



(43) International Publication Date
7 January 2016 (07.01.2016)

(10) International Publication Number
WO 2016/003505 A1

(51) International Patent Classification:

A61K 8/64 (2006.01) *A61Q 19/08* (2006.01)
A61Q 7/00 (2006.01)

(21) International Application Number:

PCT/US2015/022382

(22) International Filing Date:

25 March 2015 (25.03.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

14/321,821 2 July 2014 (02.07.2014) US

(71) Applicant: GEOFFREY BROOKS CONSULTANTS, LLC [—/US]; P.O. Box 33144, Reno, NV 89523-6812 (US).

(72) Inventors: BANHAM, Andrew, P.; 3116 Mohave Way, Jacksonville, FL 32259 (US). BHATNAGAR, Rajendra, S.; 173 Los Robles Drive, Burlingame, CA 90410 (US). BROOKS, Geoffrey, J.; 1865 Dove Mountain Court, Reno, NV 89523 (US).

(74) Agent: WOLF, Nicholas, J.; 1340 Whisper Rock Way, Reno, NV 89523 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

— with international search report (Art. 21(3))
— with sequence listing part of description (Rule 5.2(a))

(54) Title: PEPTIDE-BASED COMPOSITIONS AND METHODS OF USE

(57) Abstract: The present invention relates to skin care compositions containing a small peptide mimic of TGF- β and to methods of using such compositions to manage the health and condition of skin and scalp. More preferably, the skin care compositions contain a safe and effective amount of a peptide mimic for TGF- β , derivatives of a peptide mimic for TGF- β , and mixtures thereof; a safe and effective amount of at least one skin care active; and a dermatologically acceptable carrier.



WO 2016/003505 A1

PATENT COOPERATION TREATY APPLICATION
FOR
PEPTIDE-BASED COMPOSITIONS AND METHODS OF USE

INVENTOR(S):

Geoffrey J. Brooks
Reno, NV

Rajendra S. Bhatnagar
Burlingame, CA

Andrew P. Banham
Jacksonville, FL

Prepared by:
Wolf Patent Services LLC
1340 Whisper Rock Way
Reno, Nevada 89523
775-200-5533

PEPTIDE-BASED COMPOSITIONS AND METHODS OF USE**BRIEF DESCRIPTION OF THE INVENTION**

[0001] The present invention is directed to treating and to maintaining optimal skin health and appearance and, more particularly, to small, synthetic transforming growth factor beta (TGF- β) mimics having skin moisturizing and anti-redness activity, to topical compositions including the TGF- β mimics, and to methods of use thereof.

CROSS-REFERENCES TO RELATED APPLICATIONS

[0002] This application uses TGF- β mimics first disclosed by the same inventor in U.S. Pat. No. 5,661,127, issued August 26, 1997 and U.S. Pat. No. 5,780,436, issued July 14, 1998. Additionally, methods of their manufacture; TGF- β -R1 binding testing; human safety testing, in vivo efficacy testing for effectiveness in up-regulating dermal cells; and TGF- β wound healing conditions are described by the same inventor in U.S. Pat. No. 6,509,318, issued January 21, 2003 and U.S. Pat. No. 6,631,912, issued October 28, 2003.

STATEMENTS AS TO THE RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0003] Not applicable.

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK.

[0004] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing file entitled, GB0001USUTILSEQLIST.txt, was created on

June 25, 2014 and is 3.15 KB in size. The information in electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0005] Although the skin of an infant is initially soft, taut, and smooth, the skin of most individuals becomes increasingly more leathery, saggy and wrinkled with age. According to skin experts, these undesirable features are manifested as a result of two primary factors, intrinsic and extrinsic. Intrinsic factors include chronological aging and other biochemical changes, which disrupt the optimal homeostatic conditions for healthy skin and are thought to be inevitable as a result. Conversely, extrinsic factors are those originating externally or that are introduced to the body. Extrinsic factors include environmental pollution, wind, low humidity, ultraviolet radiation (from sun exposure), smoking, poor nutrition, and soaps. In any case, both factors combine to give rise to visible signs of aging skin including dryness, thinning, discoloration, sagging, wrinkles, and loss of hair. As a result, aged skin progressively loses its overall youthful, healthy character and coloration.

[0006] From a histological perspective, both visible signs of aging skin and damaged skin itself are a result of fewer numbers of healthy cells and blood vessels that regulate and maintain otherwise normal, healthy, youthful skin. And, although the overall measure of the damaged skin cells for a given individual is very much dependent upon the specifics surrounding his exposure to extrinsic factors, the skin for all persons realizes both decreased cell production and turnover with age. In turn, all of these factors lead not only to a reduction in normal protein synthesis in the tissues of the skin but also to an increase in proteolysis. Specifically, collagen fibers become fragmented, thickened, and more soluble. Elastic fibers also

experience fragmentation and may exhibit progressive cross-linkage and calcification. Moreover, there is a flattening of the dermal-epidermal junction which results in reduced flexibility and loss of mechanical strength normally found in younger healthier skin. See, for example, Oikarinen, "The Aging of Skin: Chronoaging Versus Photoaging," *Photodermatol. Photoimmunol. PhotoMed.*, vol. 7, pp. 3-4, 1990, which is incorporated by reference in its entirety.

Consequently, ageing and damaged skin exhibits increased inelasticity, fragmentation, and collagen bundle fragility largely as a result of insufficient and/or deficient cell function.

[0007] Currently, consumers have a wide variety of options - ranging from nonsurgical to surgical - aimed at combating the unwanted effects of aging skin and for furnishing a more youthful appearance. Nonsurgical methods include the topical use of moisturizers and keratolytic agents, cleansers, sunscreens and sunblocks, antioxidants, serums, exfoliants, and makeup. Surgical methods include chemical peels, the use of botulinum toxin or fillers (e.g., bovine collagen, silicone, and hyaluronic acid), and plastic or laser surgery. However, although the majority of the aforementioned alternatives provide at least one skin-care benefit, they are not without their drawbacks as well.

[0008] For example, many topical skin treatments contain ingredients that can clog pores, promote acne, trigger allergies, cause irritation, and block natural water evaporation. Specifically, although retinoid therapy has shown promise in the treatment of skin aging maladies, certain retinoids such as tretinoin and tazarotene, have been shown to cause burning, scaling, and dermatitis thereby limiting their acceptance by many patients. And because alpha hydroxy acids, a common additive to numerous skin care products, work mainly as an exfoliant whereby outer stratum epidermal cells are prematurely sloughed off, the resulting newly

exposed cells are susceptible to irritation and sun sensitivity. Even ingredients as seemingly benign as emollients and moisturizers (e.g., mineral oil, petrolatum and lanolin), have been known to cause burning, stinging, redness, or irritation in some cases. Lastly, some commercially available compositions contain ingredients that are supported by pseudo-scientific claims, which are misleading or unsupported by scientific evidence, and are in fact hazardous to the skin.

[0009] Alternatively, although chemical peels help to improve the appearance of aging and dull skin by stimulating cell turnover and cell function in the layers just below the treated top layer of the skin, because acids are commonly used during the procedure, the patient may experience a burning sensation. And, depending on the compound used, recovery times may take up to four weeks during which the skin may ooze and scab. Finally, although not extremely common, the procedure can cause infection, permanent scarring or discoloration, and excessively dry skin that peels too often.

[0010] Therefore, it is readily apparent that there is still a significant need for skin care compositions which not only improve and maintain the health and physical appearance of the skin but are also safe, stable, long-lasting, and effective in treating the appearance of wrinkles, fine lines, pores, discolorations, sallowness, and other forms of undesirable skin surface textures.

[0011] Growth factors are substances, such as poly-peptide hormones, which affect the growth of defined populations of animal cells in vivo or in vitro, but which are not nutrient substances. Proteins involved in the growth and differentiation of tissues may promote or inhibit growth, and promote or inhibit differentiation, and thus the general term "growth factor" includes cytokines and trophic factors.

[0012] Growth factors, typically, are polypeptides ranging in molecular weights from 5,000 to 50,000 daltons. Based on structural similarities, growth factors are categorized into families which include: insulin-like growth factors (IGFs), platelet-derived growth factors (PDGFs), fibroblast growth factors (FGFs), epidermal growth factors (EGFs), nerve growth factors (NGFs), and transforming growth factors type-beta (TGF- β s).

[0013] Transforming growth factor- β s were originally named for their ability to transform fibroblasts to cells capable of anchorage-independent growth. However, despite the name, TGF- β s are multifunctional growth factors that are required for the normal development, growth, and differentiation of various epithelial, endothelial, and mesenchymal cells. As with other cytokines, the specific effect of TGF- β s depend on the particular cell type and its surrounding environment.

[0014] On account of the wide applicability of TGF- β s in clinical therapies, they have been the focus of much research. Although much of the research involved in vitro uses, recent in vivo studies have confirmed a few of the more promising in vitro effects. As a consequence, some of the researched clinical uses for TGF- β s include the stimulation of angiogenesis, the formation of granulation tissue associated with wound healing, and the formation of bone and cartilage.

[0015] Nevertheless, although TGF- β s have been found to be useful in a number of therapeutic, clinical, research, diagnostic, and drug design applications, as previously mentioned, they are typically large. Specifically, the natural members of the transforming growth factor- β family range upwards of 25 kD molecular mass. As a result, certain therapeutic uses of TGF- β s - such as a topical application, whereby its high molecular weight (MW=44,000)

precludes its penetration deep into the skin to living cells - may be limited. In addition to skin penetration constraints, the TGF- β s' delicate molecular structures are unstable at higher temperatures and in some cosmetic vehicles.

[0016] Accordingly, in an attempt to circumvent TGF- β s' limitations for managing optimal skin health and other related applications, small, linear peptide mimics of TGF- β s were engineered by Bhatnagar (U.S. Pat. No. 5,661,127, U.S. Pat. No. 5,780,436, & U.S. Pat. No. 6,638,912) and were readily synthesized by techniques known in the art. The novel compounds have been found to mimic the broad range of activities of TGF- β 1 in various cell types, in particular both due to the peptides' ability to maintain a stable β -bend under physiological conditions and to their ability to penetrate deep into the lower levels of the skin.

[0017] It has now been discovered that topical compositions containing TGF- β mimics, alone and in composition with select cosmetic actives, provide benefits for optimizing skin appearance and health previously unrecognized in the art. Specifically, such compositions normalize natural hydration levels in dry skin and eliminate signs of aging, including visible and/or tactile discontinuities in skin texture, including fine lines, wrinkles, and skin-sagging by inducing normal function in damaged and non-functional cells.

[0018] In particular, the heptapeptide TGF- β mimic, A-N-V-A-E-N-A (SEQ ID NO: 1), termed "cytomodulin," has been examined and tested as an ingredient in compositions with the potential for improving the condition of skin upon application; a cosmetic grade cytomodulin was first synthesized according to US Patent 5,661,127 and subsequently tested to ensure both its efficacy and safety as a topically administered ingredient. Test results proved cytomodulin to

be completely non-toxic. And consumer use testing provided excellent results for improved skin appearance, texture, and wrinkle-reduction.

SUMMARY OF THE INVENTION

[0019] The present invention relates to a composition containing a safe and effective amount of one or more TGF- β mimics and/or derivatives of a TGF- β mimic; at least one additional skin care active; and a dermatologically acceptable carrier.

[0020] The present invention also relates to methods of using such compositions to treat and/or maintain the condition of human skin and scalp. Said methods generally comprise the step of topically applying the composition to the skin or scalp, a safe and effective amount of such compositions.

[0021] Preferred embodiments include the additional skin care actives glycerin or propylene glycol.

[0022] These and other features, aspects, and advantages of the present invention will become evident to those skilled in the art from a reading of the present disclosure.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING

[0023] Not applicable.

DETAILED DESCRIPTION OF THE INVENTION

[0024] While the specification concludes with the claims particularly telling and distinctly claiming the invention, it is believed that the present invention will be better

understood from the following description. All publications cited herein are hereby incorporated by reference in their entirety.

[0025] The term "skin," as used herein, refers to the mammalian organ system known as the integumentary system, which includes, but is not limited to, skin, scalp, lips, hair, nails, cuticles, etc.

[0026] The term "topical application," as used herein, means to apply or spread the compositions of the present invention onto the surface of the skin.

[0027] The term "dermatologically acceptable," as used herein, means that the compositions or compositions thereof so described are suitable for use in contact with mammalian skin without undue toxicity, incompatibility, instability, allergic response, and the like.

[0028] The term "safe and effective amount," as used herein, means an amount of a compound or composition sufficient to significantly induce a positive benefit, preferably a positive skin appearance or feel benefit, including independently or in combinations the benefits disclosed herein, but low enough to avoid serious side effects, i.e., to provide a reasonable benefit to risk ratio, within the scope of sound judgment of the skilled artisan.

[0029] The term "sagging," as used herein, means the laxity, droopiness, or like condition of the skin that occurs as a result of damage to, reduction in, alterations to, and/or abnormalities in dermal elastin.

[0030] The terms "smoothing" and "softening," as used herein, mean altering the surface of the skin such that tactile feel is improved.

[0031] "Signs of aging," as used herein, include, but are not limited to, all outward visibility and tactilely perceptible manifestations as well as any other macro or micro effects due to skin aging. Such signs may be induced or caused by intrinsic factors or extrinsic factors. These signs may result from processes which include, but are not limited to, the development of textural discontinuities such as wrinkles, skin lines, crevices, bumps, large pores (e.g., those associated with adnexal structures such as sweat gland ducts, sebaceous glands, or hair follicles), or unevenness or roughness, loss of skin elasticity (loss and/or inactivation of functional elastin), sagging (including puffiness in the eye area and jowls), loss of skin firmness, loss of skin tightness, loss of skin turgor, discoloration (including undereye dark circles), blotching, sallowness, hyperpigmented skin regions such as age spots and freckles, keratosis, abnormal differentiation, hyperkeratinization, elastosis, collagen breakdown, and other histological changes in the skin.

[0032] The term "amino acid" (AA), as used herein, means any of the natural amino acids from the group of twenty (20) amino acids known to link together via peptide bonds to form proteins. These natural amino acids have the general formula ($\text{NH}_2\text{CHR}\text{COOH}$) comprising at least one amino group ($-\text{NH}_2$) and at least one carboxyl group ($-\text{COOH}$) bound to a single carbon atom (α -carbon). In addition, the α -carbon of most amino acids harbors a side chain (R) and a single hydrogen atom (H), except in the case of glycine where R is a hydrogen atom.

[0033] The term "bioactive sequence" or "biologically active sequence," as used herein, means an amino acid sequence which has a specific biological function, here the reactivation of TGF- β signaling, resulting in both tissue repair and normal tissue homeostasis.

[0034] The term "functional peptide" or "functional peptide moiety," as used herein means a peptide moiety comprising a bioactive sequence, hence a peptide moiety exhibiting a biological activity.

[0035] The compositions of the present invention are used for prophylactically and/or therapeutically managing skin condition. Prophylactically managing a skin condition, as used herein, includes delaying, minimizing and/or preventing visible and/or tactile discontinuities in skin (e.g., textural irregularities in the skin, which may be detected visually or by touch), including signs of aging. Therapeutically managing skin condition, as used herein, includes ameliorating, e.g., diminishing, minimizing and/or effacing, discontinuities in the skin, including signs of aging.

[0036] The compositions of the present invention can comprise, consist essentially of, or consist of, the components of the present invention as well as other ingredients described herein. As used herein, "consisting essentially of" means that the composition or component may include additional ingredients, but only if the additional ingredients do not materially alter the basic and novel characteristics of the claimed compositions or methods.

[0037] Some of the compositions of the present invention may also provide additional benefits including stability, reduction of skin irritation, anti-inflammatory activity, and desirable aesthetics.

COMPONENTS OF THE COMPOSITIONS

I. TGF- β Mimics and Their Derivatives

[0038] The present invention relates to the use of amino acid sequences as bioactive sequences in a functional peptide to reactivate TGF- β signaling in damaged cells, resulting in both tissue repair and normal tissue homeostasis.

[0039] The inventors have found that these amino acid sequences mimic the function of transforming growth factor beta (TGF- β) in cells by reactivating TGF- β signaling even in the absence of TGF- β Type II receptors due in part to the sequences' ability to maintain a stable β -bend under physiological conditions

[0040] The compositions of the present invention contain a safe and effective amount of at least one TGF- β mimic bioactive, selected from TGF- β mimics, analogs of TGF- β mimics, derivatives of TGF- β mimics, and mixtures thereof.

[0041] The TGF- β mimics may have the following initial amino acid sequence, AA_i-AA_{i+1}-AA_{i+2} wherein AA_i is alanine, asparagine, or leucine, AA_{i+1} is valine or isoleucine, and AA_{i+2} is alanine. This sequence is either immediately followed by or has proximal thereto an amino acid with a carbonyl containing side-chain. Because the amino acid residue with a carbonyl containing side-chain does not necessarily have to be immediately followed by, that is adjacent to AA_{i+2}, it is referred to as AA_{i+n} where n is an integer equal to or greater than three. If n is greater than 3, then n-3 ("n minus 3") amino acid residues would be between AA_{i+2} and AA_{i+n} peptide sequence.

[0042] In one embodiment of TGF- β mimics for the invention, n equals three and the amino acid residue with the carbonyl containing side-chain is thus AA_{i+3}. This results in peptides having the following sequence: AA_i-AA_{i+1}-AA_{i+2}-AA_{i+3} wherein AA_i, AA_{i+1}, and AA_{i+2} are as above and AA_{i+3} is glutamic acid, aspartic acid, glutamine, or asparagine. The original peptide

with TGF- β activity and an especially preferred embodiment of the present invention, named cytomodulin, A-N-V-A-E-N-A (SEQ ID NO: 1) is of this class. Here, $AA_i-AA_{i+1}-AA_{i+2}-AA_{i+3}$ corresponds to the second through fifth residues from the N-terminus of cytomodulin, -N-V-A-E-. Other preferred embodiments are the peptides, L-I-A-E-A-K (SEQ ID NO: 2) and L-I-A-E-A-A (SEQ ID NO: 11). In these examples, $AA_i-AA_{i+1}-AA_{i+2}-AA_{i+3}$ corresponds to the first four residues of the peptide, L-I-A-E-.

