

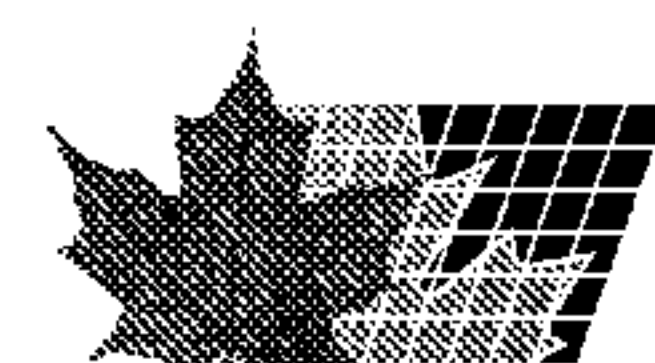


(86) Date de dépôt PCT/PCT Filing Date: 2002/06/06	(51) Cl.Int. ⁷ /Int.Cl. ⁷ A61K 31/13, A61K 31/385, A61K 31/195
(87) Date publication PCT/PCT Publication Date: 2002/12/12	(71) Demandeur/Applicant: PERRICONE, NICHOLAS V., US
(85) Entrée phase nationale/National Entry: 2003/11/26	(72) Inventeur/Inventor: PERRICONE, NICHOLAS V., US
(86) N° demande PCT/PCT Application No.: US 2002/018026	(74) Agent: PERLEY-ROBERTSON, HILL & MCDOUGALL LLP
(87) N° publication PCT/PCT Publication No.: 2002/098515	
(30) Priorités/Priorities: 2001/06/06 (09/875,317) US; 2001/07/06 (09/900,680) US; 2001/08/16 (09/931,616) US; 2002/02/27 (10/085,864) US	

(54) Titre : TRAITEMENTS TOPIQUES UTILISANT DES ALCANOLAMINES
(54) Title: TOPICAL TREATMENTS USING ALKANOLAMINES

(57) **Abrégé/Abstract:**

Skin, hair and nails are treated by topical application of compositions containing an alkanolamine such as dimethylaminoethanol to increase smoothness and surface uniformity. Application to the skin visibly decreases pore size, treats or prevents acne, diminishes or prevents cutaneous scar tissue, and/or provides a pretreatment prior to applying electrical pulses sufficient to contract subcutaneous muscles underlying the skin. Application to the hair, fingernails or toenails increases elasticity, enhances shine, and provides emolliency to keratin. Alkanolamine compositions contain at least one other adjunct ingredient such as tyrosine, lipoic acid, an α -hydroxy acid, or a fatty acid ester of ascorbic acid in most embodiments.



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 December 2002 (12.12.2002)

PCT
(10) International Publication Number
WO 02/098515 A3

(51) International Patent Classification⁷: **A61K 31/13**,
31/195, 31/385

(21) International Application Number: PCT/US02/18026

(22) International Filing Date: 6 June 2002 (06.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/875,317 6 June 2001 (06.06.2001) US
09/900,680 6 July 2001 (06.07.2001) US
09/931,616 16 August 2001 (16.08.2001) US
10/085,864 27 February 2002 (27.02.2002) US

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— with international search report

(88) Date of publication of the international search report:
4 December 2003

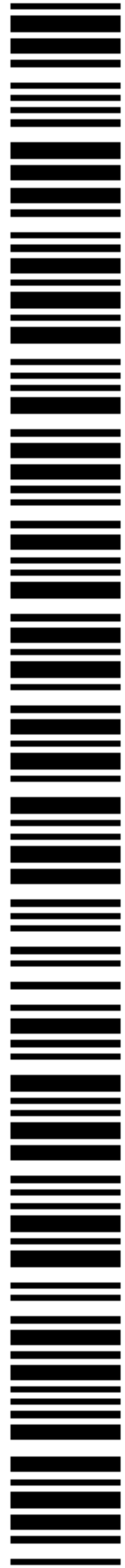
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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WO 02/098515 A3

TOPICAL TREATMENTS USING ALKANOLAMINES

CROSS-REFERENCES TO RELATED APPLICATIONS

This application claims priority benefit of U.S. application serial number 09/875,317, filed 6 June 2001, which issued as U.S. Pat. No. 6,319,942 on 20 November 2001; U.S. application number 09/900,680, filed 6 July 2001; U.S.
5 application number 09/931,616, filed 16 August 2001; and U.S. application serial number 10/085,864, filed 27 February 2002.

BACKGROUND OF THE INVENTION

Field of the Invention. This invention relates to compositions and methods for improving the appearance and health of, skin, hair, and finger- and
10 toenails, including the promotion of a homogenous, clearer skin complexion and shinier, less brittle hair and nails, the promotion of a firm skin tone and more elastic hair and nails, the reduction of skin pore size, the evening of skin texture, and the treatment of acne and cutaneous scars, providing a more attractive and youthful appearance.

15 Background of the Invention. Alkanolamines and other acetylcholine precursors and/or ingredients that produce catecholamine activity such as catecholamines and related compounds, alone or in combination with other ingredients and percutaneous penetration enhancers, have been previously described as useful for increasing skin tone and causing subcutaneous muscle contraction when topically
20 applied (U.S. Pat. Nos. 5,554,647 and 5,879,690 to Perricone; these patents and other references, including applications, cited hereafter are expressly incorporated herein in their entireties by reference). Application of these compositions penetrate the skin and shorten subcutaneous muscles, resulting in a lift in tissue on the face, chest, upper arms, upper legs or other areas of application.

- 2 -

The external wrinkled appearance of aging individuals is caused by changes in both epidermal tissue and subcutaneous changes in muscle tissue. In aging, the epidermis thins and skin appendages atrophy. Hair becomes sparse and sebaceous secretions decrease, with consequent susceptibility to dryness, chapping, and fissuring. The regularity of tissue structure is lost, and individual cells enlarge, but the total number of cells decreases approximately 30%. Intercellular collagen and elastin increases. The proportion of soluble collagen decreases, and there may be increased cross-linking between long-chain collagen macromolecules. Elastin loses its discrete structure and elasticity, and has an increased calcium content.

Changes in underlying muscle tissue accompany changes in the epidermis. When muscles are at rest, a certain amount of tautness usually remains. The residual degree of contraction in skeletal muscles is called muscle tone. In aging individuals, the degree of contraction relaxes. The effects of gravity and lengthening muscles give a sagging appearance, which is particularly obvious in the face.

Previous treatments of flaccid skin and muscles from aging typically involved plastic surgery. The plastic surgeon cuts the skin and muscle and then pulls it taut, reducing some of the tissue and discarding it, then suturing it so that the facial, chest, arm, leg, and/or buttocks muscles remain tight. As summarized above, topical application of alkanolamines diminish the effects of aging without cosmetic surgery. In one embodiment, this invention provides augmentation of these effects for improving some sagging skin conditions by using alkanolamine compositions in combination with electronic workout devices and electrical muscle stimulators used by sports trainers, professional athletes, and physical therapists.

