglycine;

Xaa^{10} is Leu; and

Xaa^{11} is Met, Met sulfoxide, Met sulfone or Norleucine.

29. The method of claim 27 wherein the "—" between residues Xaa^1 through Xaa^{11} designates

$-C(O)NH-$;

Z_1 is H_2N–; and Z_2 is –$C(O)NH_2$

30. The method of claim 27 wherein the substance P analog is selected from the group consisting of:

RPKPQQFFGLM	(SEQ ID NO.: 1);
RPKPQQFFMeGlyLM(O_2)	(SEQ ID NO.: 2);
RPKPQQFFGLM(O_2)	(SEQ ID NO.: 3);
RPKPQQFFMeGlyLM(O)	(SEQ ID NO.: 4);
RPKPQQFFGLNle	(SEQ ID NO.: 5);
RPKPQQFFPLM	(SEQ ID NO.: 6);
RPKPQQFFMeGlyLM	(SEQ ID NO.: 7);
RPKPQQFTGLM	(SEQ ID NO.: 8);
RPKPQQF(4-Cl)F(4-Cl)GLM	(SEQ ID NO.: 9); or
RPKPQQFFGLM(O)	(SEQ ID NO.: 10).

31. The method of claim 27 wherein the substance P analog is

Z_1–RPKPQQFFMeGlyLM(O_2)–Z_2;

wherein;

Z_1 is NH_2 and Z_2 is $C(O)NH_2$.

32. The method of claim 27 wherein the substance P analog is about 0.001% to about 1%.

33. The method of claim 27 further comprising water, caprylic/capric triglyceride, coco-caprylate/caprate, hexadecyl D-glucoside, octadecyl D-glucose, glycerin, xanthan gum and benzyl alcohol.

34. The method of claim 27 wherein the composition is a cream.

35. The method of claim 27 wherein the composition is an ointment.

36. The method of claim 27 wherein the composition is a lotion.

37. The method of claim 27 wherein the composition is a gel.

38. The method of claim 27 wherein the composition is a salve or balm.

39. The method of claim 27 wherein the composition is a liquid.

40. The method of claim 27 wherein the composition is an emulsion.

41. The method of claim 27 wherein the composition is an aerosol.

42. The method of claim 27 wherein the composition is atomized.

43. The method of claim 27 wherein the composition is a bandage.

44. The method of claim 27 wherein the composition is a tape.

45. The method of claim 27 wherein the composition is a patch.

46. The method of claim 27 wherein the composition further comprises alpha hydroxyl acid.

47. The method of claim 27 wherein the composition further comprises sulfur compounds.

48. The method of claim 27 wherein the composition further comprises sun block.

49. The method of claim 27 that ameliorates or improves the appearance of dry skin, severe dry skin, skin flakiness, wrinkles, blemished skin, inflammatory dermatoses, or skin atrophy.