[0043] In another embodiment, n equals four and the amino acid residue with the carbonyl containing side-chain is thus AA_{i+4} . The sequence of the peptides of this class is $AA_i-AA_{i+1}-AA_{i+2}-AA_{i+3}-AA_{i+4}$. In this series, AA_i , AA_{i+1} , and AA_{i+2} , are as above, AA_{i+3} is either proline or glycine, and AA_{i+4} is glutamic acid, aspartic acid, glutamine, or asparagine. A preferred embodiment of this class is L-I-A-G-E-G (SEQ ID NO: 14). An especially preferred embodiment is the peptide, L-I-A-P-E-A (SEQ ID NO: 3). In both examples, the first five N-terminal amino acids correspond to $AA_i-AA_{i+1}-AA_{i+2}-AA_{i+3}-AA_{i+4}$.

[0044] In yet another embodiment of the present invention, n equals five and the amino acid residue with the carbonyl containing side-chain is thus AA_{i+5} . The sequence of the peptides of this class is $AA_i-AA_{i+1}-AA_{i+2}-AA_{i+3}-AA_{i+4}-AA_{i+5}$. In this series, AA_i , AA_{i+1} , and AA_{i+2} , are as above, AA_{i+3} and AA_{i+4} are glycine, and AA_{i+5} is glutamic acid, aspartic acid, glutamine, or asparagine. An especially preferred member of this series is the peptide, L-I-A-G-G-E (SEQ ID NO: 13). In this particular example, there is a one to one correspondence between SEQ ID NO: 3 and the sequence $AA_i-AA_{i+1}-AA_{i+2}-AA_{i+3}-AA_{i+4}-AA_{i+5}$.

[0045] The peptides of the present invention, can be synthesized by various suitable methods that are well known in the art, preferably by solid phase synthesis, manual or

automated, as first developed by Merrifield and described by Stewart et al. in *Solid Phase Peptide Synthesis* (1984). Chemical synthesis joins the amino acids in the predetermined sequence starting at the C-terminus. Basic solid phase methods require coupling the C-terminal protected α -amino acid to a suitable insoluble resin support. Amino acids for synthesis require protection on the α -amino group to ensure proper peptide bond formation with the preceding residue (or resin support). Following completion of the condensation reaction at the carboxyl end, the α -amino protecting group is removed to allow the addition of the next residue. Several classes of α -protecting groups have been described, see Stewart et al. in *Solid Phase Peptide Synthesis* (1984), with the acid labile, urethan-based tertiary-butyloxycarbonyl (Boc) being the historically preferred. Other protecting groups, and the related chemical strategies, may be used, including the base labile 9-fluorenylmethyloxycarbonyl (Fmoc). Also, the reactive amino acid side-chain functional groups require blocking until the synthesis is completed. The complex array of functional blocking groups, along with the strategies and limitations to their use, have been reviewed by Bodansky in *Peptide Synthesis* (1976) and Stewart et al. in *Solid Phase Peptide Synthesis* (1984).

[0046] Solid phase synthesis is initiated by the coupling of the described C-terminal α -protected amino acid residue. Coupling requires activating agents, such as dicyclohexycarbodiimide (DCC) with or without 1-hydroxybenzo-triazole (HOBT), diisopropylcarbodiimide (DIIPC), or ethyldimethylamino-propylcarbodiimide (EDC). After coupling the C-terminal residue, the α -amino acid protected group is removed by trifluoroacetic acid (25% or greater) in dichloromethane in the case of the acid labile tertiary-butyloxycarbonyl (Boc) groups. A neutralizing step with triethylamine (10%) in dichloromethane recovers the free

amine (versus the salt). After the C-terminal residue is added to the resin, the cycle of deprotection, neutralization and coupling, with intermediate wash steps, is repeated in order to extend the protected peptide chain. Each protected amino acid is introduced in excess (three to five fold) with equimolar amounts of coupling reagent in suitable solvent. Finally, after the completely blocked peptide is assembled on the resin support, reagents are applied to cleave the peptide from the resin and to remove the side-chain blocking groups. Anhydrous hydrogen fluoride (HF) cleaves the acid labile tertiary-butyloxycarbonyl (Boc) chemistry groups. Several nucleophilic scavengers, such as dimethylsulfide and anisole, are included to avoid side reactions, especially on side-chain functional groups.

[0047] As first introduced in the present inventor's U.S. Pat. No. 5,780,436, which is hereby incorporated by reference in its entirety, using cytomodulin as a guide, two initial cytomodulin analogs, L-I-A-E-A-K (SEQ ID NO: 2) and L-I-A-P-E-A (SEQ ID NO: 3) were designed, synthesized, and tested. In both peptides, -V-A-, was replaced by -I-A- and the first two N-terminal amino acid sequence of cytomodulin was replaced with leucine. In SEQ ID NO: 2, glutamic acid is at position i+3 since it is the first side-chain after the β -bend structure. In SEQ ID NO: 3, proline is at position i+3. Since proline does not have a "side-chain," the glutamic acid was placed at position i+4. Both cytomodulin analogs, SEQ ID NO: 2 and SEQ ID NO: 3, displayed at least as much TGF- β like activity as cytomodulin.

[0048] Analogs of SEQ ID NO: 2 and SEQ ID NO: 3 were made to further probe the sequence requirements for TGF- β like activity. To that end, the following peptides were made:

L-(Aib)-A-E-A-K (SEQ ID NO: 4)

L-I-(Nme-A)-E-A-K (SEQ ID NO: 5)

L-(Abu)-A-E-A-K (SEQ ID NO: 6)

G-G-Q-I-A-N-I (SEQ ID NO: 7)

E-G-I-A-G-K (SEQ ID NO: 8)

L-I-A-D-A-K (SEQ ID NO: 9)

L-I-A-N-A-K (SEQ ID NO: 10)

L-I-A-E-A-A (SEQ ID NO: 11)

L-I-A-Q-A-K (SEQ ID NO: 12)

L-I-A-G-G-E (SEQ ID NO: 13)

L-I-A-G-E-G (SEQ ID NO: 14)

A-N-V-A-E-K (SEQ ID NO: 15) and

L-I-A-K-G-K (SEQ ID NO: 16).

Of the non-standard amino acids, Aib is α -amino isobutyric acid, Nme-A is N-methyl alanine, and Abu is α -amino butyric acid.

[0049] SEQ ID NOs 4-6, which are minor variants of SEQ ID NO: 2, mimicked the biological activities of TGF- β and cytomodulin. However, SEQ ID NOs: 7-8 did not display significant TGF- β activity. Alternatively, all peptides with the sequences represented by SEQ ID NOs: 9-16 mimicked at least one biological activity of TGF- β to some degree. As a result, the general model used for preparing peptides with TGF- β activity appears to work surprisingly well.

[0050] It is believed that slight amino acid modifications to the β -bend peptide sequences will not affect the peptides' ability to form stable β -bend structures. These modifications include techniques to confer resistance to enzymatic degradation such as adding

blocking groups to both the N- and C-terminal residues. Another method for preventing degradation is the use of unnatural amino acid substitutes in the peptide sequence. For example, N-methyl-alanine is often substituted for alanine and α -amino isobutyric acid and β -aminobutyric acid are substitutes for bulky hydrophobic amino acids. Yet another technique is replacing the L-amino acid residue in the peptide sequence with a D-amino acid counterpart. For example, an alanine may be replaced with a D-alanine.

[0051] Other derivatives are also considered to be encompassed by the TGF- β mimics in accordance with the present invention. Derivatives include derivatives of the TGF- β mimics and the substituted TGF- β mimics described herein. These derivatives include, inter alia, acyl-derivatives, which are TGF- β mimics substituted with one or more straight-chain or branched chain, long or short chain, saturated or unsaturated, substituted with a hydroxy, amino, amino acyl, sulfate, or sulfide group or unsubstituted having from 1 to 29 carbon atoms. N-acyl-derivatives include, but are not limited to, those acyl groups which can be derived from acetic acid, capric acid, lauric acid, myristic acid, octanoic acid, palmitic acid, stearic acid, behenic acid, linoleic acid, elaidic acid, 2-ethylhexanoic acid, coconut oil fatty acid, tallow fatty acid, hardened tallow fatty acid, palm kernel oil fatty acid, lanolin fatty acid, and the like. Preferable examples of the acyl group include an acetyl group, a palmitoyl group, an elaidoyl group, a myristyl group, a biotinyl group, and an octanoyl group. These acyl group may be substituted or unsubstituted. When substituted, they are preferably substituted with hydroxyl or sulfur containing groups such as, without limitation, SO_3H , SH , or S—S .

[0052] Both therapeutic and prophylactic compositions of this invention will include novel TGF- β mimics in concentrations that depend upon the effective doses required and

the modes of administration used. The TGF- β mimics and/or TGF- β mimic derivatives are preferably included in compositions in amounts from about $1 \times 10^{-6}\%$ to about 10%, more preferably from about $1 \times 10^{-6}\%$ to about 0.1%, even more preferably from about $1 \times 10^{-5}\%$ to about 0.01%, by weight of the composition.

II. Additional Skin Care Actives

[0053] The compositions of the present invention generally contain at least one additional ingredient in addition to the TGF- β mimics, their analogs, their derivatives, and/or mixtures thereof. Moreover, the compositions of the present invention may contain a multitude of additional ingredients.

[0054] For example, the compositions of the present invention may include various other and additional ingredients, which may be active, functional, and conventionally used in cosmetic, personal care, or topical/transdermal products or otherwise. Naturally, a decision to include an additional ingredient or additional ingredients depends on the specific application and product formulation for the composition.

[0055] Thus, the compositions of the present invention may include one or more additional ingredients, which provide some benefit to the object of the composition. Such additional ingredients may include one or more substances, without limitations, such as: cleaning agents, hair conditioning agents, skin conditioning agents, hair styling agents, antidandruff agents, hair growth promoters, perfumes, sunscreen and/or sunblock compounds, pigments, moisturizers, film formers, hair dyes, make-up agents, detergents, pharmaceuticals, thickening agents, emulsifiers, humectants, emollients, antiseptic agents, deodorant actives, dermatologically acceptable carriers, and surfactants.

[0056] In a preferred embodiment, where the composition is to be in contact with human skin, the additional ingredients should be suitable for application to human skin, that is, when incorporated into the composition they are suitable for use in contact with human skin without undue toxicity, incompatibility, instability, allergic response, and the like within the scope of sound medical judgment. The *CFTA Cosmetic Ingredient Handbook*, Ninth Edition (2002) describes a wide variety of non-limiting cosmetic and pharmaceutical ingredients commonly used in the skin care industry, which are suitable for use as additional ingredients in the compositions of the present invention. Non-limiting examples of these additional ingredient classes include: abrasives, adsorbents, aesthetic components such as fragrances, pigments, colorings/colorants, essential oils, skin sensates, astringents, (e.g., clove oil, menthol, camphor, eucalyptus oil, eugenol, menthyl lactate, witch hazel distillate), anti-acne agents, anti-caking agents, anti-foaming agents, antimicrobial agents (e.g., iodopropynyl butylcarbamate), antioxidants, binders, biological additives, buffering agents, bulking agents, chelating agents, chemical additives, colorants, cosmetic astringents, cosmetic biocides, denaturants, drug astringents, external analgesics, film formers or materials, i.e., polymers for aiding the film-forming properties and substantivity of the composition (e.g., copolymer of eicosine and vinyl pyrrolidone), opacifying agents, pH adjusters, propellants, reducing agents, sequestrants, skin bleaching and lightening agents (e.g., hydroquinone, kojic acid, ascorbic acid, magnesium ascorbyl phosphate, and ascorbyl glucosamine), skin-conditioning agents, (e.g., humectants, including miscellaneous and occlusive), skin soothing and/or healing agents (e.g., panthenol and its derivatives (e.g., ethyl panthenol), aloe vera, pantothenic acid and its derivatives, allantoin, bisabolol, and dipotassium glycyrrhizinate), skin treating agents, thickeners, and vitamins and derivatives thereof.

[0057] In any embodiment of the present invention, however, the additional ingredients useful herein can be categorized by the benefit they provide or by their postulated mode of action. However, it is to be understood that the additional ingredients useful herein can in some instances provide more than one benefit or operate via more than one mode of action. Therefore, classifications herein are made for the sake of convenience and are not intended to limit the additional ingredients to that particular application or to those particular applications listed.

Farnesol

[0058] The topical compositions of the present invention may contain a safe and effective amount of farnesol. Farnesol is an organic compound produced by both plants and animals. Farnesol is involved in protein modification and regulation (e.g., farnesylation of proteins), while derivatives of farnesol act as a precursor and/or intermediate in the biosynthesis of squalene, which in turn is a precursor for steroids in plants, animals and fungi. As a result, farnesol and its derivatives are important starting compounds for both natural and artificial organic synthesis.

[0059] Farnesol is present in many essential oils such as citronella, lemon grass, rose, musk and balsam. It is used commonly in perfumes as a co-solvent that regulates the volatility of the odorants. Farnesol is used also as a deodorant in cosmetic products due to its anti-bacterial activity.

[0060] Chemically, farnesol is [2E, 6E]-3,7,11-trimethyl-2,6,10-dodecatrien-1-ol and as used herein "farnesol" includes isomers and tautomers of such. Farnesol is commercially

available, e.g., under the names farnesol (a mixture of isomers from Dragoco, 10 Gordon Drive, Totowa, N.J.) and trans-trans-farnesol (Sigma Chemical Company, P.O. Box 14508, St. Louis, MO).

[0061] When present in the compositions of the present invention, the composition preferably contains from about 0.001% to about 50% by weight of the composition, more preferably from about 0.01% to about 20%, even more preferably from about 0.01% to about 15%, even more preferably from about 0.1% to about 10%, still more preferably from about 0.5% to about 5% and still more preferably from about 1% to 5% of farnesol.

Phytantriol

[0062] The topical compositions of the present invention may contain a safe and effective amount of phytantriol. Phytantriol is the common name for the chemical known as 3,7,11,15-tetramethylhexadecane-1,2,3-triol. Phytantriol is commercially available from BASF (1609 Biddle Avenue, Wyandotte, MI). For example, phytantriol is useful as a spider vessel/red blotchiness repair agent, a dark circle/puffy eye repair agent, sallowness repair agent, a sagging repair agent, an anti-itch agent, a skin thickening agent, a pore reduction agent, an oil/shine reduction agent, a post-inflammatory hyperpigmentation repair agent, a wound treatment agent, an anti-cellulite agent, and for regulating skin texture, including wrinkles and fine lines.

[0063] In the compositions of the present invention, the phytantriol is preferably included in an amount from about 0.001% to about 50% by weight of the composition, more preferably from about 0.01% to about 20%, even more preferably from about 0.1% to about 15%, even more preferably from about 0.2% to about 10%, still more preferably from about 0.5% to about 10%, and still more preferably from about 1% to 5% of phytantriol.

Desquamation Actives

[0064] A safe and effective amount of desquamation active may be added to the compositions of the present invention, more preferably from about 0.1% to about 10%, even more preferably from about 0.2% to about 5%, also preferably from about 0.5% to about 4%, by weight of the composition. Desquamation actives enhance the skin appearance benefits of the present invention. For example, the desquamation actives tend to the texture of the skin (e.g., smoothness). One desquamation system that is suitable for use herein contains sulfhydryl compounds and zwitterionic surfactants and is described in U.S. Pat. No. 5,681,852 to Bisset, incorporated herein by reference. Another desquamation system that is suitable for use herein contains salicylic acid and zwitterionic surfactants and is described in U.S. Pat. No. 5,652,228 issued to Bisset, incorporated herein by reference. Zwitterionic surfactants such as described in these applications are also useful as desquamatory agents herein, with cetyl betaine being previously preferred.

Enzymes, Enzyme Inhibitors and Enzyme Activators (Coenzymes)

[0065] The compositions of the present invention may contain a safe and effective amount of one or more enzymes, enzyme inhibitors or enzyme activators (coenzymes). Examples of enzymes are lipases, catalase, superoxidedismutase, amylases, glucuronidases, peroxidases, in particular glutathione peroxidase or lactoperoxidase, ceramidases, and hyaluronidases. All of these enzymes may be obtained by extraction or by fermentation biotechnology processes. Examples of enzyme inhibitors include trypsin inhibitors, Bowman Birk inhibitors, chymotrypsin inhibitors, botanical extracts with or without tannins, flavonoids, and quercetin which inhibit enzymatic activity. Enzyme preparations can be found, for instance, in

the product named VENUCEANE proposed by SEDERMA, France (WO 02/066668 of Aug. 28, 2002). Enzyme activators and coenzymes include coenzyme A, coenzyme Q10 (ubiquinone), glycyrrhizidine, berberine and chrysine.

Botanical Extracts and Marine Extracts

[0066] The compositions of the present invention may contain a safe and effective amount of one or more extracts obtained from vegetable or marine sources. These extracts may be obtained by standard extraction processes and may be used in powder, paste, balm, oil or liquid (i.e., solution) form, preferentially as hydroglycolic extracts of terrestrial plants or marine plants, such as seaweeds, algae, and microalgae.

Anti-Acne Actives

[0067] The compositions of the present invention may contain a safe and effective amount of one or more anti-acne actives. Examples of useful anti-acne actives include resorcinol, sulfur, salicylic acid, benzoyl peroxide, erythromycin, zinc, etc. Further examples of suitable anti-acne actives are described in further detail in U.S. Pat. No. 5,607,980 issued to McAtee et al., on Mar. 4, 1997.