Recent studies with the topical application of alkanolamines have led to the observation that the same or similar compositions improve the overall condition of the overlying skin, as well as hair and nails, in a variety of ways, so that topical application of alkanolamines provides an array of desirable effects in

- 3 -

addition to subcutaneous muscle contraction. One pronounced effect is a reduction of skin pore size.

Pores have a defined size which is susceptible to measurement. Pore size is largely determined by genetic, environmental, and physiological factors.

5 Visible pore diameter is often proportional to the size of subcutaneous sebaceous glands, and increased pore size is frequently associated with hyperactive sebaceous glands, including increased glandular activity and higher sebum production that occurs in adolescence, and with debris accumulation such as that observed in

10 corneum shedding of normal youthful skin. Hyperactive sebaceous glands generate larger amounts of sebum which expands the pilary canal and dilates pore diameter to accommodate greater internal pressure. The aging process causes deterioration of the dermal elements surrounding the follicle. These changes are manifested by internal collapse of supporting skin structure and expansion of the

15 follular canal, resulting in pore dilation and greater visibility on the skin surface. The visual appearance of skin pores also partially depends upon the texture of surrounding surfaces. Rough skin scatters light in a manner which emphasizes openings on the skin surface, so pores appear larger.

Current treatments for enlarged pores are directed primarily to cleaning

20 the skin to facilitate sebum and debris removal. Frequent washing is recommended for persons with oily skin, and washing with skin cleaners containing hydrating agents, for persons with normal and dry skin. Sebum production is commonly curbed using drying agents such as alcohol and benzoyl peroxide. Special formulations containing amphoteric, cationic, and anionic surfactants (and optional active

25 ingredients) that don't overdry or irritate skin have been suggested by McAtee, *et al.*, for reducing pore size, both as leave-on products or products that are rinsed or wiped from the skin after use (U.S. Pat. No. 5,607,980). Non-vasodilating vitamin B₃ compounds, particularly niacinamide, alone, but preferably in combination with retinoids, have been suggested for reducing skin pore size (U.S. Pat. No.

30 6,217,888 to Oblong, *et al.*). A composition comprising an oil absorbing powder,

- 4 -

a botanical astringent, and a biological compound that alters the structure of the skin and/or the function of the sebaceous glands, such as salicylic acid, farnesyl acetate, panthetine triacetate, pyridoxine hydrochloride (vitamin B₆), biotin, lysine carboxymethyl cysteinate, and mixtures thereof, has also been suggested for
5 visibly reducing the size of skin pores (U.S. Pat. Nos. 5,415,861 and 5,472,699 to Duffy, *et al.*).

Pore size reduction helps aid the treatment and prevention of acne, another remarkable effect seen in topical application of alkanolamine compositions. Acne is the most common pustular condition of the skin, disfiguring afflicted
10 persons with inflammatory and noninflammatory lesions (including pustules, papules and comedones) during the active phase, and with atrophic scars afterwards. It occurs most commonly in teenagers, but is not confined to adolescents, as increasing numbers of persons aged >20 years are seeking advice on treatment for acne (Brogden, R.N., and Goa, K.L., *Drugs*, 1997, 53: 511-519). Although
15 acne is generally considered to be self-limiting, its social effects can be substantial, and it may have its most severe effects on the psyche (*ibid.*). In about 60% of teenagers, disease severity and embarrassment are sufficient for them to self-medicate with proprietary preparations and/or seek medical advice.

Acne is a multifactorial disease affecting the pilosebaceous units of the
20 skin. Each unit consists of a large, multilobed sebaceous gland, a rudimentary hair and a wide follicular canal lined with stratified squamous epithelium. They are found over most of the body surface but are largest and most numerous on the face, chest, and upper back. Normally, desquamated follicular cells are carried to the surface by the flow of sebum. Under the abnormal circumstances of acne
25 vulgaris, an abnormal desquamation process provokes increased sloughing of the epithelium, which becomes more cohesive because of defective keratinization. This process causes blockage of the follicular orifice with accumulation of dead cells. Androgen stimulates the undifferentiated hormonally responsive cells making up the outer layer of the sebaceous gland lobule to divide and differentiate.
30 Sebum production favors proliferation of the anaerobe *Propionibacterium acnes*,

- 5 -

which is a normal commensal to the pilosebaceous unit, which can elicit hypersensitivity responses in acne.

The basic lesion of acne is the microcomedo. Accumulation of sebum and keratinous debris results in a visible closed comedo, or whitehead, and its
5 continued distension causes an open comedo, or blackhead. The dark color of blackheads is due to oxidized melanin. Blackheads and microcysts are noninflammatory lesions of acne, but some comedones evolve into inflammatory papules, pustules, or nodules, and can become chronic granulomatous lesions. The initial inflammatory cell in an acute acne papule is the CD4+T lymphocyte. Duct
10 rupture is not a prerequisite for inflammation, which is due to the release of pro-inflammatory substances from the duct. When inflammation develops, neutrophil chemotaxis occurs. These neutrophils secrete hydrolytic enzymes that cause further damage and increased permeability of the follicular wall. In pustules, neutrophils are present much earlier. More persistent lesions exhibit granuloma-
15 tous histology that can lead to scarring.

The aims of treating acne are to minimize the number and severity of lesions, prevent scarring, limit disease duration, and reduce the social and psychological stress that affects many patients, particularly teenagers. Conventional treatment is directed at correcting the three major factors that seem to cause acne:
20 (1) androgenic stimulation of the sebaceous glands and increased sebum production; (2) abnormal keratinization and impaction in the pilosebaceous canal causing obstruction to sebum flow; and (3) proliferation of *P. acnes*. Thus, topical agents that remove comedones, such as topical retinoids are particularly effective because they normalize desquamation within the follicular orifice, which allows the
25 sebum to flow freely onto the surface of the skin; adapalene, tretinoin, and tazarotene have been shown to have efficacy in treating mild to moderate acne, but all three have reported to have skin-irritating side effects including erythema, pruritis, burning/stinging, and scaling/flaking (*Physicians' Desk Reference*®, 56th ed. 2002, p. 2523, hereinafter referred to as "PDR"). The side effects of retinoid

- 6 -

use are so extreme that many individuals cannot tolerate topical application of these agents at all.

Salicylic acid and benzoyl peroxide have been used to treat acne for some time. Both agents dry the skin, which helps in acne management, but they
5 cause some skin irritation in perilesional skin areas of acne patients, especially patients with sensitive skin, and in some cases the erythema is extreme. Moreover, it has been recently reported that benzoyl peroxide seems to induce free radical production that can produce skin changes that qualitatively resemble ultraviolet B damage, *e.g.*, increases in epidermal thickness, and deleterious
10 changes in elastin and glycosaminoglycan content (Ibbotson, S.H., *et al.*, *J. Invest. Derm.*, 1999, 112: 933-938). Topical and oral antibiotics (especially tetracycline, erythromycin, and clindamycin) are sometimes prescribed for patients with inflammatory papules and pustules, but, in addition to the undesirability of antibiotic overuse in general, which can lead to enhanced susceptibility to infection, disad-
15 vantages to such treatments include phototoxicity and interactions with other medications. Other factors that play a role in exacerbating acne, including oil-based cosmetics and some drugs (*e.g.*, androgenic hormones, high-progestin birth control pills, systemic corticosteroids, and iodide- and bromide-containing agents) are often minimized during acne treatment.

20 Human sebum contains an unusual mixture of lipids, with the major lipid classes being triacylglycerides (TAG, conventional fat, $\approx$ 40 to 60%), wax esters ($\approx$ 19 to 26%), and squalene ($\approx$ 11 to 15%), but at least 15 different neutral and polar lipids have been identified in human sebaceous gland tissue (Downie, M.M.T., and Kealey, T., *J. Invest. Derm.*, 1998, 111: 199-205). Re-
25 cent studies have shown that people with acne have abnormal sebum secretions in that the ratios of essential fatty acids in sebaceous triacylglycerides (TAG, conventional fat) are skewed, as are the proportions of TAG, squalene and wax esters. It has been hypothesized that the viscosity and irritant level of these substances contribute to sebum obstruction and rupture of pilosebaceous units observed in.

- 7 -

acne. Lipogenesis in human sebaceous glands varies depending upon the metabolic state of the cells, glandular fluctuations, and the presence or absence of different substrates or other substances effecting competition between sterol and TAG pathways (Downie and Kealey, cited above).

5 Studies with patients having acne led to the observation that alkanol-amine compositions are also particularly useful for reducing or inhibiting scars, particularly hypertrophic and keloid scars, and striae distensae (stretch marks), caused by acne, minor lacerations, surgical wounds, vaccines, burns, and abrasions, as well as stretch marks observed in aging and after weight loss or child-
10 birth and various types of fibroses. Scars result from wound healing, which occurs in three separate phases: inflammation, formation of granulation tissue, and matrix formation. (For a review, see Sahl, W.J., and Clever, H., *Internat. J. Derm.*, 1994, 33: 681-691 (part I) and 763-769 (part II)). During the first phase, damage to endothelial cells, complement, and platelets at the wound site release
15 chemotactic factors that result in the infusion of neutrophils, lymphocytes and macrophages, which aids in the removal of infection and foreign debris. As in all inflammatory processes, there is generation of free radicals, which damages cell membranes and results in formation of oxidized proteins and fats, and cross-linked new collagen, laying a scaffold for the next phase.

20 At the end of the inflammatory phase, the granulation phase begins with an influx of fibroblasts and endothelial cells to the wound. Other key cells in this phase are macrophages and platelets. Macrophages induce the beginning of granulation by releasing platelet-derived growth factor (PDGF), tumor necrosis growth factor (TGF)- α , and an epidermal growth factor-like substance. Activated
25 platelets release epidermal growth factor (EGF), PDGF, TGF- α , and TGF- β . Together these play roles in the re-epithelialization process wherein keratinocytes cells migrate in sheaths over a provisional matrix consisting primarily of fibrin, fibronectin, type V collagen, and tenascin, and produce their own fibronectin receptors.

- 8 -

Once re-epithelization has occurred, keratinocytes resume their normal differentiated form, and matrix formation begins. Matrix formation consists primarily of the construction of derma matrix, which is regulated by fibroblasts. Chemotaxis of fibroblasts results in the production of abundant quantities of

5 hyaluronate, fibronectin, and types I and III collagen. These components comprise the bulk of the provisional extracellular matrix in the early part of this wound repair phase. Hyaluronic acid (HA) creates an open-weave pattern in the collagen/fibronectin scaffold, facilitating fibroblast movement. HA production falls after about the fifth day of wound healing, and levels of chondroitin sulfate in

10 dermatan sulfate increase. Fibronectin deposits in the collagen, and wound contraction begins. Biochemically during the contraction stage, hyaluronidase and proteinase are present, type I collagen synthesis is stimulated, and increased levels of chondroitin sulfate, dermatin sulfate and proteoglycans are observed; together these restructure the matrix. At the end of the healing process, the final scar

15 shows collagen fibers mostly parallel to the epidermis.

Hypertrophic and keloid-type scars result in extension of scar tissue so that a bulky lesion results. A keloid is an exuberant scar that proliferates beyond the original wound. It should be noted that keloids only occur in humans, often causing burning, stinging and itching sensations as well as cosmetic embarrassment.

20 ment. The etiology of unsightly keloid formation is not known. However, in keloids, fibronectin formation continues for years, while fibronectin formation in normal scars disappears within a few days after wound closure. Keloid scars exhibit a high rate of collagen synthesis in comparison to normal scars, and a low proportion of cross-linked collagen.

25 Hypertrophic scars sometimes are difficult to distinguish from keloid scars histologically and biochemically, but unlike keloids, hypertrophic scars remain confined to the injury site and often mature and flatten out over time. Both types secrete larger amounts of collagen than normal scars, but typically the hypertrophic type exhibits declining collagen synthesis after about six months. However,

30 hypertrophic scars contain nearly twice as much glycosaminoglycan as normal

- 9 -

scars, and this and enhanced synthetic and enzymatic activity result in significant alterations in the matrix which affects the mechanical properties of the scars, including decreased extensibility that makes them feel firm.

Atrophic scars are characterized by a thinning and diminished elasticity
5 of the skin due to a loss of normal skin architecture. An example of an atrophic scar is striae distensae, also known as stretch marks. Striae commonly occur in postpartum women after childbirth and also during times of larger-than-average weight gain and also in association with steroids. Atrophic scars are sometimes also observed after trauma, infection and disease, and may show loss of surface
10 markings and smoothness or dry, fine wrinkles over time.

Many scar treatments have been suggested, but few are satisfactory. Treatment of keloid or hypertrophic scars have consisted of surgical excision followed by graft application. Pressure has also been used to cause scar thinning;
15 for example, pressure bandages placed over scars have resulted in some scar thinning, but a pressure of at least about 25 mm Hg must be maintained constantly for approximately six months in usual situations for any visually observable effect. Ionizing radiation therapy has also been employed. Other treatments include application of silicone pads to the scar tissue surface, sometimes under pressure
20 provided by an elastomeric bandage, topical application of silicone gel sheets, with or without added vitamin E (Palmieri, B., *et al.*, *J. Derm.*, 1995, 34: 506-509), and topical or intralesional treatment with corticosteroids.