Anti-Wrinkle Actives/Anti-Atrophy Actives

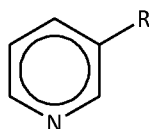
[0068] The compositions of the present invention may further contain a safe and effective amount of one or more anti-wrinkle actives or anti-atrophy actives. Exemplary anti-wrinkle/anti-atrophy actives suitable for use in the compositions of the present invention include sulfur containing D and L amino acids and their derivatives and salts, particularly the N-acetyl derivatives, a preferred example of which is N-acetyl-L-cysteine; thiols (e.g., ethane thiol);

hydroxy acids (e.g., alpha hydroxy acids such as lactic acid and glycolic acid or beta hydroxy acids such as salicylic acid and salicylic acid derivatives such as the octanoyl derivative), phytic acid, lipoic acid; lysophosphatidic acid, skin peel agents (e.g., phenol and the like), vitamin B₃ compounds and retinoids which enhance the keratinous tissue appearance benefits of the present invention, especially in regulating keratinous tissue condition, e.g., skin condition.

a) Vitamin B₃ Compounds

[0069] The compositions of the present invention may contain a safe and effective amount of a vitamin B₃ compound. Vitamin B₃ compounds are particularly useful for regulating skin condition as described in U.S. Pat. No. 5,939,082 issued to Oblong et al., on August 17, 1999. When vitamin B₃ compounds are present in the compositions of the instant invention, the compositions preferably contain from about 0.01% to about 50%, more preferably from about 0.1% to about 10%, even more preferably from about 0.5% to about 10%, and still more preferably from about 1% to about 5%, still more preferably from about 2% to about 5%, by weight of the composition, of the vitamin B₃ compound.

[0070] As used herein, "vitamin B₃ compound" means a compound having the formula:



wherein R is —CONH₂ (i.e., niacinamide), —COOH (i.e., nicotinic acid) or —CH₂OH (i.e., nicotinyl alcohol); derivatives thereof; and salts of any of the foregoing.

[0071] Exemplary derivatives of the foregoing vitamin B₃ compounds include nicotinic acid esters, including non-vasodilating esters of nicotinic acid (e.g., tocopheryl nicotinate), nicotinyl amino acids, nicotinyl alcohol esters of carboxylic acids, nicotinic acid N-oxide and niacinamide N-oxide.

[0072] Examples of suitable vitamin B₃ compounds are well known in the art and are commercially available from a number of sources, e.g., the Sigma Chemical Company (St. Louis, Mo.); ICN Biomedicals, Inc. (Irvin, Calif.) and Aldrich Chemical Company (Milwaukee, Wis.).

[0073] The vitamin compounds may be included as the substantially pure material, or as an extract obtained by suitable physical and/or chemical isolation from natural (e.g., plant) sources.

b) Retinoids

[0074] The compositions of the present invention may also contain a retinoid. As used herein, "retinoid" includes all natural and/or synthetic analogs of vitamin A or retinol-like compounds which possess the biological activity of vitamin A in the skin as well as the geometric isomers and stereoisomers of these compounds. The retinoid is preferably retinol, retinol esters (e.g., C₂—C₂₂ alkyl esters of retinol, including retinyl palmitate, retinyl acetate, retinyl propionate), retinal, and/or retinoic acid (including all-trans retinoic acid and/or 13-cis-retinoic acid), more preferably retinoids other than retinoic acid. These compounds are well known in the art and are commercially available from a number of sources, e.g., Sigma Chemical Company (St. Louis, Mo.), and Boehringer Mannheim (Indianapolis, Ind.). Other retinoids which are useful herein are described in U.S. Pat Nos. 4,677,120, issued Jun. 30, 1987 to Parish et al.; U.S. Pat. No. 4,885,311, issued Dec. 5, 1989 to Parish et al.; U.S. Pat. No. 5,049,584, issued Sep. 17, 1991 to

Purcell et al.; U.S. Pat. No. 5,124,356, issued Jun. 23, 1992 to Purcell et al.; and U.S. Pat No. Reissue 34,075, issued Sep. 22, 1992 to Purcell et al. Other suitable retinoids are tocopheryl-retinoate, [tocopherol ester of retinoic acid (trans- or cis-)], adapalene {6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid}, and tazarotene (ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)-ethynyl]nicotinate). Preferred retinoids are retinol, retinyl palmitate, retinyl acetate, retinyl propionate, retinal and combinations thereof.

[0075] The retinoid may be included as the substantially pure material, or as an extract obtained by suitable physical and/or chemical isolation from natural (e.g., plant) sources. The retinoid is preferably substantially pure, more preferably essentially pure.

[0076] The composition of this invention may contain a safe and effective amount of the retinoid, such that the resultant composition is safe and effective for regulating overall skin condition, preferably for regulating visible and/or tactile discontinuities in skin texture associated with skin aging. The compositions preferably contain from about 0.005% to or about 2%, more preferably 0.01% to or about 2%, by weight of the composition, of the retinoid. Retinol is preferably used in amount of from or about 0.01% to or about 0.15%; retinol esters are preferably used in an amount of from or about 0.01% or about 2% (e.g., about 1%); retinoic acids are preferably used in an amount of from about 0.01% to or about 0.25%; tocopheryl-retinoate, adapalene, and tazarotene are preferably used in an amount of from or about 0.01% to or about 2%.

[0077] Where the compositions of the present invention contain both a retinoid and a Vitamin B₃ compound, the retinoid is preferably used in the above amounts, and

the Vitamin B₃ compound is preferably used in an amount of from or about 0.1% to or about 10%, more preferably from or about 2% to or about 5%.

c) Hydroxy Acids

[0078] The compositions of the present invention may contain a safe and effective amount of a hydroxy acid. Preferred hydroxy acids for use in the compositions of the present invention include salicylic acid and salicylic acid derivatives. When present in the compositions of the present invention, salicylic acid is preferably used in an amount of from about 0.01% to about 50%, more preferably from about 0.1% to about 20%, even more preferably from 0.1% to about 10%, still more preferably from about 0.5% to about 5%, and still more preferably from about 0.5% to about 2%.

Peptides

[0079] Additional peptides, including but not limited to di, tri, and tetrapeptides and derivatives thereof, may be included in the compositions of the present invention in amounts that are safe and effective. As used herein, "peptide" refers to both the naturally occurring peptides and synthesized peptides. Also useful herein are naturally occurring and commercially available compositions that contain peptides.

[0080] Suitable dipeptides for use herein include Carnosine® (beta-ala-his). Suitable tripeptides for use herein include gly-his-lys, arg-lys-arg, his-gly-gly. Preferred tripeptides and derivatives thereof include palmitoyl-gly-his-lys, which may be purchased as Biopeptide CL® (100 ppm of palmitoyl-gly-his-lys commercially available from Sederma, France); Peptide CK (arg-lys-arg); Peptide CK+ (ac-arg-lys-arg-NH₂); and a copper derivative of his-gly-gly-

sold commercially as lamin, from Sigma Chemical Company (St. Louis, Mo.). Suitable tetrapeptides for use herein include Peptide E, arg-ser-arg-lys (SEQ ID NO: 17).

[0081] Preferably, the additional peptide is selected from palmitoyl-gly-his-lys, beta-ala-his, and their derivatives, and combinations thereof. More preferably, the additional peptide is selected from palmitoyl-gly-his-lys, their derivatives, and combinations thereof.

[0082] When included in the present compositions, the additional peptides are preferably included in amounts of from about $1 \times 10^{-6}\%$ to about 19%, more preferably from about $1 \times 10^{-6}\%$ to about 0.1%, even more preferably from about $1 \times 10^{-5}\%$ to about 0.01%, by weight of the composition. In certain embodiments which include the peptide, Carnosine®, the compositions preferably contain from about 0.1% to about 5%, by weight of the composition, of such peptides. In other embodiments wherein the peptide-containing composition Biopeptide CL® is included, the resulting composition preferably contains about 0.1% to about 10%, by weight of the composition, of the Biopeptide CL®.

Anti-Oxidants/Radical Scavengers

[0083] The compositions of the present invention may include a safe and effective amount of an anti-oxidant/radical scavenger. The anti-oxidant/radical scavenger is especially useful for providing protection against UV radiation which can cause increased scaling or texture changes in the stratum corneum and against other environmental agents, which can cause skin damage.

[0084] A safe and effective amount of an anti-oxidant/radical scavenger may be added to the compositions of the subject invention, preferably from about 0.1% to about 10%, more preferably from about 1% to about 5%, of the composition.

[0085] Anti-oxidants/radical scavengers such as ascorbic acid (vitamin C) and its salts, ascorbyl esters of fatty acids, ascorbic acid derivatives (e.g., magnesium ascorbyl phosphate, sodium ascorbyl phosphate, ascorbyl sorbate), tocopherol (vitamin E), tocopherol sorbate, tocopherol acetate, other esters of tocopherol, butylated hydroxy benzoic acids and their salts, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (commercially available under the trade name Trolox®), gallic acid and its alkyl esters, especially propyl gallate, uric acid and its salts and alkyl esters, sorbic acid and its salts, lipoic acid, amines (e.g., N,N-diethylhydroxylamine, amino-guanidine), sulfhydryl compounds (e.g., glutathione), dihydroxy fumaric acid and its salts, lysine pidolate, arginine pilolate, nordihydroguaiaretic acid, bioflavonoids, curcumin, lysine, methionone, proline, superoxide dismutase, silymarin, tea extracts, grape skin/seed extracts, melanin, and rosemary extracts may be used. Preferred anti-oxidants/radical scavengers are selected from tocopherol sorbate and other esters of tocopherol, more preferably tocopherol sorbate. For example, the use of tocopherol sorbate in topical composition and applicable to the present invention is described in U.S. Pat. No. 4,847,071, issued on Jul. 11, 1989 to Bisset et al.

Chelators

[0086] The compositions of the present invention may also contain a safe and effective amount of a chelator or chelating agent. As uses herein, "chelator" or "chelating agent" means an active agent capable of removing a metal ion from a system by forming a complex so

that the metal ion cannot readily participate in or catalyze chemical reactions. The inclusion of a chelating agent is especially useful for providing protection against UV radiation which can contribute to excessive scaling or skin texture changes and against other environmental agents, which can cause skin damage.

[0087] A safe and effective amount of a chelating agent may be added to the composition of the subject invention, preferably from about 0.1% to about 10%, more preferably from about 1% to about 5%, of the composition. Exemplary chelators that are useful herein are disclosed in U.S. Pat. No. 5,487,884, issued Jan. 30, 1996 to Bissett et al.; U.S. Pat. No. 5,462,963, issued Oct. 31, 1995 to Bush et al.; and U. S. Pat. No. 5,364,617, issued Nov. 15, 1994 to Bush et al. Preferred chelators useful in compositions of the subject invention are furildioxime, furilmonooxime, and derivatives thereof.

Flavonoids

[0088] The compositions of the present invention may optionally contain a flavonoid compound. Flavonoids are broadly disclosed in U.S. Pat. Nos. 5,686,082 and 5,686,367, both of which are herein incorporated by reference. Flavonoids suitable for use in the present invention are flavanones selected from unsubstituted flavanones, mono--substituted flavanones, and mixtures thereof; chalcones selected from unsubstituted chalcones, mono-substituted chalcones, di-substituted chalcones, tri-substituted chalcones, and mixtures thereof; flavones selected from unsubstituted flavones, mono-substituted flavones, di-substituted flavones, and mixtures thereof; one or more isoflavones; coumarins selected from unsubstituted coumarins, mono-substituted coumarins, di-substituted coumarins, and mixtures thereof; chromones selected from unsubstituted chromones, mono-substituted chromones, di-

substituted chromones, and mixtures thereof; one or more dicoumarols; one or more chromoanones; one or more chromanols; isomers (e.g., cis/trans isomers) thereof; and mixtures thereof. The term "substituted" as used herein means flavonoids wherein one or more hydrogen atom of the flavonoid has been independently replaced with a hydroxyl, a C₁-C₈ alkyl, a C₁-C₄ alkoxy, or a O-glycoside, and the like or a mixture of these substituents.

[0089] Examples of suitable flavonoids include, but are not limited to, unsubstituted flavanone, mono-hydroxy flavanones (e.g., 2'-hydroxy flavanone, 6-hydroxy flavanone, 7-hydroxy flavanone, etc.), mono-alkoxy flavanones, (e.g., 5-methoxy flavanone, 6-methoxy flavanone, 7-methoxy flavanone, 4'-methoxy flavanone, etc.), unsubstituted chalcone (especially unsubstituted trans-chalcone), mono-hydroxy chalcones (e.g., 2'-hydroxy chalcone, 4'-hydroxy chalcone, etc.), di-hydroxy chalcones (e.g., 2',4'-dihydroxy chalcone, 2',4'-dihydroxy chalcone, 2,2'-dihydroxy chalcone, 2',3'-dihydroxy chalcone, 2',5'-dihydroxy chalcone, etc.), and tri-hydroxy chalcones (e.g., 2',3',4'-trihydroxy chalcone, 4,2',4'-trihydroxy chalcone, 2,2',4'-trihydroxy chalcone, etc.), unsubstituted flavone, 7,2'-dihydroxy flavone, 3',4'-dihydroxy naphthoflavone, 4'-hydroxy flavone, 5,6-benzoflavone, and 7,8-benzoflavone, unsubstituted isoflavone, daidzein (7,4'-dihydroxy isoflavone), 5,7-dihydroxy-4'-methoxy isoflavone, soy isoflavones, (a mixture extracted from soy), unsubstituted coumarin, 4-hydroxy coumarin, 7-hydroxy coumarin, 6-hydroxy-4-methyl coumarin, unsubstituted chromone, 3-formyl chromone, 3-formyl-6-isopropyl chromone, unsubstituted dicoumarol, unsubstituted chromanone, unsubstituted chromanol, and mixtures thereof.

[0090] Preferred for use herein are unsubstituted flavanone, methoxy flavanones, unsubstituted chalcone, 2',4'-dihydroxy chalcone, and mixtures thereof. More

preferred are unsubstituted flavanone, unsubstituted chalcone (especially the trans isomer), and mixtures thereof.

[0091] They can be synthetic materials or obtained as extracts from natural sources (e.g., plants). The naturally sourced material can also further be derivatized (e.g., an ester or ether derivative prepared following extraction from a natural source). Flavonoid compounds useful herein are commercially available from a number of sources, e.g., Indofine Chemical Company, Inc. (Somerville, N.J.), Steraloids, Inc. (Wilton, N.H.), and Aldrich Chemical Company, Inc. (Milwaukee, Wisc.).

[0092] The herein described flavonoid compounds are preferably present in the subject invention at concentrations from about 0.01% to about 20%, more preferably from about 0.1% to about 10%, and still more preferably from about 0.5% to about 5% of the composition.

Anti-Inflammatory Agents

[0093] A safe and effective amount of anti-inflammatory agent may be added to the composition of the present invention, preferably from about 0.1% to about 10%, more preferably from about 0.5% to about 5%, of the composition. The anti-inflammatory agent enhances the skin-appearance-benefits of the present invention, i.e., such agents contribute to a more uniform and acceptable skin tone and color. The exact amount of anti-inflammatory agent to be used in the compositions will depend on the particular anti-inflammatory agent utilized since such agents vary widely in potency.

[0094] Steroidal anti-inflammatory agents, including but not limited to, corticosteroids such as hydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone,

dexamethasone-phosphate, beclomethasone dipropionated, clobetasol valerate, desonide, desoxymethasone, desoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, difluocortolone valerate, fluadrenolone, flucolorolone acetonide, fluocinonide, flucortine butylesters, fluocortolone, fluprednidene (fluprednylidene) acetate, flurandrenolone, halcinonide, hydrocortosine acetate, hydrocortosine butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, fludrocortisone, difluorosone diacetate, fluradrenolone, fludrocortisone, difluorosone diacetate, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of it esters, chloroprednisone, chlorprednisone acetate, clorcortelone, clescinolone, dichlorisone, diflurprednate, flucoronide, flunisolid, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortamate meprednisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone, and mixtures thereof may be used. The preferred steroidal anti-inflammatory for use is hydrocortisone.

[0095] A second class of anti-inflammatory agents which is useful in compositions includes the non-steroidal anti-inflammatory agents. The variety of compounds encompassed by this group are well-known to those skilled in the art. For detailed disclosure of the chemical structure, synthesis, side effects, etc. of non-steroidal anti-inflammatory agents, one may refer to standard texts, including *Anti-inflammatory and Anti-Rheumatic Drugs*, K.D. Rainsford, Vol. I-III, CRC Press, Boca Raton, (1985), and *Anti-inflammatory Agents, Chemistry and Pharmacology*, 1, R.A. Scherrer et al., Academic Press, New York (1974).

[0096] Specific non-steroidal anti-inflammatory agents useful in the composition invention include, but are not limited to:

- 1) the oxicams, such as piroxicam, isoxicam, tenoxicam, sudoxicam, and CP-14,304;
- 2) the salicylates, such aspirin, disalcid, benorylate, trisilate, safapryn, solprin, diflunisal, and fendosal;
- 3) the acetic acid derivatives, such as diclofenac, fenclofenac, tiopenac, zidometacin, acematacin, fentiazac, zomepirac, clindanac, oxepinac, felbinac, and ketorolac;
- 4) the fenamates, such as mefenamic, meclofenamic, flufenamic, niflumic, and tolfenamic acids;
- 5) the propionic acid derivatives, such as ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, piroprofen, carprofen, oxaprozin, pranoprofin, miroprofen, tioxaprofen, suprofen, alminoprofen, and tiaprofenic acid; and
- 6) the pyrazoles, such as phenylbutazone, oxyphenbutazone, feprazone, azapropazone, and trimethazone.

[0097] Mixtures of these non-steroidal anti-inflammatory agents may also be employed, as well as the dermatologically acceptable salts and esters of these agents. For example, etofenamate, a flufenamic acid derivative, is particularly useful for topical application. Of the non-steroidal anti-inflammatory agents, ibuprofen, naproxen, flufenamic acid, etofenamate, aspirin, mefenamic acid, meclofenamic acid, piroxicam and felbinac are preferred; ibuprofen, naproxen, ketoprofen, etofenamate, aspirin, and flufenamic acid are more preferred.