While not wishing to be bound to any theory, it is possible that alkanolamines such as dimethylaminoethanol, alone or in combination with adjunct
25 ingredients and therapies, are efficacious for decreasing pore size and treating acne and scars because they act as free radical scavengers and neutralizers, and prevent the cross-linking of cell membranes and proteins such as collagen and keratin. By the same token, alkanolamines modulate free radicals and other oxidative species involved in the activation of proinflammatory and inflammatory cascades that
30 cause the formation of toxic intermediates and end products, resulting in further,

- 10 -

continuous, and ultimately greater damage than that caused by the initial transient reactive species. As summarized above, transcription factors such as NF κ B and AP1 are activated in inflammation, which in turn cause production of proinflammation mediators. These mediators, such as TF α and various interleukins, cause a
5 burst of cytokines. Arachadonic acid is released, which is itself toxic, and it is oxidized to biologically active mediators. When arachadonic acid is oxidized via the cyclooxygenase or lipoxygenase pathways, for example, prostaglandins, leukotrienes, and hydroxyeicosatetraenoic acid (HETE) are produced, which cause erythema, edema, and additional free radical production accelerating the process.
10 These and other undesirable metabolites permeate and disrupt cell membranes, mitochondrial membranes, and nuclear membranes. Compositions of the invention appear to help to reverse this incessant membrane damage, including the deleterious cross-linkage and/or cleavage of proteins such as collagen and keratin and lipoproteins and oxidation of membrane lipids and lipoproteins, largely by by
15 stabilizing membranes and stimulating the formation of healthy tissue, resulting in a variety of desirable effects when applied topically to skin, hair, and nails.

BRIEF SUMMARY OF THE INVENTION

It is a primary objective of the invention to provide a composition that can be used topically to improve the appearance of skin, hair, and nails, rendering
20 them more uniform and smoother. It is a more specific objective to provide topical compositions that increase smoothness and surface uniformity by reducing pores, treating and preventing acne, treating and preventing scars, and increasing subcutaneous muscle tone. Hair and nails are rendered more uniform and smoother by softening and adding emolliency to the keratin matrix to increase elasticity
25 and luster.

These and other objectives are accomplished by this invention, which provides topical compositions containing an alkanolamine such as ethylaminoethanol, methylaminoethanol, dimethylaminoethanol, isopropanolamine, triethanolamine, isopropanoldimethylamine, ethylethanolamine, 2-butanolamine, choline,

- 11 -

serine, and mixtures thereof, which are applied to mammalian skin, hair and nails to render them more uniform and smoother. Dimethylaminoethanol is particularly preferred. Amounts of active alkanolamine ingredient range from about 0.1 to about 10%, more narrowly from about 1% to about 3%, by weight of the total composition. Adjunct ingredients such as tyrosine, lipoic acid, a fatty acid ester of ascorbic acid, *e.g.*, ascorbyl palmitate, and/or an α -hydroxy acid, *e.g.*, glycolic acid, may be added to formulations of the invention. Compositions of the invention may also be used in combination with a sulfur-containing ingredient and/or conventional acne medications for treating acne, or a muscle stimulating device in embodiments for enhancing skin tone. Methods and compositions of the invention are particularly efficacious for reducing pores on the face and scalp, including the enlarged pores often observed in adolescence and aging, for firming the skin, and for treating acne and acneform scars.

Treated hair becomes softer, shinier and more manageable, and nails become less brittle and more lustrous. Pronounced cosmetic benefits are achieved.

BRIEF DESCRIPTION OF THE INVENTION

In the practice of the invention, compositions that contain an effective amount of an alkanolamine of the formula



wherein X, Y and Z are selected from the group consisting of hydrogen, C₁-C₃ alkyl groups, C₂-C₄ alkanol group, wherein at least one of X, Y, or Z is a C₂-C₄ alkanol group bearing at least one hydroxyl group and optionally at least one carboxyl group, are topically applied to skin areas, hair, or nails to render them more uniform and smoother. As used herein, the term "nails" includes either fingernails or toenails, or both. Useful compounds for the invention include, but are not limited to, ethylaminoethanol, methylaminoethanol, dimethylaminoethanol, isopropanolamine, triethanolamine, isopropanoldimethylamine, ethylethanolamine, 2-butanolamine, choline, serine, and mixtures thereof. Many preferred embodi-

- 12 -

ments employ methylaminoaminoethanol, dimethylaminoethanol, ethylaminoethanol, and/or triethanolamine; particularly preferred is dimethylaminoethanol (DMAE).

5 The amount of alkanolamine necessary to treat skin, hair, or nails is not fixed *per se*, and necessarily is dependent upon the identity of alkanolamine employed, the amount and type of other active and adjunct ingredients employed, the user's skin, hair, or nail type, and the severity and extent of the conditions treated. Most compositions of the invention contain from about 0.1% to about 10% by weight, more narrowly from about 0.25% to about 5% to 7% by weight, and in
10 many cases from about 1% to about 3% by weight, alkanolamine such as dimethylaminoethanol in the total composition, typically in association with a dermatologically acceptable carrier more fully described below. In some examples that follow, efficacious compositions illustrating the invention contain from about 2% to 3% DMAE.

15 Many alkanolamine compositions of the invention contain at least one adjunct ingredient in addition to active ingredients. Adjunct ingredients include, but are not limited to, tyrosine, lipoic acid, α -hydroxy acids, fatty acid esters of ascorbic acid, and vitamin A and vitamin A derivatives, and, in the case of acne treatments, a sulfur-containing ingredient. Many embodiments employ more than
20 one adjunct ingredient. Where employed, adjunct ingredients have additive effects if not synergistic effects due to different mechanisms of action.

Alkanolamine compositions of the invention that comprise tyrosine typically are formulated to contain from about 0.01% to about 6%, more narrowly
25 from about 0.03% to about 5% by weight, and, in many embodiments, from about 0.2% to about 3% by weight tyrosine, based on the total composition. Compositions illustrated in the examples that follow contain from 0.1 to 5% tyrosine.

As used herein, the term " α -hydroxy acid" has reference to and encompasses the general class of organic compounds containing at least one hydroxy

- 13 -

group and at least one carboxyl group, and wherein at least one hydroxyl group is located on the α -carbon atom. Typically, the compounds are organic acids having at least one carboxylic acid group and at least one hydroxyl group on the α -carbon atom, and may contain other functional groups including additional hydroxyl and
5 carboxylic acid moieties. Preferred α -hydroxy acids and/or α -hydroxy acid derivatives are less bulky structurally so that they penetrate the skin well, and thus have a backbone of from one to three carbon atoms such as those more fully described in U.S. Pat. No. 5,965,618 to Perricone at column 6 lines 4 to 29. Where employed, glycolic and/or lactic acid or their derivatives are preferred;
10 glycolic acid is especially efficacious. Glycolic acid or other α -hydroxy acids are typically present in amounts ranging from about 1% to about 10%, more narrowly from about 3% to about 7% of the total composition.