[0098] Finally, so-called "natural" anti-inflammatory agents are useful in methods of the present invention. Such agents may suitably be obtained as an extract by

suitable physical and/or chemical isolation from natural sources (e.g., plants, fungi, by-products of microorganisms) or can be synthetically prepared. For example, candelilla wax, bisabolol (e.g., alpha bisabolol), aloe vera, plant sterols (e.g., phytosterol). Manjistha (extracted from plants in genus *Rubia*, particularly *Rubia Cordifolia*), and Guggal (extracted from plants in the genus *Commiphora*, particularly *Commiphora Mukul*), kola extract, chamomile, red clover extract, and sea whip extract, may be used.

[0099] Additional anti-inflammatory agents useful herein include compounds of the Licorice (the plant genus/species *Glycyrrhiza glabra*) family, including glycyrrhetic acid, glycyrrhizic acid, and derivatives thereof (e.g., salts and esters). Suitable salts of the foregoing compounds include metal and ammonium salts. Suitable esters include C₂—C₂₄. Specific examples of the foregoing include oil soluble licorice extract, the glycyrrhizic and glycyrrhetic acids themselves, monoammonium glycyrrhetinate, 1-beta-glycyrrhetic acid, stearyl glycyrrhetinate, and 3-stearyloxy-glycyrrhetinic acid, and disodium 3-succinyloxy-beta-glycyrrhetinate. Stearyl glycyrrhetinate is preferred.

Anti-Cellulite Agents

[00100] The composition of the present invention may also contain a safe and effective amount of an anti-cellulite agent. Suitable agents may include, but are not limited to, xanthine compounds (e.g., caffeine, theophylline, theobromine, and aminophylline).

Topical Anesthetics

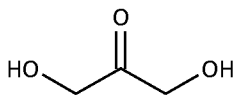
[00101] The compositions of the present invention may also contain a safe and effective amount of a topical anesthetic. Examples of topical anesthetic drugs include

benzocaine, lidocaine, bupivacaine, chlorprocaine, dibucaine, etidocaine, mepivacaine, tetracaine, dyclonine, hexylcaine, procaine, cocaine, ketamine, pramoxine, phenol, and pharmaceutically acceptable salts thereof.

Tanning Additives

[00102] The composition of the present invention may contain a tanning active. When present, it is preferable that the compositions contain from about 0.1% to about 20%, more preferably from about 2% to about 7%, and still more preferably from about 3% to about 6%, by weight of the composition, of dihydroxyacetone as an artificial tanning active.

[00103] Dihydroxyacetone, which is also known as DHA or 1,3-dihydroxy-2-propanone, is a white to off-white, crystalline powder. This material can be represented by the chemical formula $C_3H_6O_3$ and the following chemical structure:



[00104] The compound can exist as a mixture of monomers and dimers, with the dimers predominating in the solid crystalline state. Upon heating or melting, the dimers break down to yield the monomers. This conversion of the dimeric form to the monomeric form also occurs in aqueous solution. Dihydroxyacetone is also known to be more stable at acidic pH values. *See the Merck Index*, Tenth Edition, entry 3167, p. 463 (1983), and "Dihydroxyacetone for Cosmetics", E. Merck Technical Bulletin, 03-304 110, 319 897, 180 588.

Skin Lightening Agents

[00105] The compositions of the present invention may contain a skin lightening agent. When used, the compositions preferably contain from about 0.1% to about 10%, more preferably from about 0.2% to about 5%, also preferably from about 0.5% to about 2%, by weight of the composition, of a skin lightening agent. Suitable skin lightening agents include those known in the art, including kojic acid, arbutin, ascorbic acid and derivatives thereof (e.g., magnesium ascorbyl phosphate or sodium ascorbyl phosphate), and extracts (e.g., mulberry extract, placental extract). Skin lightening agents suitable for use herein also include those described in the World Patent No. WO 1995034280A1 in the name of Hillebrand, Greg G., corresponding to PCT Application No. U.S. Ser. No. 95/07432, filed Jun. 12, 1995; and World Patent No. WO 1995023780A3 in the names of Kvalnes et al., corresponding to PCT Application No. U.S. Ser. No. 95/002809, filed March 1, 1995.

Hair Growth Promoters

[00106] The compositions of the present invention may contain a hair growth promoter. Hair growth promoters suitable for use herein include minoxidil, procyanidine B-2, prostaglandins, fluridil, ketoconazole, spironolactone, melatonin, and estrogens. A safe and effective amount of a hair growth promoter may be added to the compositions of the present invention, in amounts preferably from about 0.1% to about 30%, more preferably from about 0.5% to about 20%, still more preferably from about 1% to about 5%, by weight of the composition formed.

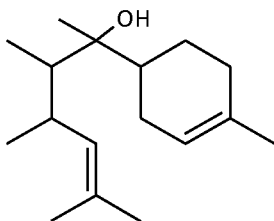
Skin Soothing and Skin Healing Active

[00107] The compositions of the present invention may comprise a skin soothing or skin healing active. Skin soothing or skin healing actives suitable for use herein include

panthenoic acid derivatives (including panthenol, dexpanthenol, ethyl panthenol), aloe vera, allantoin, bisabolol, and dipotassium glycyrrhizinate. A safe and effective amount of skin soothing or skin active may be added to the present composition, preferably from about 0.1% to about 30%, more preferably from about 0.5% to about 20%, still more preferably from about 0.5% to about 10%, by weight of the composition formed.

a) bisabolol

[00108] The topical compositions of the present invention may also contain a safe and effective amount of bisabolol. Bisabolol is a naturally occurring unsaturated monocyclic terpene alcohol having the following structure:



[00109] It is the primary active component of chamomile extract/oil. Bisabolol can be synthetic (d,l-alpha-isomer or (+/-)-alpha-isomer) or natural ((-)-alpha-isomer) in origin and can be used as essentially pure compounds or mixtures of compounds (e.g., extracts from natural sources such as chamomile). The alpha form of bisabolol (α -bisabolol) is used in a variety of cosmetic products as a skin conditioning or soothing agent. As used herein, "bisabolol" includes chamomile extract or oil and any isomers and tautomers of such. Suitable bisabolol compounds are commercially available as natural material from Dragoco (Totowa, N.J.) under the product name alpha-bisabolol natural and as a synthetic material from Fluka (Milwaukee, Wis.) under the product name alpha-bisabolol.

[00110] In the compositions of the present invention, the composition preferably contains about 0.001% to about 50% by weight of the composition, more preferably from about 0.01% to about 20%, even more preferably from about 0.01% to about 10%, of bisabolol, even more preferably from about 0.1% to about 5%.

Antimicrobial and Antifungal Actives

[00111] The composition of the present invention may contain an antimicrobial or antifungal active. Such actives are capable of destroying microbes, preventing the development of microbes or preventing the pathogenic action of microbes. A safe and effective amount of an antimicrobial or antifungal active may be added to the present composition, preferably, from about 0.001% to about 10%, more preferably from about 0.01% to about 5%, and still more preferably from about 0.05% to about 2%.

[00112] Examples of antimicrobial and antifungal actives include β -lactam drugs, quinolone drugs, ciprofloxacin, norfloxacin, tetracycline, erythromycin, amikacin, 2,4,4'-trichloro-2'-hydroxy diphenyl ether, 3,4,4'-trichlorobanilide, phenoxyethanol, phenoxypropanol, phenoxyisopropanol, doxycycline, capreomycin, chlorhexidine, chlortetracycline, oxytetracycline, elindamycin, ethambutol, hexamidine, isethionate, metronidazole, pentamidine, gentamicin, kanamycin, lineomycin, methacycline, methenamine, minocycline, neomycin, netilmicin, paromomycin, streptomycin, tobramycin, miconazole, tetracycline hydrochloride, erythromycin, zinc erythromycin, erythromycin stearate, amikacin sulfate, chlorhexidine gluconate, chlorhexidine hydrochloride, chlortetracycline hydrochloride, oxytetracycline hydrochloride, clindamycin hydrochloride, ethambutol hydrochloride, metronidazole hydrochloride, pentamidine hydrochloride, gentamicin sulfate, kanamycin sulfate, lineomycin hydrochloride, methacycline

hydrochloride, methenamine hippurate, methenamine mandelate, minocycline hydrochloride, neomycin sulfate, netilmicin sulfate, paromomycin sulfate, streptomycin sulfate, tobramycin sulfate, miconazole hydrochloride, ketoconazole, amantadine hydrochloride, amantadine sulfate, octopirox, parachlormeta xlenol, nystatin, tolnaftate, zinc pyrithione, and clotrimazole.

[00113] Preferred examples of actives useful herein include those selected from salicylic acid, benzoyl peroxide, 3-hydroxybenzoic acid, glycolic acid, lactic acid, 4-hydroxy benzoic acid, acetyl salicylic acid, 2-hydroxybutanoic acid, 2-hydroxypentanoic acid, 2-hydroxyheanoic acid, cis-retinoic acid, trans-retinoic acid, retinol, phytic acid, N-acetyl-L-cysteine, lipoic acid, azelaic acid, arachidonic acid, benzoyl peroxide, tetracycline, ibuprofen, naproxen, hydrocortisone, acetaminophen, resorcinol, phenoxyethanol, phenoxypropanol, phenoxyisopropanol, 2,4,4'-trichloro-2'-hydroxy diphenyl ether, 3,4,4'-trichlorocarbanilide, octopirox, lidocaine hydrochloride, clotrimazole, miconazole, ketoconazole, neocycin sulfate, and mixtures thereof.

Sunscreen Actives

[00114] Exposure to ultraviolet light can result in excessive scaling and texture changes of the stratum corneum layer of the epidermis. Therefore, the compositions of the subject invention may optionally contain a sunscreen active. As used herein, "sunscreen active" includes both sunscreen agents and physical sun-blocks. Suitable sunscreen actives may be organic or inorganic.

[00115] Inorganic sunscreens useful herein include the following metallic oxides; titanium dioxide having an average primary particle size of from about 15 nm to about 100 nm, zinc oxide having an average primary particle size of from about 15 nm to about 150 nm,

zirconium oxide having an average primary particle size of from about 15 nm to about 150 nm, iron oxide having an average primary particle size of from about 15 nm to about 500 nm, and mixtures thereof. When used herein, the inorganic sunscreens, are present in the amount of from about 0.1% to about 20%, preferably from about 0.5% to about 10%, more preferably from about 1% to about 5%, by weight of the composition.

[00116] A wide variety of conventional organic sunscreen actives are suitable for use herein. Sagarin, et al., at Chapter VIII, pages 189 et seq., of *Cosmetics Science and Technology* (1972), discloses numerous suitable actives. Specific suitable sunscreen actives include, for example: p-aminobenzoic acid, its salts and its derivatives (ethyl, isobutyl, glyceryl esters; p-dimethylaminobenzoic acid); anthranilates (i.e., o-amino-benzoates; methyl, menthyl, phenyl, benzyl, phenylethyl, linalyl, terpinyl, and cyclohexenyl esters); salicylates (amyl, phenyl, octyl, benzyl, menthyl, glyceryl, and di-pro-pyleneglycol esters); cinnamic acid derivatives (menthyl and benzyl esters, α -phenyl cinnamionitrile; butyl cinnamoyl pyruvate); dihydroxycinnamic acid derivatives (umbelliferone, methylumbelliferone, methylaceto-umbelliferone); trihydroxy-cinnamic acid derivatives (esculetin, methyl esculetin, daphnetin, and the glucosides, esculin and daphnin); hydrocarbons (diphenylbutadiene, stilbene); dibenzalacetone and benzalacetophenone; naphthosulfonates (sodium salts of 2-naphthol-3,6-disulfonic and of 2-naphthol-6,8-disulfonic acids); di-hydroxynaphthoic acid and its salts; o- and p-hydroxybiphenyldisulfonates; coumarin derivatives (7-hydroxy, 7-methyl, 3-phenyl); diazoles (2-acetyl-3-bromoindazole, phenyl benzoxazole, methyl naphthoxazole, various aryl benzothiazoles); quinine salts (bisulfate, sulfate, chloride, oleate, and tannate); quinoline derivatives (8-hydroxyquinoline salts, 2-phenylquinoline); hydroxy- or methoxy-substituted

benzophenones; uric and violuric acids; tannic acid and its derivatives (e.g., hexaethylether); (butyl carbotol) (6-propyl piperonyl) ether; hydroquinone; benzophenones (oxybenzene, sulisobenzone, dioxybenzone, benzoescorcinol, 2,2',4,4'-tetrahydroxybenzophenone, 2,2'-dihydroxy-4,4'-dimethoxybenzophenone, octabenzene; 4-isopropylidibenzoylmethane; butylmethoxydibenzoylmethane, octocrylene, octocrylene; [3-(4'-methylbenzylideneboman-2-one)], terephthalidene dicamphor sulfonic acid, and 4-isopropyl-di-benzoylmethane.

[00117] Of these, 2-ethylhexyl-p-methoxycinnamate (commercially available as PARSOL MCX), 4,4'-t-butylmethoxydibenzoyl-methane (commercially available as PARSOL 1789), 2-hydroxy-4-methoxybenzophenone, octyldimethyl-p-aminobenzoic acid, digalloyltriolate, 2,2'-dihydroxy-4-methoxybenzophenone, ethyl-4-(bis(hydroxy-propyl))aminobenzoate, 2-ethylhexyl-2-cyano-3,3-diphenylacrylate, 2-ethylhexyl-salicylate, glyceryl-p-aminobenzoate, 3,3,5-trimethylcyclohexylsalicylate, methylanthranilate, p-dimethyl-aminobenzoic acid or aminobenzoate, 2-ethylhexyl-p-dimethyl-aminobenzoate, 2-phenylbenzimidazole-5-sulfonic acid, 2-(p-dimethylaminophenyl)-5-sulfonic-benzoic acid, octocrylene and mixtures of these compounds, are preferred.

[00118] More preferred organic sunscreen actives useful in the compositions are 2-ethylhexyl-p-methoxycinnamate, butylmethoxydibenzoylmethane, 2-hydroxy-4-methoxybenzophenone, 2-phenylbenzimidazole-5-sulfonic acid, octyldimethyl-p-aminobenzoic acid, octocrylene, and mixtures thereof.

[00119] Also particularly useful in the compositions are sunscreen actives such as those disclosed in U.S. Pat. No. 4,937,370 issued to Sabatelli on Jun. 26, 1990, and U.S. Pat. No. 4,999,186 issued to Sabatelli & Spirnak on Mar. 12 1991. The sunscreen agents disclosed

therein have, in a single molecule, two distinct chromophore moieties which exhibit different ultra-violet radiation absorption spectra. One of the chromophore moieties absorbs predominantly in the UVB radiation range and the other absorbs strongly in the UVA radiation range.

[00120] Preferred members of this class of sunscreen agents are 4-N,N-(2-ethylhexyl)methyl-aminobenzoic acid ester of 2,4-dihydroxybenzophenone; N,N-di-(2-ethylhexyl)-4-aminobenzoic acid ester with 4-hydroxydibenzoylmethane; 4-N,N-(2-ethylhexyl)methyl-aminobenzoic acid ester with 4-hydroxydibenzoylmethane; 4-N,N-(2-ethylhexyl)methyl-aminobenzoic acid of 2-hydroxy-4-(2-hydroxyethoxy)benzophenone; 4-N,N-(2-ethylhexyl)-methylaminobenzoic acid ester of 4-(2-hydroxyethoxy)dibenzoylmethane; N,N-di-(2-ethylhexyl)-4-aminobenzoic acid ester of 2-hydroxy-4-(2-hydroxyethoxy)benzophenone; and N,N-di-(2-ethylhexyl)-4-aminobenzoic acid ester of 4-(2-hydroxyethoxy)dibenzoylmethane and mixtures thereof.

[00121] Especially preferred sunscreen actives include 4,4'-t-butylmethoxydibenzoylmethane, 2-ethylhexyl-p-methoxycinnamate, phenyl benzimidazole sulfonic acid, and octocrylene.

[00122] A safe and effective amount of the organic sunscreen active is used, typically from about 1% to about 20%, more typically from about 2% to about 10% by weight of the composition. Exact amounts will vary depending upon the sunscreen or sunscreens chosen and the desired Sun Protection Factor (SPF).

Particulate Material

[00123] The compositions of the present invention may contain a particulate material, preferably a metallic oxide. These particulates can be coated or uncoated, charged or uncharged. Charged particulate materials are disclosed in U.S. Pat. No. 5,997,887 to Ha et al., issued Dec 7, 1999 and incorporated herein by reference. Particulate materials useful herein include: bismuth oxychloride, iron oxide, mica, mica treated with barium sulfate and titanium dioxide, silica, nylon, polyethylene, talc, styrene, polypropylene, ethylene/acrylic acid copolymer, sericite, aluminum oxide, silicone resin, barium sulfate, calcium carbonate, cellulose acetate, titanium dioxide, polymethyl methacrylate, and mixtures thereof.

[00124] Inorganic particulate materials, e.g., TiO_2 , ZnO , or ZrO_2 are commercially available from a number of sources. One example of a suitable particulate material contains the material available from U.S. Cosmetics (TRONOX TiO_2 series, SAT-T CR837, a rutile TiO_2). Preferably, particulate materials are present in the composition in levels from about 0.01% to about 2%, more preferably from about 0.05% to about 1.5%, still more preferably from about 0.1% to about 1%, by weight of the composition.