Fat-soluble fatty acid esters of ascorbic acid (vitamin C) is employed as
15 an adjunct ingredient in other embodiments, alone or in combination with tyrosine and/or α -hydroxy acids. The more oxidation-resistant saturated fatty acid esters of ascorbic acid are preferred, including, but not limited to, ascorbyl laurate, ascorbyl myristate, ascorbyl palmitate, ascorbyl stearate, and ascorbyl behenate. As is known by skilled workers, ascorbic acid esters include mono-, di-, tri- and
20 tetraesters, and mixtures thereof. Ascorbyl palmitate is used in one embodiment. As denoted herein, where fatty acid esters are described, *e.g.*, ascorbyl stearate, compositions having predominantly that ester, *e.g.*, predominantly stearate, are included. The esters may be prepared using hydrogenated oils or fats, or fractions thereof, and contain small amounts of another ester. Ascorbyl stearate prepared
25 using canola, for example, commonly contain about 4% ascorbyl palmitate. It is an advantage of the invention that where fatty acid esters of ascorbic acid are employed as an adjunct ingredient, they help stabilize the alkanolamine in the composition. Ascorbyl palmitate and the like ascorbyl esters are typically present in amounts ranging from about 0.5% to about 15%, preferably from about 1% to
30 about 7% to 10%, of the total composition. Vitamin A or vitamin A derivatives may be alternative or additional adjunct ingredients in like concentrations.

- 14 -

Vitamin A and vitamin A derivatives include, but are not limited to, retinol, retinyl palmitate, retinoic acid, retinal, and retinyl propionate.

As summarized above, compositions of the invention are efficacious as acne treatments. As used herein, the term "acne" includes all types of acne
5 involving the skin and its oil glands and hair follicles in all stages, including acne vulgaris observed in adolescents, acne observed in endocrinologic conditions characterized by excess androgen secretion, and the like, in the active inflammatory (pustule-, papule-, comedone-forming) and noninflammatory (blackhead- and cyst-forming) phases, and post-inflammatory (healing, scarring, and scarred)
10 phase. By "reducing redness and inflammation" is meant visibly reducing apparent erythema in the skin. In typical embodiments, erythema is visibly reduced in both the acne lesions and in perilesion areas surrounding microcomedos. Improved acne products and therapies of the invention visibly decrease the number of blackheads, whiteheads, pimples, and blemishes, decrease the severity of lesions
15 and shorten their healing time, and minimize or eliminate erythema.

Compositions of the invention may be formulated with effective amounts of other active ingredients found in conventional medications or used in therapies with conventional medications. "Conventional acne medications" encompasses previously described compositions containing effective amounts of active anti-acne
20 ingredients. The term includes, but is not limited to, the over-the-counter acne drug products set out in 21 C.F.R. § 333.310 for the management and treatment of acne, namely sulfur, resorcinol, resorcinol monoacetate, combinations of sulfur and resorcinol, and salicylic acid, as well as readily available commercial products that contain benzoyl peroxide as an active ingredient. "Conventional acne medica-
25 tions" also include previously described anti-acne compositions that contain effective amounts of comedolytic and keratolytic agents and/or compounds that dry the skin and absorb sebum generally available without a prescription including, but not limited to, other peroxides such as lauroyl peroxide or carbamide peroxide, ethanol, phenoxy ethanol, propanol, phenoxy propanol, ethyl acetate, azelaic acid,
30 fuming acid, dehydroacetic acid, pyruvic acid, urea, cetyl betaine, scymnol sulfate,

- 15 -

cholate, deoxycholate, flavinoids, and soaps and natural plant extracts that diminish the oily/shiny appearance of skin. "Conventional acne medications" further include those typically available with a prescription, including anti-acne compositions containing effective amounts of retinoids or antibiotics. Adalpalene, tretinoin, and tazarotene are retinoids that have been used in conventional acne medications. Antibiotics used in anti-acne medications administered orally or topically, typically the latter, include effective amounts of erythromycin, antibiotics of the lincomycin family, particularly lincomycin and clindamycin, and antibiotics of the tetracycline family, particularly tetracycline, doxycycline, meclocycline, and minocycline.

Compositions of the invention that are particularly efficacious for acne contain a sulfur ingredient such as, but is not limited to, sulfur, sulfacetamide, a combination of sulfur and resorcinol (often called "sulfur resorcinol" in the literature), a combination of sulfur and resorcinol monoacetate, lipoic acid, glutathione, and their biologically active derivatives. Sulfur ingredients are typically present in the alkanolamine compositions of the invention in amounts ranging from about 0.1% to 0.5% up to 15%, more narrowly from about 0.5% to 10% by weight. Sulfur (5%) and sodium sulfacetamide (10%) are active ingredients marketed as a Plexion™ suspension. Where sulfur and resorcinol or sulfur and resorcinol monoacetate are all are part of the sulfur ingredient, typical concentrations range from about 3% to about 8 to 10% by weight of the composition.

Lipoic acid is the sulfur ingredient used in some embodiments illustrated hereafter. The term "lipoic acid" encompasses thioctic acid (1,2-dithiolane-3-pentanoic acid; 1,2-dithiolane-3-valeric acid), $C_8H_{14}O_2S_2$, formula weight 206.32, and its reduced form, dihydrolipoic acid. It has been variously known as acetate replacing factor, protogen A, and pyruvate oxidation factor. As used herein, where the properties and advantages of "lipoic acid" (or LA) are discussed as an active ingredient in the practice of the invention, both lipoic acid and its derivatives are encompassed. "Lipoic acid derivatives" include thioctic acid esters,

- 16 -

particularly alkyl esters such as fatty acid esters, amides, particularly those isolated from or mimicking naturally occurring lipoamides, salts, particularly alkali metal salts, anhydrides and specifically includes the reduced form, dihydro-lipoic acid and its esters, amides and salts. One particularly efficacious derivative
5 that exhibits increased cellular uptake and biological activity useful in the practice of the invention is N,N-dimethyl,N-2-amidoethyl lipoate recently described by Sen, C.K., *et al.* (*Free Radical Biol. Med.*, 1998, 25: 89) and called lipoic acid plus (LA-Plus). Derivatives may also include those involving other reactive groups known to those skilled in the art. As used herein, the term "derivatives"
10 includes metabolic precursors of lipoic acid. Where lipoic acid derivatives are employed, they must be functionally equivalent to lipoic acid.