Conditioning Agents

[00125] The compositions of the present invention may contain a conditioning agent selected from humectants, moisturizers, or skin conditioners. A variety of these materials can be employed and each can be present at a level of from about 0.01% to about 20%, more preferably from about 0.1% to about 10%, and still more preferably from about 0.5% to about 7% by weight of the composition. These materials include, but are not limited to guanidine, urea, glycolic acid and glycolate salts (e.g., ammonium and quaternary alkyl ammonium), salicylic acid, lactic acid and lactate salts (e.g., ammonium and quaternary alkyl ammonium), aloe vera in any

of its variety of forms (e.g., aloe vera gel), polyhydroxy alcohols such as sorbitol, mannitol, xylitol, erythritol, glycerol, hexanetriol, butanetriol, propylene glycol, butylene glycol, hexylene glycol and the like, polyethylene glycols, sugars (e.g., melibiose) and starches, sugar and starch derivatives (e.g., alkoxylated glucose, fructose, glucosamine), hyaluronic acid, lactamide monoethanolamine, acetamide monoethanolamine, panthenol, allantoin, and mixtures thereof. Also useful herein are the propoxylated glycerols described in U.S. Pat. No. 4,976,953 to Orr et al., issued Dec. 11, 1990.

[00126] Also useful are various C₁—C₃₀ monoesters and polyesters of sugars related materials. These esters are derived from a sugar or polyol moiety and one or more carboxylic acid moieties. Such ester materials are further described in U.S. Pat. No. 2,831,854 to Martin et al., issued Apr. 22, 1958; U.S. Pat. No. 4,005,196 to Jandacek, issued Jan. 25, 1977; U.S. Pat. No. 4,005,195 to Jandacek, issued Jan. 25, 1977; U.S. Pat. No. 5,306,516 to Letton et al., issued Apr. 26, 1994; U.S. Pat. No. 5,306,515 to Letton et al., issued Apr. 26, 1994; U.S. Pat. No. 5,305,514 to Letton et al., issued Apr. 26, 1994; U.S. Pat. No. 4,797,300 to Jandacek et al., issued Jan 10, 1989; U.S. Pat. No. 3,963,699 to Rizzi et al., issued Jun. 15, 1976; U.S. Pat. No. 4,518,772 to Volpenhein, issued May 21, 1985, and U.S. Pat. No. 4,517,360 to Volphein, issued May 21, 1985.

[00127] Preferably, the conditioning agent is selected from glycerine, propylene glycol, urea, guanidine, sucrose, polyester, panthenol, dexapanthenol, allantoin, and combinations thereof.

Structuring Agents

[00128] The compositions hereof, and especially the emulsions hereof, may contain a structuring agent. Structuring agents are particularly preferred in the oil-in-water emulsions of the present invention. Without being limited by theory, it is believed that the structuring agent assists in providing rheological characteristics to the composition which contribute to the stability of the composition. For example, the structuring agent tends to assist in the formation of the liquid crystalline gel network structures. The structuring agent may also function as an emulsifier or surfactant. Preferred compositions of this invention contain from about 0.1% to about 20%, more preferably from about 0.1% to about 10%, still more preferably from about 0.5% to about 9% by weight of the composition, of one or more structuring agents.

[00129] Preferred structuring agents are those having an HLB of from about 1 to about 8 and having a melting point of at least about 45 °C. Suitable structuring agents are those selected from saturated C₁₄ to C₃₀ fatty alcohols, saturated C₁₆ to C₃₀ fatty alcohols containing from about 1 to about 5 moles of ethylene oxide, saturated C₁₆ to C₃₀ diols, saturated C₁₆ to C₃₀ monoglycerol ethers, saturated C₁₆ to C₃₀ hydroxy fatty acids, C₁₄ to C₃₀ hydroxylated and nonhydroxylated saturated fatty acids, C₁₄ to C₃₀ saturated ethoxylated fatty acids, amines and alcohols containing from about 1 to about 5 moles of ethylene oxide diols, C₁₄ to C₃₀ saturated glyceryl mono esters with monoglyceride content of at least 40%, C₁₄ to C₃₀ saturated polyglycerol esters having from about 1 to about 3 alkyl group and from about 2 to 3 saturated glycerol units, C₁₄ to C₃₀ glycerol monoethers, C₁₄ to C₃₀ sorbitan mono/diesters, C₁₄ to C₃₀ saturated ethoxylated methyl glucoside esters with about 1 to about 5 moles of ethylene oxide, C₁₄ to C₃₀ saturated polyglucosides having an average of between 1 to 2 glucose units and mixtures thereof, having a melting point of at least about 45 °C.

[00130] The preferred structuring agents of the present invention are selected from stearic acid, palmitic acid, stearyl alcohol, cetyl alcohol, behenyl alcohol, the polyethylene glycol ether of stearyl alcohol having an average of about 1 to about 5 ethylene oxide units, the polyethylene glycol ether of cetyl alcohol having an average of about 1 to about 5 ethylene oxide units, and mixtures thereof. More preferred structuring agents of the present invention are selected from stearyl alcohol, cetyl alcohol, behenyl alcohol, the polyethylene glycol ether of stearyl alcohol having an average of about 2 ethylene oxide units (steareth-2), the polyethylene glycol ether of cetyl alcohol having an average of about 2 ethylene oxide units, and mixtures thereof. Even more preferred structuring agents are selected from stearic acid, palmitic acid, stearyl alcohol, cetyl alcohol, behenyl alcohol, steareth-2, and mixtures thereof.

Thickening Agent (including thickeners and gelling agents)

[00131] The compositions of the present invention can contain one or more thickening agents, preferably from about 0.1% to about 5%, more preferably from about 0.1% to about 4%, and still more preferably from about 0.25% to about 3%, by weight of the composition.

[00132] Non-limiting classes of thickening agents include those selected from the following:

a) Carboxylic Acid Polymers

[00133] These polymers are crosslinked compounds containing one or more monomers derived from acrylic acid, substituted acrylic acids, and salts and esters of these acrylic acids and of the substituted acrylic acids, wherein the crosslinking agent contains two or

more carbon-carbon double bonds and is derived from a polyhydric alcohol. Polymers useful in the present invention are more fully described in U.S. Pat. No. 5,087,445 to Haffey et al., issued Feb. 11 1992; U.S. Pat. No. 4,509,949 to Huang et al., issued Apr. 5, 1985; U.S. Pat. No. 2,798,053 to Brown, issued Jul. 2, 1957; and in *CTFA International Cosmetic Ingredient Dictionary*, Fourth Edition, 1991, pp. 12 and 80.

[00134] Examples of commercially available carboxylic acid polymers useful herein include the carbomers, which are homopolymers of acrylic acid crosslinked with allyl ethers or sucrose or pentaerythritol. The carbomers are available as the Carbopol® 900 series from B.F. Goodrich (e.g., Carbopol® 954). In addition, other suitable carboxylic acid polymeric agents include copolymers of C₁₀₋₃₀ alkyl acrylates with one or more monomers of acrylic acid, methacrylic acid, or one of their short chain (i.e., C₁₋₄ alcohol) esters, wherein the crosslinking agent is an allyl ether of sucrose or pentaerythritol. These copolymers are known as acrylates/C₁₀—C₃₀ alkyl acrylate crosspolymers and are commercially available as Carbopol® 1342, Carbopol® 1382, Pemulen TR-1, and Pemulen TR-2, from B.F. Goodrich. In other words, examples of carboxylic acid polymer thickeners useful herein are those selected from carbomers, acrylates/C₁₀—C₃₀ alkyl acrylate crosspolymers, and mixtures thereof.

b) Crosslinked Polyacrylate Polymers

[00135] The compositions in the present invention can optionally contain crosslinked polyacrylate polymers useful as thickening or gelling agents including both cationic and nonionic polymers, with the cationics being generally preferred. Examples of useful crosslinked nonionic polyacrylate polymers and crosslinked cationic polyacrylate polymers are those described in U.S. Pat. No. 5,100,660 to Hawe et al., issued Mar. 31, 1992; U.S. Pat. No.

4,849,484 to Heard, issued Jul. 18, 1989; U.S. Pat. No. 4,835,206 to Farrar et al., issued May 30, 1989; U.S. Pat. No. 4,628,078 to Glover et al., issued Dec. 9, 1986; U.S. Pat. No. 4,599,379 to Flesher et al., issued Jul. 8, 1986; and EP 228, 868 to Farrar et al., published Jul. 15, 1987.

c) Polyacrylamide Polymers

[00136] The compositions of the present invention can optionally contain polyacrylamide polymers, especially nonionic polyacrylamide polymers including substituted, branched, or unbranched polymers. More preferred among these polyacrylamide is the nonionic polymer given the CTFA designation polyacrylamide and isoparaffin and laureth-7, available under the trade name Sepigel 305 from Seppic Corporation (Fairfield, N.J.).

[00137] Other polyacrylamide polymers useful herein include multi-block copolymers of acrylamides and substituted acrylamides, with acrylic acids and substituted acrylic acids. Commercially available examples of these multi-block copolymers include Hypan SR150H, SS500V, SS500W, SSSA100H from Lipo Chemicals , Inc. (Patterson, N.J.).

d) Polysaccharides

[00138] A wide variety of polysaccharides are useful herein. "Polysaccharides" refer to gelling agents which contain a backbone of repeating sugar (i.e., carbohydrate) units. Non-limiting examples of polysaccharide gelling agents include those selected from cellulose, carboxymethylhydroxyethylcellulose, cellulose acetate propionate carboxylate, hydroxyethylcellulose, hydroxyethylethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, methyl hydroxyethylcellulose, microcrystalline cellulose, sodium cellulose sulfate, and mixtures thereof. Also useful herein are the alkyl substituted celluloses. In

these polymers, the hydroxy groups of the cellulose polymer is hydroxylated (preferably hydroxyethylated or hydroxypropylated) to form a hydroxylated cellulose which is then further modified with a C₁₀—C₃₀ straight chain or branched chain alkyl group through an ether linkage. Typically, these polymers are ethers of C₁₀—C₃₀ straight or branched chain alcohols with hydroxyalkylcelluloses. Examples of alkyl groups useful herein include those selected from stearyl, isostearyl, lauryl, myristyl, cetyl, isocetyl, cocoyl (i.e., alkyl groups derived from the alcohols of coconut oil), palmityl, oleyl, linoeyl, linolenyl, ricinoleyl, behenyl, and mixtures thereof. Preferred among the alkyl hydroxyalkyl cellulose ethers is the material given the CFTA designation cetyl hydroxyethylcellulose, which is the ether of cetyl alcohol and hydroxyethylcellulose. This material is sold under the trade name Natrosol® CS Plus from Aqualon Corporation (Wilmington, Del.).

[00139] Other useful polysaccharides include scleroglucans which are a linear chain of (1—3) linked glucose units with a (1—6) linked glucose every three units, a commercially available example of which is Clearogel™ CS11 from Michel Mercier Products Inc. (Mountainside, N.J.).

e) Gums

[00140] Other thickening and gelling agent useful herein include materials which are primarily derived from natural sources. Non-limiting examples of these gelling agent gums include acacia, agar, algin, alginic acid, ammonium alginate, amylopectin, calcium alginate, calcium carrageenan, carnitine, carrageenan, dextrin, gelatin, gellan gum, guar gum, guar hydroxypropyltrimonium chloride, hectorite, hyaluronic acid, hydrated silica, hydroxypropyl chitosan, hydroxypropyl guar, karaya gum, kelp, locust bean gum, natto gum, potassium alginate,

potassium carrageenan, propylene glycol alginate, sclerotium gum, sodium carboxymethyl dextran, sodium carrageenan, tragacanth gum, xanthan gum, and mixtures thereof.

Aquaporin Stimulators

[00141] The compositions of the present invention may contain a safe and effective amount of an aquaporin stimulator. Aquaporin stimulators are particularly useful for maintaining optimal hydration levels in the skin as described in U.S. Application Ser. No.12/297,734, filed Mar. 28, 2007 (corresponding to PCT No. PCT/EP07/52978). Non-limiting examples of aquaporin stimulators suitable for use in the compositions of the present invention include glycerol glycosides, in particular hexosyl glycerides and/or (hexosyl)hexosyl glycerides; cAMP analogs; PKA-(adenylyl cyclase) activators; and phosphodiesterase inhibitors, in particular caffeine and theophylline.

[00142] In the compositions of the present invention, the aquaporin stimulator preferably is included in an amount from about 0.0001% to about 20%, more preferably from about 0.0005% to about 10%, and still more preferably from about 0.001% to about 5%, by weight of the composition.

III. Dermatologically Acceptable Carrier

[00143] The topical compositions of the present invention also contain a dermatologically acceptable carrier. The phrase "dermatologically acceptable carrier," as used herein, means that the carrier is suitable for topical application to the epidermal layer of the skin, has good aesthetic properties, is compatible with the actives of the present invention and any other components, and will not cause any untoward safety or toxicity concerns. A safe and

effective amount of carrier is from about 50% to about 99.99%, preferably from about 80% to about 99.99%, more preferably from about 90% to about 98%, and even more preferably from about 90% to about 95% of the composition.

[00144] The carrier can be in a wide variety of forms. For example, emulsion carriers, including, but not limited to, oil-in-water, water-in-oil, water-in-oil-in-water, and oil-in-water-in-silicone emulsions, are useful herein.

[00145] Preferred carriers contain an emulsion such as oil-in-water emulsions, water-in-oil emulsions, and water-in-silicone emulsions. As will be understood by the skilled artisan, a given component will distribute primarily into either the water or oil/silicone phase, depending on the water solubility/dispersibility of the component in the composition. Oil-in-water emulsions are especially preferred.

[00146] Emulsions according to the present invention generally contain a solution as described above and a lipid or oil. Lipids and oils may be derived from animals, plants, or petroleum and may be natural or synthetic (i.e., man-made). Preferred emulsions also contain a humectant, such as glycerin. Emulsions will preferably further contain from about 0.01% to about 10%, more preferably from about 0.1% to about 5%, of an emulsifier, based on the weight of the carrier. Emulsifiers may be nonionic, anionic, or cationic. Suitable emulsifiers are disclosed in, for example, U.S. Pat. No. 3,755,560 to Dickert et al., issued Aug. 28, 1973; U.S. Pat. No. 4,421,769 to Dixon et al., issued Dec. 20, 1983; and McCutcheon's Detergents and Emulsifiers, North American Addition, pages 317-324 (1986).

[00147] The emulsion may also contain an anti-foaming agent to minimize foaming upon application to the epidermal layer. Anti-foaming agents include high molecular weight silicones and other materials well known in the art for such use.

[00148] Suitable emulsions may have a wide range of viscosities, depending on the desired product form. Exemplary low viscosity emulsions, which are preferred, have a viscosity of about 50 centistokes or less, more preferably about 10 centistokes or less, still more preferably 5 centistokes or less.

[00149] Preferred water-in-silicone and oil-in-water emulsions are described in greater detail below.

A) Water-in-Silicone Emulsion

[00150] Water in silicone emulsions contain a continuous silicone phase and a dispersed aqueous phase.

(1) Continuous Silicone Phase

[00151] Preferred water-in-silicone emulsions of the present invention contain from about 5% to about 40%, more preferably from about 10% to about 20%, by weight of a continuous silicone phase. The continuous silicone phase exists as an external phase that contains or surrounds the discontinuous aqueous phase described hereinafter.

[00152] The continuous silicone phase contains a polyorganosiloxane oil. A preferred water-in-silicone emulsion system is formulated to provide an oxidatively stable vehicle for a retinoid. The continuous silicone phase of the preferred emulsions contain between about 50% and about 99.9% by weight of organopolysiloxane oil and less than about 50% by

weight of a non-silicone oil. In an especially preferred embodiment, the continuous silicone phase contains at least about 50%, preferably from about 60% to about 99.9%, more preferably from about 70% to about 99.9%, and even more preferably from about 80% to about 99.9%, polyorganosiloxane oil by weight of the continuous silicone phase, and up to about 50% non-silicone oils, preferably less about 40%, more preferably less than about 30%, even more preferably less than about 10%, and even more preferably less than about 2%, by weight of the continuous silicone phase. These preferred emulsion systems provide more oxidative stability to the retinoid over extended periods of time than comparable water-in-oil emulsions containing lower concentrations of the polyorganosiloxane oil. Concentrations of non-silicone oils in the continuous silicone phase are minimized or avoided altogether so as to further enhance the oxidative stability of the selected retinoid in the composition. Water-in-silicone emulsions of this type are described in World Patent No. WO 1997021423A1 in the names of Hillebrand et al., corresponding to PCT Application No. U.S. Ser. No. 96/019302, filed Dec. 4, 1996.

[00153] The polyorganosiloxane oil for use in the composition may be volatile, non-volatile, or a mixture of volatile and non-volatile silicones. The term "non-volatile" as used in the context refers to those silicones that are liquid under ambient conditions and have a flash point (under one atmosphere of pressure) of or greater than about 100 °C. The term "volatile" as used in this context refers to all other silicone oils. Suitable organopolysiloxanes can be selected from a wide variety of silicones spanning a broad range of volatilities and viscosities. Examples of suitable organopolysiloxane oils include polyalkylsiloxanes, cyclic polyalkylsiloxanes, and polyalkylarylsiloxanes.

[00154] Polyalkylsiloxanes useful in the composition herein include polyalkylsiloxanes with viscosities of from about 0.5 to about 1,000,000 centistokes at 25 °C. Such polyalkylsiloxanes can be represented by the general chemical formula $R_3SiO[R_2SiO]_xSiR_3$ wherein R is an alkyl group having one to about 30 carbon atoms (preferably R is methyl or ethyl, more preferably methyl; also mixed alkyl groups can be used in the same molecule), and x is an integer from 0 to about 10,000, chosen to achieve the desired molecular weight which can range to over about 10,000,000. Commercially available polyalkylsiloxanes include the polydimethylsiloxanes, which are also known as dimethicones, examples of which include the Vicasil® series sold by General Electric Company and the Dow Corning® 200 series sold by Dow Corning Corporation. Specific examples of suitable polydimethylsiloxanes include Dow Corning® 200 fluid having a viscosity of 0.65 centistokes and a boiling point of 100 °C, Dow Corning® 225 fluid having a viscosity of 10 centistokes and a boiling point greater than 200 °C, and Dow Corning® 200 fluids having viscosities of 50, 350, and 12,500 centistokes, respectively, and boiling points greater than 200 °C. Suitable dimethicones include those represented by the chemical formula $(CH_3)_3SiO[(CH_3)_2SiO]_x[CH_3RSiO]_ySi(CH_3)_3$ wherein R is a straight or branched chain alkyl having from about 2 to about 30 carbon atoms and x and y are each integers of 1 or greater selected to achieve the desired molecular weight which can range to over about 10,000,000. Examples of these alkyl-substituted dimethicones include cetyl dimethicone and lauryl dimethicone.