Since lipoic acid is both fat- and water-soluble, it is an advantage of the invention that, where employed, lipoic acid can be used as an active ingredient in either lipid or aqueous-based compositions, and it readily crosses cellular mem-
15 branes and disperses in extracellular and intracellular tissue components. It is another advantage of the invention that lipoic acid has been used previously for the treatment of scars (U.S. Pat. No. 5,965,618 to Perricone), including atrophic acneform scars, and for the treatment of acne (U.S. Ap. Ser. No. 09/475,514, filed 30 December 1999 and allowed on 21 December 2001). Employing it with
20 alkanolamines and other active ingredients significantly improves the effect. Lipoic acid-containing formulations typically contain from about 0.1% to about 7% by weight lipoic acid. Many embodiments contain more than 1 weight % lipoic acid, *e.g.*, from about 1.1% to about 3 to 5% by weight lipoic acid. One efficacious embodiment contains from about 2% to about 3% lipoic acid by
25 weight.

Another sulfur ingredient useful in alkanolamine acne compositions and illustrated hereafter is glutathione. The term "glutathione" encompasses the tripeptide N-(N-L- γ -glutamyl-L-cysteinyl)glycine, often called L-glutathione, glutathione-SH, or γ -Glu-Cys-Gly, and sold under a variety of tradenames such as
30 Agifutol STM, CoprenTM, DeltathioneTM, IsethionTM, NeuthionTM, TathiclonTM, TathionTM

- 17 -

and Triptide™. An advantage of this embodiment of the invention is that glutathione, the major low molecular weight thiol in living plant or animal cells, is readily available and known to be safe when applied topically. As used herein, where the properties and advantages of "glutathione" (or GSH) are discussed as an active ingredient in the practice of the invention, biologically active glutathione derivatives are encompassed. "Glutathione derivatives" include, but are not limited to, reduced glutathione (or GSSG), glutathione salts, particularly reduced glutathione potassium or sodium salts, and glutathione alkyl esters, particularly C₁ to C₁₀ alkyl esters, especially monoesters such as monomethyl and monoethyl esters which have the glycine carboxylic acid group acylated, as these have been shown to increase cellular levels of glutathione (U.S. Pat. No. 4,710,489 to Meister), and corresponding amides and imides (such as those set out in U.S. Pat. No. 5,541,162 to Ohmori, *et al.* Where employed, glutathione-containing compositions of the invention contain from about 0.5% to about 15%, more narrowly from about 5% to about 10% by weight, and even more narrowly from about 8% to about 10% by weight glutathione.

Compositions of the invention may be formulated to contain other anti-acne active ingredients used in conventional acne medications including, but not limited to, peroxides such as benzoyl peroxide, lauroyl peroxide, and carbamide peroxide; alcohols such as ethanol, phenoxy ethanol, propanol, phenoxy propanol, resorcinol; other compounds known to dry skin such as ethyl acetate; acids such as salicylic acid, azelaic acid, fuming acid, dehydroacetic acid, and pyruvic acid; urea and/or cetyl betaine; scymnol sulfate; cholate and/or deoxycholate; retinoids such as adapalene, tretinoin, and tazarotene; antibiotics such as erythromycin, lincomycin, clindamycin, tetracycline and meclocycline; and the others previously mentioned, and mixtures of any of these. As summarized above, using other anti-acne active ingredients in combination with alkanolamine active ingredients improves the overall therapy in many cases. Conventional anti-acne active ingredients are added to alkanolamine compositions in effective amounts such as those found in commercial products; example ranges are set out below with their descriptions. However, many formulations containing other active

- 18 -

ingredients in alkanolamine compositions have a short shelf life. Therefore, preferred methods of the invention which incorporate conventional acne medications are those in which the alkanolamine composition is applied topically to affected skin areas before or after topical application of a commercial acne
5 product. In preferred embodiments, the alkanolamine composition is applied before applying the conventional acne medication. Further details about this embodiment are given below.

In embodiments especially adapted to the treatment of aging and sagging skin and subcutaneous muscle tissue involving the use of a muscle stimulator,
10 compositions of the invention are preferably formulated with an adjunct ingredient that exhibits catecholamine activity, *i.e.*, a catecholamine, a catecholamine-related compound and/or a catecholamine mimic. By "catecholamine" is meant any one of a group of amines that act upon nerve cells as neurotransmitters or hormones. This group of similar compounds having a sympathomimetic action typically are
15 molecules having an aromatic portion derived from catechol (2-hydroxyphenol) and an aliphic amine portion. Catecholamines include, but are not limited to, dopamine (5-hydroxytryptamine), norepinephrine (noradrenaline; 4-(2-amino-1-hydroxyethyl)-1,2-benzenediol), and epinephrine (adrenaline; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-benzenediol). As used herein, dopa (3,4-dihydroxy-
20 phenylalanine) and serotonin (5-hydroxytryptamine) are also included in this group.

Catecholamine-related compounds include catecholamine precursors, catecholamine mimics, chemicals that augment the release of catecholamines, and mixtures of these with each other and with catecholamine. Catecholamine precursors include any in the synthetic pathway such as, for example, tyrosine, dopa,
25 phenylalanine, and mixtures thereof. Tyrosine is particularly preferred. Catecholamine mimics include, but are not limited to, sympathomimetic amines that function similarly, augmenting, for example, the release of norepinephrine, such as tyramine, ephedrine, amphetamine, and mixtures thereof. Chemicals that
30 augment the release of catecholamines specifically include those that augment

- 19 -

release such as co-factors of enzymes in the metabolic pathway, *e.g.*, tetrahydrobiopterin and pyridoxine, as well as inhibitors of enzymes that inactivate catecholamines such as inhibitors of catechol-O-methyltransferase and monoamine oxidase.

5 Only effective amounts of alkanolamine compositions are needed to provide observable improvement in skin, hair, and nails when used alone, or in combination with other ingredients, so generally topical application is accomplished in association with a carrier, and particularly one in which the alkanolamine active ingredient is soluble *per se* or is effectively solubilized (*e.g.*, as an
10 emulsion or microemulsion). Where employed, the carrier is inert in the sense of not bringing about a deactivation or oxidation of the active ingredient(s), and in the sense of not bringing about any adverse effect on the skin areas to which it is applied. In one preferred practice of the invention, the active ingredients are applied in admixture with a dermatologically acceptable carrier or vehicle (*e.g.*, as
15 a lotion, cream, ointment, soap, stick, or the like) so as to facilitate topical application and, in some cases, provide additional therapeutic effects as might be brought about, *e.g.*, by moisturizing of the affected skin and cuticle areas, or the hair. While the carrier for dermatological compositions can consist of a relatively simple solvent or dispersant such as water, it is generally preferred that the carrier
20 comprise a composition more conducive to topical application, and particularly one which will form a film or layer on the skin to which it is applied so as to localize the application and provide some resistance to washing off by immersion in water or by perspiration and/or aid in the percutaneous delivery of the active agent(s). Many preparations are known in the art, and include lotions containing oils and/or
25 alcohols and emollients vegetable oils, hydrocarbon oils and waxes, silicone oils, animal or marine fats or oils, glyceride derivatives, fatty acids or fatty acid esters or alcohols or alcohol ethers, lecithin, lanolin and derivatives, polyhydric alcohols or esters, wax esters, sterols, phospholipids and the like, and generally also emulsifiers (nonionic, cationic or anionic), although some of the emollients
30 inherently possess emulsifying properties. These same general ingredients can be formulated into a cream rather than a lotion, or into gels, or into solid sticks by

- 20 -

utilization of different proportions of the ingredients and/or by inclusion of thickening agents such as gums or other forms of hydrophilic colloids. One preferred embodiment is a solution used to saturate a pad used to wipe affected areas; another is a cleanser; another is a shampoo; and others are lotions, 5 creams, and gels. Such compositions are referred to herein as dermally or dermatologically acceptable carriers, and are formulated using conventional techniques known to those of ordinary skill in the art.

Suitable carriers include water, alcohols, oils and the like, chosen for their ability to dissolve or disperse active ingredients. Generally, even low 10 concentrations of active ingredients in a carrier are suitable, depending upon the application regimen and the active and adjunct ingredients employed. Mild skin and hair conditions typically require lower concentrations of active ingredients than do acute conditions. As a practical matter, however, to avoid the need for repeated application, it is desirable that the topically applied composition be 15 formulated to contain the amounts of active ingredients set out above. Generally in the practice of methods of the invention, the composition is topically applied to the affected skin areas as needed to the face, to lesions and scars, often as a tinted cover-up, or at predetermined intervals as a cleanser or a lotion, cream, or gel for the skin, hair, or nails, it generally being the case that gradual improvement is 20 noted with each successive application. Insofar as has been determined based upon clinical studies to date, no adverse side effects are encountered. It is an advantage of the invention that compositions of the invention do not require a pharmaceutical prescription.

Topical compositions of the invention can comprise additional ingredi- 25 ents commonly found in skin and hair care compositions and cosmetics, such as, for example, tinting agents, tinting agents, emollients, skin conditioning agents, emulsifying agents, humectants, preservatives, antioxidants, perfumes, chelating agents, *etc.*, provided that they are physically and chemically compatible with other components of the composition. Preservatives include, but are not limited 30 to, C₁-C₃ alkyl parabens and phenoxyethanol, typically present in an amount

- 21 -

ranging from about 0.5% to about 2.0% by weight percent, based on the total composition. Emollients, typically present in amounts ranging from about 0.01% to 5% of the total composition include, but are not limited to, fatty esters, fatty alcohols, mineral oils, polyether siloxane copolymers, and mixtures thereof.

5 Humectants, typically present in amounts ranging from about 0.1% to about 5% by weight of the total composition include, but are not limited to, polyhydric alcohols such as glycerol, polyalkylene glycols (*e.g.*, butylene glycol, propylene glycol, dipropylene glycol, polypropylene glycol, and polyethylene glycol) and derivatives thereof, alkylene polyols and their derivatives, sorbitol, hydroxy

10 sorbitol, hexylene glycol, 1,3-dibutylene glycol, 1,2,6-hexanetriol, ethoxylated glycerol, propoxylated glycerol, and mixtures thereof. Emulsifiers, typically present in amounts from about 1% to about 10% by weight of the composition, include, but are not limited to, stearic acid, cetyl alcohol, stearyl alcohol, steareth 2, steareth 20, acrylates/C₁₀₋₃₀ alkyl acrylate crosspolymers, and mixtures thereof.

15 Chelating agents, typically present in amounts ranging from about 0.01% to about 2% by weight, include, but are not limited to, ethylenediamine tetraacetic acid (EDTA) and derivatives and salts thereof, dihydroxyethyl glycine, tartaric acid, and mixtures thereof. Antioxidants, typically present in an amount ranging from about 0.02% to about 0.5% by weight of the composition, include, but are not

20 limited to, butylated hydroxy toluene (BHT); vitamin C and/or vitamin C derivatives, such as fatty acid esters of ascorbic acid, particularly ascorbyl palmitate; butylated hydroanisole (BHA); phenyl- α -naphthylamine; hydroquinone; propyl gallate; nordihydroquiaretic acid; vitamin E and/or derivatives of vitamin E, including tocotrienol and/or tocotrienol derivatives; calcium pantothenates; green

25 tea extracts; mixed polyphenols; and mixtures of any of these. As mentioned above, particularly preferred antioxidants are those that provide additional benefits to the skin such as ascorbyl palmitate. (See additional ingredients and methods in U.S. Pat. Nos. 4,775,530, 5,376,361, 5,409,693, 5,545,398, 5,574,063, 5,643,586, 5,709,868, 5,879,690, 5,965,618, 5,968,618, 6,051,244, 6,162,419,

30 and 6,191,121 to Perricone).

- 22 -

Buffering agents are employed in many compositions. Preferably, the amount of buffering agent is one that results in compositions having a pH ranging from about 4.5 to about 8.5, more preferably from about 5.5 to about 8.5, most preferably from about 6.5 to about 8.0. Typical buffering agents are chemically
5 and physically stable agents commonly found in cosmetics, and can include compounds that are also adjunct ingredients such as citric acid, malic acid, and glycolic acid buffers.

As summarized above, alkanolamine compositions of the invention may be applied before or after application of a conventional acne medication available
10 over-the-counter or by prescription. These methods are particularly efficacious in therapies for moderate to severe acne and advantageously combine the anti-inflammatory and anti-acne properties of alkanolamine compositions of the invention, and take advantage of the comedolytic, keratolytic, and drying properties of other anti-acne ingredients previously described, while minimizing the
15 redness and inflammation often caused by when these products are applied to skin, especially sensitive skin. Many conventional acne medications contain 0.5% to 2% salicylic acid or 3% to 10% benzoyl peroxide, marketed as Aveeno®, Benvoxyl®, Bioré®, Clean and Clear®, Clinac™, Clearasil®, ClearLogix®, Fostex®, Oxy Balance®, PanOxy®, SalAc®, Stridex®, Triz®, and ZapZit® products sold as
20 gels, creams, lotions, astringents, bars, and cleansers. A 20% azelaic acid cream is sold under the name Finevin™.

Alkanolamine compositions of the invention are especially useful when used before or after topical application of a composition containing at least one retinoid. Useful retinoids include commercially available adapalene, tazarotene
25 and/or tretinoin. Adapalene, for example, is sold as a gel or solution marketed as Differin®. Tretinoin can be obtained as a cream, gel or encapsulated microsphere marketed as Avita®, Renova®, Retin-A®, or Retin-A® Micro®. Tazarotene is marketed as a Tazorac® gel. Effective formulations typically contain from about 0.025% to about 0.1% by weight retinoid or retinoid mixture. It is an advantage
30 of the invention that use of alkanolamine compositions with retinoid compositions

- 23 -

methods for treating acne that can employ less retinoid than would be required if a retinoid is used alone, further minimizing skin irritation observed in some patients. It is unfortunate that many acne patients in their zeal to rid themselves of blemishes and pimples tend to overuse the medications. Using compositions of the invention can reduce this amount and the duration of drug use in patients presenting acne conditions warranting the beneficial normalizing desquaminating properties that retinoids can provide, and alleviate side effects. Compositions of the invention also minimize or eliminate skin irritation, particularly in areas surrounding acne lesions, while at the same time treating acne lesions and reducing pore size.