[00155] Cyclic polyalkylsiloxanes suitable for use in the composition include those represented by the chemical formula $[SiR_2—O]_n$ wherein R is an alkyl group (preferably R is methyl or ethyl, more preferably methyl) and n is an integer from about 3 to about 8, more

preferably n is an integer from about 3 to about 7, and still more preferably n is an integer from about 4 to about 6. When R is methyl, these materials are typically referred to as cyclomethicones. Commercially available cyclomethicones include Dow Corning® 244 fluid having a viscosity of 2.5 centistokes, and a boiling point of 172 °C, which primarily contains the cyclomethicone tetramer (i.e., $n=4$), Dow Corning® 344 fluid having a viscosity of 2.5 centistokes and a boiling point of 178 °C, which primarily contains the cyclomethicone pentamer (i.e., $n=5$), Dow Corning® 245 fluid having a viscosity of 4.2 centistokes and a boiling point of 205 °C, which primarily contains a mixture of the cyclomethicone tetramer and pentamer (i.e., $n=4$ and 5), and Dow Corning® 345 fluid having a viscosity of 4.5 centistokes and a boiling point of 217 °C, which primarily contains a mixture of the cyclomethicone tetramer, pentamer, and hexamer (i.e., $n=4$, 5, and 6).

[00156] Also useful are materials such as trimethylsiloxysilicate, which is a polymeric material corresponding to the general chemical formula $[(CH_3)_3SiO_{1/2}]_x[SiO_2]_y$, wherein x is an integer from about 1 to about 550 and y is an integer from about 1 to about 500. A commercially available trimethylsiloxysilicate is sold as a mixture with dimethicone as Dow Corning® 593 fluid.

[00157] Dimethiconols are also suitable for use in the composition. These compounds can be represented by the chemical formulas $R_3SiO[R_2SiO]_xSiR_2OH$ and $HOR_2SiO[R_2SiO]_xSiR_2OH$, wherein R is an alkyl group (preferably R is methyl or ethyl, more preferably methyl) and n is an integer from about 0 to about 500, chosen to achieve the desired molecular weight. Commercially available dimethiconols are typically sold as mixtures with dimethicone or cyclomethicone (e.g., Dow Corning® 1401, 1402, and 1403 fluids).

[00158] Polyalkylaryl siloxanes are also suitable for use in the composition.

Polymethylphenyl siloxanes having viscosities from about 15 to about 65 centistokes at 25 °C are especially useful.

[00159] Preferred for use herein are organopolysiloxanes selected from polyalkylsiloxanes, alkyl substituted dimethicones, cyclomethicones, trimethylsiloxysilicated, dimethiconols, polyalkylaryl siloxanes, and mixtures thereof. More preferably for use herein are polyalkylsiloxanes and cyclomethicones. Preferred among the polyalkylsiloxanes are dimethicones.

[00160] As stated above, the continuous silicone phase may contain one or more non-silicone oils. Concentrations of non-silicone oils in the continuous silicone phase are preferably minimized or avoided altogether so as to further enhance oxidative stability of the selected retinoid in the composition. Suitable non-silicone oils have a melting point of about 25 °C or less under about one atmosphere of pressure. Examples of non-silicone oils suitable for use in the continuous silicone phase are those well known in the chemical arts in topical personal care products in the form of water-in-oil emulsions, e.g., mineral oil, vegetable oils, synthetic oils, semi-synthetic oils etc.

(2) Dispersed Aqueous Phase

[00161] The topical compositions of the present invention contain from about 30% to about 90%, more preferably from about 50% to about 85%, and still more preferably from about 70% to about 80% of a dispersed aqueous phase. In emulsion technology, the term "dispersed phase" is a term well-known to one skilled in the art, which means that the phase exists as small particles or droplets that are suspended in and surrounded by a continuous phase.

The dispersed phase is also known as the internal or discontinuous phase. The dispersed aqueous phase is a dispersion of small aqueous particles or droplets suspended in or surrounded by the continuous silicone phase described hereinbefore.

[00162] The aqueous phase can be water or a combination of water and one or more water soluble or dispersible ingredients. Non-limiting examples of such ingredients thickeners, acids, bases, salts, chelants, gums, water-soluble or dispersible alcohols and polyols, buffers preservatives, sunscreen agents, colorings, and the like.

[00163] The topical compositions of the present invention will typically contain from about 25% to about 90%, preferably from about 40% to about 80%, more preferably from about 60% to about 80%, water in the dispersed aqueous phase by weight of the composition.

(3) Emulsifier for Dispersing the Aqueous Phase

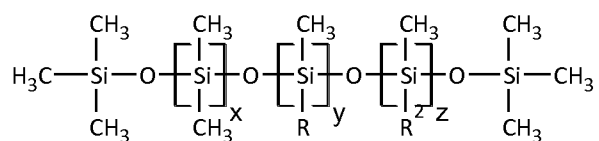
[00164] The water-in-silicone emulsions of the present invention preferably contain an emulsifier. In a preferred embodiment, the composition contains from about 0.1% to about 10% emulsifier, more preferably from about 0.5% to about 7.5%, still more preferably from about 1% to about 5%, emulsifier by weight of the composition. The emulsifier helps disperse and suspend the aqueous phase within the continuous silicone phase.

[00165] A wide variety of emulsifying agents can be employed herein to form the preferred water-in-silicone emulsion. Known or conventional emulsifying agents can be used in the composition, provided that the selected emulsifying agent is chemically and physically compatible with components of the composition of the present invention, and provides the desired dispersion characteristics. Suitable emulsifiers include silicone emulsifiers, non-silicone-

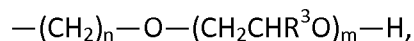
containing emulsifiers, and mixtures thereof, known by those skilled in the art for use in topical personal care products. Preferably these emulsifiers have an HLB value of or less than about 14, more preferably from about 2 to about 14, and still more preferably from about 4 to about 14. Emulsifiers having a HLB value outside of these ranges can be used in combination with other emulsifiers to achieve an effective weighted average HLB for the combination that falls within these ranges.

[00166] Silicone emulsifiers are preferred. A wide variety of silicone emulsifiers are useful herein. These silicone emulsifiers are typically organically modified organopolysiloxanes, also known to those skilled in the art as silicone surfactants. Useful silicone emulsifiers include dimethicone copolyols. These materials are polydimethylsiloxanes which have been modified to include polyether side-chains such as polyethylene oxide chains, polypropylene oxide chains, mixtures of these chains, and polyether chains containing moieties derived from both ethylene oxide and propylene oxide. Other examples include alkyl-modified dimethicone copolyols, i.e., compounds which contain C₂—C₃₀ pendant side-chains. Still other useful dimethicone copolyols include materials having various cationic, anionic, amphoteric, and zwitterionic pendant moieties.

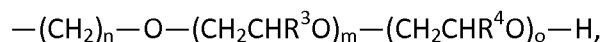
[00167] The dimethicone copolyol emulsifiers useful herein can be described by the following general structure:



wherein R is C₁—C₃₀ straight, branched, or cyclic alkyl and R² is selected from the group consisting of

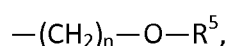


and



wherein n is an integer from 3 to about 10; R³ and R⁴ are selected from the group consisting of H and C₁—C₆ straight or branched chain alkyl such that R₃ and R₄ are not simultaneously the same ; and m, o, x, and y are selected such that the molecule has an overall molecular weight from about 200 to about 10,000,000, with m, o, x, and y being independently selected from integers of zero or greater such that m and o are not both simultaneously zero, and z being independently selected from integers of 1 or greater. It is recognized that positional isomers of these copolyols can be achieved. The chemical representations depicted above for the R² moieties containing the R³ and R⁴ groups are not meant to be limiting but are shown as such for convenience.

[00168] Also useful herein, although not strictly classified as dimethicone copolyols, are silicone surfactants as depicted in the structures in the previous paragraph wherein R² is:



wherein R⁵ is a cationic, anionic, amphoteric, or zwitterionic moiety.

[00169] Non-limiting examples of the dimethicone copolyols and other silicone surfactants useful as emulsifiers herein include polydimethylsiloxane polyether copolymers with pendant polyethylene oxide side-chains, polydimethylsiloxane polyether copolymers with

pendant polypropylene oxide side-chains, polydimethylsiloxane polyether copolymers with pendant mixed polyethylene oxide and polypropylene oxide side-chains, polydimethylsiloxane polyether copolymers with pendant mixed poly(ethylene)(polypropylene)oxide side-chains, polydimethylsiloxane polyether copolymers with pendant organobetaine side-chains, polydimethylsiloxane polyether copolymers with pendant carboxylate side-chains, polydimethylsiloxane polyether copolymers with pendant quaternary ammonium side-chains; and also further modifications of the preceding copolymers containing pendant C₂—C₃₀ straight, branched, or cyclic alkyl moieties. Examples of commercially available dimethicone copolyols useful herein sold by Dow Corning Corporation are Dow Corning® 190, 193, Q2-5220, 2501 Wax, 2-5324 fluid, and 3225C (this later material being sold as a mixture with cyclomethicone). Cetyl dimethicone copolyol is commercially available as a mixture with polyglyceryl-4 isostearate (and) hexyl laurate and is sold under the trade name ABIL®WE-09 (available from Goldschmidt). Cetyl dimethicone copolyol is also commercially available as a mixture with hexyl laurate (and) polyglyceryl-3 oleate (and) cetyl dimethicone and is sold under the trade name ABIL®WS-08 (also available from Goldschmidt). Other non-limiting examples of dimethicone copolyols also include lauryl dimethicone copolyol, dimethicone copolyol acetate, dimethicone copolyol adipate, dimethicone copolyolamine, dimethicone copolyol behenate, dimethicone copolyol butyl ether, dimethicone copolyol hydroxy stearate, dimethicone copolyol methyl ether, dimethicone copolyol phosphate, and dimethicone copolyol stearate. *See International Cosmetic Ingredient Dictionary*, Fifth Edition, 1993.

[00170] Dimethicone copolyol emulsifiers useful herein are described for example in U.S. Pat. No. 4,960,764 to Figueroa, Jr. et al., issued Oct. 2, 1990; European Pat. No.

EP 330,369 to SanoGueira, published Aug. 30, 1989; G.H. Dahms et al., "New Formulation Possibilities Offered by Silicone Copolyols," *Cosmetics & Toiletries*, vol. 110, pp. 91-100, March 1995; M.E. Carlotti et al., "Optimization of W/O-S Emulsions and Study of the Quantitative Relationships between Ester Structure and Emulsion Properties," *J. Dispersion Science and Technology*, 13(3), 315-336 (1992); P. Hameyer, "Comparative Technological Investigations of Organic and Organosilicone Emulsifiers in Cosmetic Water-in-Oil Emulsion Preparations," *HAPPI* 28(4), pp. 88-128 (1991); J. Smid-Korber et al., "Efficiency and usability of silicone surfactants in emulsions," *Provisional Communication International Journal of Cosmetic Science*, 12, 135-139 (1990); and D.G. Krzysik et al., "A New Silicone Emulsifier for Water-in-Oil Systems," *Drug and Cosmetic Industry*, vol. 146(4) pp. 28-81 (April 1990).

[00171] Among the non-silicone-containing emulsifiers useful herein are various non-ionic and anionic emulsifying agents such as sugar esters and polyesters, alkoxyated sugar esters and polyesters, C_1-C_{30} fatty acid esters of C_1-C_{30} fatty alcohols, alkoxyated derivatives of C_1-C_{30} fatty acid esters of C_1-C_{30} fatty alcohols, alkoxyated ethers of C_1-C_{30} fatty alcohols, polyglyceryl esters of C_1-C_{30} fatty acids, C_1-C_{30} esters of polyols, C_1-C_{30} ethers of polyols, alkyl phosphates, polyoxyalkylene fatty ether phosphates, fatty acid amides, acyl lactylates, soaps, and mixtures thereof. Other suitable emulsifiers are described, for example, in McCutcheon's, *Detergents and Emulsifiers*, North American Edition (1986), published by Allured Publishing Corporation; U.S. Pat. No. 5,011,681 to Ciotti et al., issued Apr. 30, 1991; U.S. Pat. No. 4,421,769 to Dixon et al., issued Dec. 30, 1983; and U.S. Pat. No. 3,755,560 to Dickert et al., issued Aug. 28, 1973.

[00172] Non-limiting examples of these non-silicone-containing emulsifiers

include: polyethylene glycol 20 sorbitan monolaurate (Polysorbate 2), polyethylene glucol 5 soya sterol, Steareth-20, Cetareth-20, PPG-2 methyl glucose ether distearate, Ceteth-10, Polysorbate 80, cetyl phosphate, potassium cetyl phosphate, diethanolamine cetyl phosphate, Polysorbate 60, glyceryl stearate, PEG-100 stearate, polyoxyethylene 20 sorbitan trioleate (Polysorbate 85), sorbitan monolaurate, polyoxyethylene 4 lauryl ether sodium stearate, polyglyceryl-4 isostearate, hexyl laurate, steareth-20, cetareth-20, PPG-2 methyl glucose ether distearate, Ceteth-10, diethanolamine cetyl phosphate, glyceryl stearate, PEG-100 stearate, and mixtures thereof.

B) Oil-in-Water Emulsions

[00173] Other preferred topical carriers include oil-in-water emulsions, having a

continuous aqueous phase and a hydrophobic, water-insoluble phase ("oil phase") dispersed therein. Examples of suitable oil-in-water emulsion carriers are described in U.S. Pat. No.

5,073,371 to Turner, D.J. et al., issued Dec. 17, 1991, and U.S. Pat. No. 5,073,372 to Turner, D.J.

et al., issued De. 17, 1991. An especially preferred oil-in-water emulsion, containing a structuring agent, hydrophilic surfactant, and water is described in detail hereinafter.

(1) Structuring Agent

[00174] A preferred oil-in-water emulsion contains a structuring agent to assist

in the formation of a liquid crystalline gel network structure. Without being limited by theory, it is believed that the structuring agent assists in providing rheological characteristics to the composition which contribute to the stability of the compound. The structuring agent may also function as an emulsifier or surfactant. Preferred compositions of this invention contain from

about 0.5% to about 20%, more preferably from about 1% to about 10%, even more preferably from about 1% to about 5%, by weight of the composition, of a structuring agent.

[00175] The preferred structuring agents of the present invention include stearic acid, palmitic acid, stearyl alcohol, cetyl alcohol, behenyl alcohol, stearic acid, palmitic acid, the polyethylene glycol ether of stearyl alcohol having an average of about 1 to about 21 ethylene oxide units, the polyethylene glycol ether of cetyl alcohol having an average about 1 to about 5 ethylene oxide units, and mixtures thereof. More preferred structuring agents of the present invention are selected from stearyl alcohol, cetyl alcohol, behenyl alcohol, the polyethylene glycol ether of stearyl alcohol having an average of about 2 ethylene oxide units (steareth-2), the polyethylene glycol ether of cetyl alcohol having an average of about 2 ethylene oxide units, and mixtures thereof. Even more preferred structuring agents are selected from stearic acid, palmitic acid, stearyl alcohol, cetyl alcohol, behenyl alcohol, steareth-2, steareth-21, and mixtures thereof.

(2) Hydrophilic Surfactant

[00176] The preferred oil-in-water emulsions contain from about 0.05% to about 10%, preferably from about 1% to about 6%, and more preferably from about 1% to 3% of at least one hydrophilic surfactant, which can disperse the hydrophobic materials in the water phase (percentages by weight of the topical carrier). The surfactant, at a minimum, must be hydrophilic enough to disperse in water.

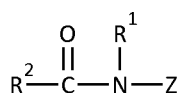
[00177] Preferred hydrophilic surfactants are selected from nonionic surfactants. Among those nonionic surfactants that are useful herein are those that can be broadly defined as condensation products of long chain alcohols, e.g., C₈—C₃₀ alcohols, with

sugar or starch polymers, i.e., glycosides. These compounds can be represented by the formula $(S)_n-O-R$ wherein S is a sugar moiety such as glucose, fructose, mannose, and galactose; n is an integer of from about 1 to about 1,000, and R is a C_8-C_{30} alkyl group. Examples of long chain alcohols from which the alkyl group can be derived include decyl alcohol, cetyl alcohol, stearyl alcohol, lauryl alcohol, myristyl alcohol, oleyl alcohol, and the like. Preferred examples of these surfactants include those wherein S is a glucose moiety, R is a C_8-C_{20} alkyl group, and n is an integer from about 1 to about 9. Commercially available examples of these surfactants include decyl polyglucoside (available as APG 325 CS from Henkel) and lauryl polyglucoside (available as APG 600 CS and 625 CS from Henkel).

[00178] Other useful nonionic surfactants include the condensation products of alkylene oxides with fatty acids (i.e., alkylene oxide esters of fatty acids). These materials have the general formula $RCO(X)_nOH$ wherein R is a $C_{10}-C_{30}$ alkyl group, X is $-OCH_2CH_2-$ (i.e., derived from ethylene glycol or oxide) or $-CH_2CH_2CH_2-$ (i.e., derived from propylene glycol or oxide), and n is an integer from about 6 to about 200. Other nonionic surfactants are the condensation products of alkylene oxides with 2 moles of fatty acids (i.e., alkylene oxide diesters of fatty acids). These materials have the general formula $RCO(X)_nOOCR$ wherein R is a $C_{10}-C_{30}$ alkyl group, X is $-OCH_2CH_2-$ (i.e., derived from ethylene glycol or oxide) or $-CH_2CH_2CH_2-$ (i.e., derived from propylene glycol or oxide), and n is an integer from about 6 to about 100. Other nonionic surfactants are the condensation products of alkylene oxides with fatty alcohols (i.e., alkylene oxide ethers of fatty alcohols). These materials have the general formula $R(X)_nOR'$ wherein R is a $C_{10}-C_{30}$ alkyl group, X is $-OCH_2CH_2-$ (i.e., derived from ethylene glycol or oxide) or $-CH_2CH_2CH_2-$ (i.e., derived from propylene glycol or oxide), and n is an integer from about 6

to about 100 and R' is H or a C₁₀—C₃₀ alkyl group. Still other nonionic surfactants are the condensation products of alkylene oxides with both fatty acids and fatty alcohols [i.e., wherein the polyalkylene oxide portion is esterified on one end with a fatty acid and etherified (i.e., connected via an ether linkage) on the other end with a fatty alcohol]. These materials have the general formula RCO(X)_nOR' wherein R and R' are C₁₀—C₃₀ alkyl groups, X is —OCH₂CH₂— (i.e., derived from ethylene glycol or oxide) or —CH₂CH₂CH₂— (i.e., derived from propylene glycol or oxide), and n is an integer from about 6 to about 100. Non-limiting examples of these alkylene oxide derived nonionic surfactants include ceteth-6, ceteth-10, ceteth-12, cetareth-6, cetareth-10, cetareth-12, steareth-6, steareth-10, steareth-12, steareth-21, PEG-6 stearate, PEG-10 stearate, PEG-100 stearate, PEG-12 stearate, PEG-20 glyceryl stearate, PEG-80 glyceryl tallowate, PEG-10 glyceryl stearate, PEG-30 glyceryl cocoate, PEG-80 glyceryl cocoate, PEG-200 glyceryl tallowate, PEG-8 dilaurate, PEG-10 distearate, and mixtures thereof.

[00179] Still other useful nonionic surfactants include polyhydroxy fatty acid amide surfactants corresponding to the structural formula:



wherein R¹ is H, C₁—C₄ alkyl, 2-hydroxyethyl, 2-hydroxypropyl, preferably C₃—C₄ alkyl, more preferably methyl or ethyl, most preferably methyl; R² is C₅—C₃₁ alkyl or alkenyl, preferably C₇—C₁₉ alkyl or alkenyl, more preferably C₉—C₁₇ alkyl or alkenyl, most preferably C₁₁—C₁₅ alkyl or alkenyl; and Z is a polyhydroxyhydrocarbyl moiety having a linear hydrocarbyl chain with at least 3 hydroxyls directly connected to the chain, or an alkoxylated derivative (preferably ethoxylated or propoxylated) thereof. Z preferably is a sugar moiety selected from the group consisting of

glucose, fructose, maltose, lactose, galactose, mannose, xylose, and mixtures thereof. An especially preferred surfactant corresponding to the above structure is coconut alkyl N-methylglucoside amide (i.e., wherein the R^2CO- moiety is derived from coconut fatty acids). Processes for making compositions containing polyhydroxy fatty acid amides are disclosed, for example, in G.B. Patent Specifications 809,060, published Feb. 18, 1959 by Thomas Hedley & Co., Ltd.; U.S. Pat. No. 2,965,576 to Wilson, E.R., issued Dec. 20, 1960; U.S. Pat. No. 2,703,798 to Schwartz, A.M., issued Mar. 8, 1955; and U.S. Pat. No. 1,985,424 to Piggott, issued Dec. 25, 1934; which are incorporated herein by reference in their entirety.

[00180] Preferred among the nonionic surfactants are those selected from the group consisting of steareth-21, cetareth-20, cetareth-12, sucrose cocoate, steareth-100, PEG-100 stearate, and mixtures thereof.

[00181] Other nonionic surfactants suitable for use herein include sugar esters and polyesters, alkoxyated sugar esters and polyesters, C_1-C_{30} fatty acid esters of C_1-C_{30} fatty alcohols, alkoxyated derivatives of C_1-C_{30} fatty acid esters of C_1-C_{30} fatty alcohols, alkoxyated ethers of C_1-C_{30} fatty alcohols, polyglyceryl esters of C_1-C_{30} fatty acids, C_1-C_{30} esters of polyols, C_1-C_{30} ethers of polyols, alkyl phosphates, polyoxyalkylene fatty ether phosphates, fatty acid amides, acyl lactylates, and mixtures thereof. Non-limiting examples of these emulsifiers include: polyethylene glycol 20 sorbitan monolaurate (Polysorbate 20), polyethylene glycol 5 soya sterol, Steareth-20, Cetareth-20, PPG-2 methyl glucose ether distearate, Ceteth-10, Polysorbate-80, cetyl phosphate, potassium cetyl phosphate, diethanolamine cetyl phosphate, Polysorbate-60, glyceryl stearate, polyoxyethylene 20 sorbitan trioleate (Polysorbate 85),

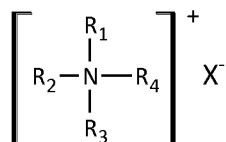
sorbitan monolaurate, polyoxyethylene 4 lauryl ether sodium stearate, polyglyceryl-4 isostearate, PEG-100 stearate, and mixtures thereof.

[00182] Another group of nonionic surfactants useful herein are fatty acid ester blends based on a mixture of sorbitan or sorbitol fatty acid ester and sucrose fatty acid ester, the fatty acid in each instance being preferably C_8-C_{24} , more preferably $C_{10}-C_{20}$. The preferred fatty acid ester emulsifier is a blend of sorbitan or sorbitol $C_{16}-C_{20}$ fatty acid ester with sucrose $C_{10}-C_{16}$ fatty acid ester, especially sorbitan stearate and sucrose cocoate. This is commercially available from ICI under the trade name Arlatone 2121.

[00183] Other suitable surfactants useful herein include a wide variety of cationic, anionic, zwitterionic, and amphoteric surfactants such as are known in the art and discussed more fully below. See, e.g., McCutcheon's, *Detergents and Emulsifiers*, North American Edition (1986), published by Allured Publishing Corporation; U.S. Pat. No. 5,011,681 to Ciotii et al., issued Apr. 30, 1991; U.S. Pat. No. 4,412,769 to Dixon et al., issued Dec. 20, 1983; and U.S. Pat. No. 3,755,560 to Dickert et al., issued Aug 28, 1973; these four (4) references are incorporated herein by reference in their entirety. The hydrophilic surfactants useful herein can contain a single surfactant or any combination of suitable surfactants. The exact surfactant (or surfactants) chosen will depend upon the pH of the composition and the other components present.

[00184] Also useful herein are cationic surfactants, especially dialkyl quaternary ammonium compounds, examples of which are described in U.S. Pat. No. 5,151,209; U.S. Pat. No. 5,515,210; U.S. Pat. No. 5,120,532; U.S. Pat. No. 4,387,090; U.S. Pat. No. 3,155,591; U.S. Pat. No. 3,929,678; U.S. Pat. No. 3,959,461; McCutcheon's *Detergents and Emulsifiers*, North American

Edition, M.C. Publishing Co. (1989); and Schwartz et al., *Surface Active Agents, Their Chemistry and Technology*, New York: Interscience Publishers, (1949); which descriptions are incorporated herein by reference. The cationic surfactants useful herein include cationic ammonium salts such as those having the formula:



wherein R_1 is an alkyl group having from about 12 to about 30 carbon atoms, or an aromatic, aryl, or alkaryl group having from about 12 to about 30 carbon atoms; R_2 , R_3 , and R_4 are independently selected from hydrogen, an alkyl group having from about 1 to 22 carbon atoms, or aromatic, aryl, or alkaryl groups having from about 12 to about 22 carbon atoms; and X is any compatible anion, preferably selected from chloride, bromide, iodide, acetate, phosphate, nitrate, sulfate, methyl sulfate, ethyl sulfate, tosylate, lactate, citrate, glycolate, and mixtures thereof. Additionally, the alkyl groups of R_1 , R_2 , R_3 , and R_4 can also contain an ester and/or ether linkages, or hydroxy or amino group substituents (e.g., the alkyl groups can contain polyethylene glycol and polypropylene glycol moieties).

[00185] More preferably, R_1 is an alkyl group having from about 12 to about 22 carbon atoms; R_2 is selected from H or an alkyl group having from about 1 to about 22 carbon atoms; R_3 and R_4 are independently selected from H or an alkyl group having from about 1 about 3 carbon atoms; and X is as described previously.

[00186] Still more preferably, R_1 is an alkyl group having from about 12 to about 22 carbon atoms; R_2 , R_3 , and R_4 are selected from H or an alkyl group having from about 1 to about 3 carbon atoms; and X is as described previously.

[00187] Alternatively, other useful cationic emulsifiers include amino-amides, wherein in the above structure R_1 is instead $R_5\text{CONH}-(\text{CH}_2)_n$, wherein R_5 is an alkyl group having from about 12 to about 22 carbon atoms, and n is an integer from about 2 to about 6, more preferably from about 2 to about 4, and still more preferably from about 2 to about 3. Non-limiting examples of these cationic emulsifiers include stearamidopropyl PG-dimonium chloride phosphate, behenamidopropyl PG dimonium chloride, stearamidopropyl ethyldimonium ethosulfate, stearamidopropyl dimethyl(myristyl acetate) ammonium chloride, stearamidopropyl dimethyl cetearyl ammonium tosylate, stearamidopropyl dimethyl ammonium chloride, stearamidopropyl dimethyl ammonium lactate, and mixtures thereof. Especially preferred is behenamidopropyl PG dimonium chloride.

[00188] Non-limiting examples of quaternary ammonium salt cationic surfactants include those selected from cetyl ammonium chloride, cetyl ammonium bromide, lauryl ammonium chloride, lauryl ammonium bromide, stearyl ammonium chloride, stearyl ammonium bromide, cetyl dimethyl ammonium chloride, cetyl dimethyl ammonium bromide, lauryl dimethyl ammonium chloride, lauryl dimethyl ammonium bromide, stearyl dimethyl ammonium chloride, stearyl dimethyl ammonium bromide, cetyl trimethyl ammonium chloride, cetyl trimethyl ammonium bromide, lauryl trimethyl ammonium chloride, lauryl trimethyl ammonium bromide, stearyl trimethyl ammonium chloride, stearyl trimethyl ammonium bromide, dicetyl ammonium chloride, dicetyl ammonium bromide, dilauryl ammonium chloride,

dilauryl ammonium bromide, distearyl ammonium chloride, distearyl ammonium bromide, dicetyl methyl ammonium chloride, dicetyl methyl ammonium bromide, dilauryl methyl ammonium chloride, dilauryl methyl ammonium bromide, distearyl methyl ammonium chloride, distearyl methyl ammonium bromide, and mixtures thereof. Additional quaternary ammonium salts include those wherein the C₁₂ to C₃₀ alkyl carbon chain is derived from a tallow fatty acid or from a coconut fatty acid. The term "tallow" refers to an alkyl group derived from tallow fatty acids (usually hydrogenated tallow fatty acids), which generally have mixtures of alkyl chains in the C₁₆ to C₁₈ range. The term "coconut" refers to an alkyl group derived from a coconut fatty acid, which generally have mixtures of alkyl chains in the C₁₂ to C₁₄ range. Examples of quaternary ammonium salts derived from these tallow and coconut sources include ditallow dimethyl ammonium chloride, ditallow dimethyl ammonium sulfate, di(hydrogenated tallow) dimethyl ammonium chloride, di(hydrogenated tallow) dimethyl ammonium acetate, ditallow dipropyl ammonium phosphate, ditallow dimethyl ammonium nitrate, di(coconutalkyl)dimethyl ammonium chloride, di(coconutalkyl)dimethyl ammonium bromide, tallow ammonium chloride, coconut ammonium chloride, stearamidopropyl PG-dimonium chloride phosphate, stearamidopropyl ethyldimonium ethosulfate, stearamidopropyl dimethyl (myristyl acetate) ammonium chloride, stearamidopropyl dimethyl cetearyl ammonium tosylate, stearamidopropyl dimethyl ammonium chloride, stearamidopropyl dimethyl ammonium lactate, and mixtures thereof. An example of a quaternary ammonium compound having an alkyl group with an ester linkage is ditallowyl oxyethyl dimethyl ammonium chloride.

[00189]

More preferred cationic surfactants are those selected from behenamidopropyl PG-dimonium chloride, dilauryl dimethyl ammonium chloride, distearyl

dimethyl ammonium chloride, dimyristyl dimethyl ammonium chloride, dipalmityl dimethyl ammonium chloride, stearamidopropyl PG-dimonium chloride phosphate, stearamidopropyl ethyldiammonium ethosulfate, stearamidopropyl dimethyl (myristyl acetate) ammonium chloride, stearamidopropyl dimethyl cetearyl ammonium tosylate, stearamidopropyl diethyl ammonium chloride, stearamidopropyl dimethyl ammonium lactate, and mixtures thereof.

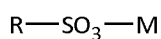
[00190] Still more preferred cationic surfactants are those selected from behenamidopropyl PG-dimonium chloride, dilauryl dimethyl ammonium chloride, distearyl dimethyl ammonium chloride, dimyristyl dimethyl ammonium chloride, dipalmityl dimethyl ammonium chloride, and mixtures thereof.

[00191] A preferred combination of cationic surfactants and structuring agent is behenamidopropyl PG-dimonium chloride and/or behenyl alcohol, wherein the ratio is preferably optimized to maintain and to enhance physical and chemical stability, especially when such a combination contains ionic and/or highly polar solvents. This combination is especially useful for delivery of sunscreen agents such as zinc oxide and octyl methoxycinnamate.

[00192] A wide variety of anionic surfactants are also useful herein. See, e.g., U.S. Pat. No. 3,929,678 to Laughlin et al., issued Dec. 30, 1975, which is incorporated herein by reference in its entirety. Non-limiting examples of anionic surfactants include the alkyl isethionates and the alkyl and alkyl ether sulfates. The alkyl isethionates typically have the formula $\text{RCO—OCH}_2\text{CH}_2\text{SO}_3\text{M}$ wherein R is alkyl or alkenyl of from about 10 to about 30 carbon atoms, and M is a water-soluble cation such as ammonium, sodium, potassium, or triethanolamine. Non-limiting examples of these isethionates include those alkyl isethionates

selected from ammonium cocoyl isethionate, sodium cocoyl isethionate, sodium lauroyl isethionate, sodium stearyl isethionate, and mixtures thereof.

[00193] The alkyl and alkyl ether sulfates typically have the respective formulae ROSO_3M and $\text{RO}(\text{C}_2\text{H}_4\text{O})_x\text{SO}_3\text{M}$, wherein R is alkyl or alkenyl of from about 10 to about 30 carbon atoms, x is from about 1 to about 10, and M is a water-soluble cation such as ammonium, sodium, potassium, or triethanolamine. Another suitable class of anionic surfactants are the water-soluble salts of the organic, sulfuric acid reaction products of the general formula:



wherein R is chosen from the group including a straight or branched chain, saturated aliphatic hydrocarbon radical having from about 8 to about 24, preferably from about 10 to about 16 carbon atoms; and M is a cation. Still other anionic synthetic surfactants include the class designated as succinamates, olefin sulfonates having about 12 to about 24 carbon atoms, and β -alkoxy alkane sulfonates. Examples of these materials are sodium lauryl sulfate and ammonium lauryl sulfate.

[00194] Other anionic materials useful herein are soaps (i.e., alkali metal salts, e.g., sodium or potassium salts) of fatty acids typically having from about 8 to about 24 carbon atoms, preferably from about 10 to about 20 carbon atoms. The fatty acids used in making soap can be obtained from natural sources such as, for instance, plant or animal derived glycerides (e.g., palm oil, coconut oil, soybean oil, castor oil, tallow, lard, etc.). The fatty acids can also be synthetically prepared. Soaps are described in more detail in U.S. Pat. No. 4,557,853 to Collins, issued Dec. 10, 1985.

[00195] Amphoteric and zwitterionic surfactants are also useful herein.

Examples of amphoteric and zwitterionic surfactants which can be used in the compositions of the present invention are those which are broadly described as derivatives of aliphatic secondary and tertiary amines in which the aliphatic radical can be straight or branched chain and wherein one of the aliphatic substituents contains from about 8 to about 22 carbon atoms (preferably C₈—C₁₈) and one contains an anionic water solubilizing group, e.g., carboxy, sulfonate, sulfate, phosphate, or phosphonate. Examples are alkyl imino acetates, and iminodialkanoates and aminoalkanoates of the formulas $RN[CH_2]_mCO_2M]_2$ and $RNH(CH_2)_mCO_2M$ wherein m is from 1 to 4, R is a C₈—C₂₂ alkyl or alkenyl, and M is H, alkali metal, alkaline earth metal, ammonium, or alkanolammonium. Also included are imidazolinium and ammonium derivatives. Specific examples of suitable amphoteric surfactants include sodium 3-dodecyl-amino proprionate, sodium 3-dodecylaminopropane sulfonate, N-alkyltaurines such as the one prepared by reacting dodecylamine with sodium isethionate according to the teaching of U.S. Pat. No. 2,658,072 which is incorporated herein by reference in its entirety; N-higher alkyl aspartic acids such as those produced according to the teaching of U.S. Pat. No. 2,438,091 which is incorporated herein by reference in its entirety; and the products sold under the trade name "Miranol" and described in U.S. Pat. No. 2,528,378, which is incorporated herein by reference in its entirety. Other examples of useful amphoteric surfactants include phosphates, such as cocamidopropyl PG-dimonium chloride phosphate (commercially available as Monaquat PTC, from Mona Corp.).

[00196] Other amphoteric or zwitterionic surfactants useful herein include betaines. Examples of betaines include the higher alkyl betaines, such as coco dimethyl carboxymethyl betaine, lauryl dimethyl carboxymethyl betaine, lauryl dimethyl alphacarboxyethyl

betaine, cetyl dimethyl carboxymethyl betaine, cetyl dimethyl betaine (available as Lonzone 16SP from Lonza Corp.), lauryl bis-(2-hydroxyethyl) carboxymethyl betaine, stearyl bis-(2-hydroxypropyl) carboxymethyl betaine, oleyl dimethyl gamma-carboxypropyl betaine, lauryl bis-(2-hydroxypropyl) alpha-carboxyethyl betaine, coco dimethyl sulfopropyl betaine, stearyl dimethyl sulfopropyl betaine, lauryl dimethyl sulfoethyl betaine, lauryl bis-(2-hydroxyethyl) sulfopropyl betaine, and amidobetaines and amidosulfobetaines (wherein the $RCONH(CH_2)_3$ radical is attached to the nitrogen atom of the betaine), oleyl betaine (available as amphoteric Velvetex OLB-50 from Henkel), and cocamidopropyl betaine (available as Velvetex BK-35 and BA-35 from Henkel).

[00197] Other useful amphoteric and zwitterionic surfactants include the sultaines and hydroxysultaines such as cocamidopropyl hydroxysultaine (available as Mirataine CBS from Rhone-Poulenc), and the alkonyl sarcosinates corresponding to the formula $RCON(CH_3)CH_2CH_2CO_2M$ wherein R is alkyl or alkenyl of about 10 to about 20 carbon atoms, and M is a water-soluble cation such as ammonium, sodium, potassium and trialkanolamine (e.g., triethanolamine), a preferred example of which is sodium lauroyl sarcosinate.

(3) Water

[00198] The preferred oil-in-water emulsion contains from about 25% to about 98%, preferably from about 65% to about 95%, more preferably from about 10% to about 90% water by weight of the topical carrier.

[00199] The hydrophobic phase is dispersed in the continuous aqueous phase. The hydrophobic phase may contain water insoluble or partially insoluble materials such as are known in the art, including but not limited to the silicones described herein in reference to

silicone-in-water emulsions, and other oils and lipids such as described above in reference to emulsions.

[00200] The topical compositions of the subject invention, including but not limited to lotions and creams, may contain a dermatologically acceptable emollient. Such compositions preferably contain from about 1% to about 50% of the emollient. As used herein, "emollient" refers to a material useful for the prevention of relief of dryness, as well as for the protection of the skin. A wide variety of suitable emollients are known and may be used herein. Sagarin's, *Cosmetics Science and Technology*, 2nd Edition, vol. 1, pp. 32-43 (1972), incorporated herein by reference, contains numerous examples of materials suitable as an emollient. A preferred emollient is glycerin. Glycerin is preferably used in an amount from or about 0.001% to about 30%, more preferably from or about 0.01% to about 20%, still more preferably from or about 0.1% to about 10%, e.g., 5%.

[00201] Lotions and creams according to the present invention generally contain a solution carrier system and one or more emollients. Lotions and creams typically contain from about 1% to about 50%, preferably from about 1% to about 20%, of emollient, from about 50% to about 90%, preferably from about 60% to about 80%, water; and the TGF- β mimic and/or TGF- β mimic derivative and the additional skin care active (or active) in the above described amounts. Creams are generally thicker than lotions due to high levels of emollients or higher levels of thickeners.

[00202] Ointments in the present invention may contain a simple carrier base of animal or vegetable oils or semi-solid hydrocarbons (oleaginous); absorption ointment bases which absorb water to form emulsions; or water soluble carriers, e.g., a water soluble solution

carrier. Ointments may further contain a thickening agent, such as described in Sagarin's, *Cosmetic Science and Technology*, 2nd Edition, Vol. 1, pp. 72-73 (1972), incorporated herein by reference, and/or an emollient. For example, an ointment may contain from about 2% to about 10% of an emollient; from about 0.1% to about 2% of a thickening agent; and the TGF- β mimic and/or the TGF- β mimic derivative and the additional skin care active (or actives) in the above described amounts.

[00203] Compositions of this invention useful for cleansing ("cleansers") are formulated with a suitable carrier, e.g., as described above, and preferably contain, in addition to the TGF- β mimic and/or TGF- β mimic derivative and the additional skin care active (or actives) in the above described amounts, from about 1% to about 90%, more preferably from about 5% to about 10%, of a dermatologically acceptable surfactant. The surfactant is suitably selected from anionic, nonionic, zwitterionic, amphoteric, and ampholytic surfactants, as well as mixtures of these surfactants. Such surfactants are well known to those skilled in the detergency art. Non-limiting examples of possible surfactants include isoceteth-20, sodium methyl cocoyl taurate, sodium methyl oleoyl taurate, and sodium lauryl sulfate. See U.S. Pat. No. 4,800,197 to Kowcz et al., issued Jan. 24, 1989, which is incorporated herein by reference in its entirety, for exemplary surfactants useful herein. Examples of a broad variety of additional surfactants useful herein are described in McCutcheon's, *Detergents and Emulsifiers*, North American Edition (1986), published by Allured Publishing Corporation. The cleansing compositions can optionally contain, at their art-established levels, other materials which are conventionally used in cleansing compositions.

[00204] The physical form of the cleansing compositions is not critical. The compositions can be, for example, formulated as toilet bars, liquids, shampoos, bath gels, hair conditioners, hair tonics, pastes, and mousses. Rinse-off cleansing compositions, such as shampoos, require a delivery system adequate to deposit sufficient levels of actives on the skin and scalp. A preferred delivery system involves the use of insoluble complexes. For a more complete disclosure of such delivery systems, see U.S. Pat. No. 4,835,148 to Barford et al., issued May 30, 1989.

[00205] As used herein, the term "foundation" refers to a liquid, semi-liquid, semi-solid, or solid skin cosmetic which includes, but is not limited to lotions, creams, gels, pastes, cakes, and the like. Typically, the foundation is used over a large area of the skin, such as over the face, to provide a particular look. Foundations are typically used to provide an adherent base for color cosmetics such as rouge, blush, powder and the like, and tend to hide skin imperfections and impart a smooth, even appearance to the skin. Foundations of the present invention include a dermatologically carrier and may include conventional ingredients such as oils, colorants, pigments, emollients, fragrances, waxes, stabilizers, and the like. Exemplary carriers and such other ingredients which are suitable for use herein are described, for example, in World Patent No. WO 1996033689A1 in the names of Barford et al., corresponding to PCT Application No. U.S. Ser. No. 96/004302, filed Mar. 29, 1996.

COMPOSITION PREPARATION

[00206] The compositions of the present invention are generally prepared by conventional methods such as are known on the art of making topical compositions. Such

methods typically involve mixing of the ingredients in one or more steps to a relatively uniform state, with or without heating, cooling, under reduced pressures, and the like.

METHODS FOR MANAGING SKIN CONDITION

[00207] The compositions of the present invention are useful for managing and optimizing mammalian skin health by way of both prophylactic and therapeutic means. For example, methods are directed to thickening various skin layers (i.e., epidermis or dermis); preventing the thinning of the skin; preventing and/or retarding the appearance of spider vessels and/or red blotchiness of the skin; preventing and/or retarding the appearance of dark circles under the eyes; preventing and/or retarding sallowness of the skin; improving firmness and elasticity of the skin; softening and/or smoothing lips, hair and nails; preventing and/or relieving itch; preventing and/or eliminating wrinkles and fine lines; stimulating collagen synthesis; reducing recovery time following chemical peels, and stimulating natural hydration of the skin.

[00208] The method of improving skin appearance involves topically applying to the skin an effective amount of the composition of the present invention. The amount of the composition required, the frequency of the application, and the duration of use will depend on the amount of TGF- β mimic, analogs, or derivatives thereof contained in the composition as well as on the specific combination with the other ingredients in the composition and on the level of effect desired.

[00209] Ideally, the composition is applied regularly to the skin. "Regularly," as used herein, means over an extended period of time during the subject's lifetime, preferably for a period of at least one week, more preferably for a period of at least about one month, even more preferably for at least about three months, even more preferably for at least about six

months, and more preferably still for at least about one year. While benefits will be realized after various periods of use (e.g., weeks, months, years), due to the prophylactic properties of the present invention, it is preferred that regular application continue throughout the subject's lifetime. Typically, applications would be on the order of about once a day over such extended periods, however, application rates can vary from about once per week up to about three times per day or more as needed.

[00210] Amounts of the composition and products applied to the skin are, per application, preferably in the range of from about 0.1 mg/cm² to about 10 mg/cm². A particularly useful application amount is about 1 mg/cm² to about 2 mg/cm².

[00211] The method of managing optimal skin health with the present invention is preferably practiced by, but not limited to, applying the composition in the form of a skin lotion, cream, gel, foam, ointment, paste, emulsion, spray, conditioner, tonic, cosmetic make-up, lipstick, foundation, after-shave, and the like, to the skin and allowing the composition to remain there. The composition can be applied manually, with the aid of spatulas, wipes, or similar cosmetic tools. It can also be applied by the use of an occlusive or semi-occlusive patch, as well as with an adhesive or non-adhesive tissue.

EXAMPLES

[00212] The following examples are provided to further describe and demonstrate embodiments within the scope of the present invention. Numerous samples of the below listed examples were packaged in airless, polyethylene, pump containers, and were subjected to stability testing at 40 °C for a period of three (3) months; during which all of the samples remained stable with no change in viscosity, color or odor. In addition, numerous

samples of the below listed examples were subjected to freeze-thaw testing during which all of the samples also remained stable with no change in viscosity, color or odor. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

Example 1

Skin Moisturizer and Anti-Wrinkle Cream

Ingredient	% by weight
water	qs to 100
ANVAENA	0.01
glycerin	3.00
trimethylolpropane tricaprylate/tricaprate	7.50
cetearyl alcohol	3.00
glyceryl stearate	3.00
dimethicone	1.00
hydrogenated polydecene	1.00
sorbitan laurate	0.20
ceteareth 20	0.10
PEG 100 stearate	0.10
steareth 2	0.10
ceteth 24	0.10
phospholipids	0.10
trideceth 6	0.10
sodium acrylate/sodium acryoyldimethyl taurate copolymer	0.20
preservative	qs
fragrance	qs

[00213] The peptide is readily synthesized according to techniques well-known in the art. Separately, Sub Micron Emulsion Concentrates #1 PF (SMEC), commercially available

from the Personal Care Division of Lonza Group Ltd. located in South Plainfield, NJ, is diluted approximately 50% by volume with water. Subsequently, the peptide is added to the diluted SMEC at room temperature and mixed to ensure a uniform product.

Example 2

Soothing Hair Re-growth Treatment

Ingredient	% by weight
water	qs to 100
ANVAENA	0.01
propylene glycol	25.0
ethanol	20.0
minoxidil	2.5

[00214] The peptide is readily synthesized according to techniques well-known in the art. Separately, the water, propylene glycol, ethanol and minoxidil are blended together and stirred at room temperature until a well-mixed emulsion results. Subsequently, the peptide is added to the solution, and the final composition is stirred until a uniform product is achieved.

[00215] While the present invention has been illustrated and described herein in terms of a preferred embodiment and several alternatives, it is to be understood that the techniques described herein can have a multitude of additional uses and applications. Accordingly, the invention should not be limited to just the particular description and various drawing figures contained in this specification that merely illustrate a preferred embodiment and application of the principles of the invention.

WHAT IS CLAIMED IS:

1. A skin care composition, comprising:

(a) a safe and effective amount of a TGF- β mimic having TGF- β signaling activity, and being a six or seven amino acid peptide, having the sequence AA_i-AA_{i+1}-AA_{i+2} as an initial
 5 sequence defining the N-terminus of said peptide or having the sequence Ala-AA_i-AA_{i+1}-AA_{i+2}, said peptide further having an AA_{i+n} adjacent or proximal to said sequence in the C-terminus direction, wherein n is 3, 4, or 5 such that said peptide contains n-3 additional amino acid residues in between AA_{i+2} and AA_{i+n} and wherein

AA_i is alanine, asparagine, or leucine,

10 AA_{i+1} is valine, isoleucine, α -amino isobutyric acid, or α -amino butyric acid,

AA_{i+2} is alanine or N-methyl alanine, and

AA_{i+n} is glutamic acid, aspartic acid, glutamine, or asparagine, or other amino acid,

whereby the peptide forms a stable β -bend structure in physiologic conditions under which TGF- β has a stable β -bend and elicits at least one biological activity of TGF- β ;

15 (b) a safe and effective amount of at least one additional skin care active selected from the group consisting of desquamation actives, anti-acne actives, vitamin B₃ compounds, humectants, hair growth promoters, retinoids, hydroxy acids, radical scavengers, chelators, anti-inflammatory agents, topical anesthetics, tanning actives, skin lightening agents, anti-cellulite agents, flavonoids, antimicrobial actives, skin healing agents, antifungal actives, farnesol,
 20 phytantriol, allantoin, glucosamine, and mixtures thereof; and

(c) a dermatologically acceptable carrier.

2. The skin care composition as in claim 1 wherein the TGF- β mimic has $n=3$ and the sequence further comprises AA_{i+4} - AA_{i+5} wherein AA_{i+4} and AA_{i+5} are alanine.

3. The skin care composition as in claim 1 wherein the TGF- β mimic has $n=4$ and the amino acid residue in between AA_{i+2} and AA_{i+n} is proline or glycine.

5 4. The skin care composition as in claim 1 wherein the TGF- β mimic has $n=5$ and the two amino acid residues in between AA_{i+2} and AA_{i+n} are glycine.

5. The skin care composition as in claim 1, wherein the TGF- β mimic is selected from the group consisting of

A-N-V-A-E-N-A (SEQ ID NO: 1),

10 L-I-A-E-A-K (SEQ ID NO: 2),

L-I-A-P-E-A (SEQ ID NO: 3),

L-(Aib)-A-E-A-K (SEQ ID NO: 4),

L-I-(Nme-A)-E-A-K (SEQ ID NO: 5),

L-(Abu)-A-E-A-K (SEQ ID NO: 6),

15 L-I-A-D-A-K (SEQ ID NO: 9),

L-I-A-N-A-K (SEQ ID NO: 10),

L-I-A-E-A-A (SEQ ID NO: 11),

L-I-A-Q-A-K (SEQ ID NO: 12),

L-I-A-G-G-E (SEQ ID NO: 13),

20 L-I-A-G-E-G (SEQ ID NO: 14),

A-N-V-A-E-K (SEQ ID NO: 15) and

L-I-A-K-G-K (SEQ ID NO: 16).

6. The skin care composition as in claim **5**, wherein the TGF- β mimic is A-N-V-A-E-N-A (SEQ ID NO: 1).

7. The skin care composition as in claim **1**, wherein the additional skin care active is a humectant selected from the group consisting of glycerin, propylene glycol, polyethylene glycols, polymeric polyols, alpha hydroxy acids, sugar alcohols, guanidine, urea, aloe vera gel, panthenol, dexapanthenol, allantoin, and mixtures thereof.

8. The skin care composition as in claim **7**, wherein the humectant is glycerin.

9. The skin care composition as in claim **7**, wherein the humectant is propylene glycol.

10. The skin care composition as in claim **1**, wherein the additional skin care active is a hair growth promoter selected from the group consisting of minoxidil, procyanidine B-2, prostaglandins, fluridil, ketoconazole, spironolactone, melatonin, and estrogens.

11. The skin care composition as in claim **10**, wherein the hair growth promoter is minoxidil.

12. The skin care composition as in claim **1**, wherein the additional skin care active is a retinoid selected from the group consisting of retinol, retinal, retinol esters, retinyl propionate, retinoic acid, retinyl palmitate, and mixtures thereof.

13. The skin care composition as in claim **12**, wherein the retinoid is retinol.

14. The skin care composition as in claim **1**, wherein the additional skin care active is a radical scavenger selected from the group comprising of ascorbic acid, tocopherol, tocopherol sorbate, tocopherol acetate, gallic acid, uric acid, sorbic acid, lipoic acid, dihydroxy fumaric acid, and mixtures thereof.

15. The skin care composition as in claim **14**, wherein the radical scavenger is tocopherol sorbate.

16. The skin care composition as in claim **14**, wherein the radical scavenger is tocopherol acetate.

17. The skin care composition as in claim **1**, wherein the additional skin care active is a mixture of glycerin, retinol, and tocopherol sorbate.

5 **18.** The skin care composition as in claim **1**, wherein the additional skin care active is a mixture of propylene glycol and minoxidil.

19. A method of managing the condition of skin, said method comprising the step of topically applying to the skin, a safe and effective amount of the composition in claim **1**.

20. A method of managing the condition of a scalp, said method comprising the step of
10 topically applying to said scalp, a safe and effective amount of the composition in claim **1**.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/022382

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K8/64 A61Q7/00 A61Q19/08 ADD.		
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) A61K A61Q		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data, BIOSIS, Sequence Search, EMBASE, EMBL, INSPEC, CHEM ABS Data, SCISEARCH		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/002594 A1 (BHATNAGAR RAJENDRA S [US]) 4 January 2007 (2007-01-04) paragraphs [0002] - [0005], [0015], [0024] - [0031], [0044] - [0064], [0074] - [0082], [0088] - [0097], [0108]; examples 1,3,4-6; tables 2,3 <div style="text-align: center;">-----</div>	1-20
<div style="display: flex; justify-content: space-between;"> <input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex. </div>		
<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-size: 1.2em;">26 May 2015</div>		Date of mailing of the international search report <div style="text-align: center; font-size: 1.2em;">11/06/2015</div>
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-size: 1.2em;">Steffen, Pierre</div>

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2015/022382

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007002594 A1	04-01-2007	US 2006293227 A1	28-12-2006
		WO 2007002594 A1	04-01-2007