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Alkanolamine compositions may also be used in combination with topical antibiotics such as tetracycline, clindamycin, and erythromycin sometimes used for acne cases, particularly for patients with inflammatory papules and pustules. Clindamycin, for example, is sold in a gel, lotion, solution, marketed as BenzaClin™, Cleocin T®, Clindagel™, and Clindets® (which also contains 5% benzoyl peroxide). Erythromycin is sold in a gel marketed as Emgel®. Doxycycline is a tetracycline marketed as a Vibramycin® monohydrate suspension; another tetracycline, minocycline, is also marketed as a Minocin® suspension. Topical antibiotics typically contain from about 0.05% to 0.5% to about 2% active ingredient; formulations containing 1% antibiotic are common. As with retinoid therapy, an advantage of using alkanolamine compositions with antibiotics in cases where the latter are indicated is that a lower antibiotic dose or a shorter antibiotic regimen may be employed. As has been mentioned, it is now recognized that prevalent use of antibiotics in general is undesirable, and long-term use of antibiotics can cause enhanced susceptibility to infection, nausea, gastrointestinal upset, phototoxicity, and interactions with other medications. Use of alkanolamines advantageously augments the treatment and minimizes the amount of antibiotic necessary to cause improvement in patients presenting with an extreme inflammatory phase of acne, and helps to minimize or eliminate side effects.

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In therapies that combine topical application of compositions of the invention and topical application of conventional acne medications, alkanolamine

- 24 -

compositions are preferably applied first, followed by application of a commercial product. This prevents erythema caused by the product. Saturated pads were used for this purpose in examples that follow; alkanolamine compositions were wiped on affected skin areas, which were then treated with a gel or cream containing a
5 retinoid, a peroxide, or an antibiotic. However, as set out above, any other topical administration may be used. In alternate embodiments, alkanolamine compositions are administered after treatment with a conventional medication or during treatment. Best results are obtained if the two compositions are applied immediately before or immediately after one another, but the invention encompasses
10 es embodiments involving a lag period between dosings.

In embodiments where an electronic muscle stimulator or other device is used to enhance subcutaneous muscle tone after application of an alkanolamine composition of the invention, the composition is typically applied to aging and sagging skin areas, and then electrical pulses sufficient to cause subcutaneous
15 muscles to contract are applied to the areas. Typical stimulators deliver pulses having a relatively high voltage-to-width ratio and a steep waveform to achieve optimal muscle contraction without discomfort. Any previously described muscle stimulating device such as that used by athletes and their trainers and physical therapists may be used, and facial exercisers are particularly preferred. (See, for
20 example U.S. Pat. No. 3,861,651 to Icenbice, U.S. Pat. No. 3,387,147 to Radwan, and U.S. Pat. No. 4,062,365 to Kameny.) These employ batteries or wall current, and typically comprise terminals applied to affected skin areas attached to a regulating device, but facial masks containing electrodes may also be employed.

25 Optimum stimulation typically requires pulses having a relatively high voltage-to-width ratio and a steep waveform. High voltage, wide-width pulses having a low rising wave front produce undesirable stinging sensations. Low voltage, wide-width pulses do not induce proper muscular contraction. Preferred devices provide a pulse output having an adjustable amplitude level to suit the
30 needs of the individual user; these ordinarily exhibit a sharp rising voltage

- 25 -

waveform of an optimum width to induce proper muscle contractions. Most devices comprise at least three electrodes, but one or two will suffice, and the number may be extended to any desired number. Preferred individual pulses have a total duration not over a few seconds, preferably not over about 5 seconds, and
5 optimally between about one-fourth of a second and 2 seconds, delivering an output current of up to about 120 mA, but lower or higher pulses varying frequency, pulse width, intensity and pulse signals can be used to control the amount and strength of the impulses as described by the device manufacturer. (See, for example, FlexTONE™ instructions at <http://www.flextone.com>.) Commercially
10 available muscle stimulators include, but are not limited to, Derma-Tone™ facial exercisers and FlexTONE™ electronic muscle stimulators. After a pulse, there is a rest period of a duration not over a few seconds, preferably not over about 10 seconds, and optimally between about one-half and four seconds, when there is no output current.

15 The peak-to-peak current delivery mimics the natural brain stimulation of muscle tissue, delivering gentle electrical pulses to the muscles, causing them to contract and then relax, as if the message were coming from the brain. An advantage to this embodiment of the invention is that it mimics nature. Also electronic muscle stimulation not only improves subcutaneous muscle tone as part
20 of the anti-aging treatment and provides cosmetic benefits by improving an individual's appearance, but muscle stimulation often provides relief from minor pain, tiredness, and stress, contributing to an overall relaxed and refreshed feeling after treatment.

A muscle stimulator that delivers appropriate electrical pulses using electrodes in the fingertips of a device that fits on the hand as fingertips (Perricone
25 U.S. Des. Ap. Ser. Nos. 29/148,554, filed 24 September 2001 and allowed 7 March 2002, or 29,151,068, filed 31 September 2001 and allowed 8 March 2002) or a glove (Perricone U.S. Des. Ap. Ser. No. 29/148,565, filed 21 September 2001, and allowed 21 March 2002) have been described. The designs allow for
30 efficient and easy application of electrical stimuli to whatever regions of the body

- 26 -

the user desires, without the cumbersome attachment of current terminals or electrodes. Treatment cycles are conveniently short. The device is compact, portable, and lightweight. Simple designs by others may also be employed; see, for example the facial exercisers depicted in U.S. Des. Pat. No. 282,949 to Arve
5 and U.S. Des. Pat. No. 397,173 to Edell.

For scar treatments, a silicone gel sheet or other linament to which alkanolamine compositions of the invention have been added may be employed. These may be pressure or adhesive bandages. Silicone gel sheets useful in the practice of the invention are typically cross-linked polydimethylsiloxane containing
10 or impregnated with alkanolamine. It is an advantage of the invention that DMAE and other active alkanolamines augment the effectiveness of previously disclosed methods of using lipoic acid and/or silicone pads or gel sheets for diminishing scars (see U.S. Pat. No. 5,965,618 to Perricone and Palmieri, *et al.*, cited above).

15 It an advantage of the invention that topical administration of alkanol-amine compositions provide a number of beneficial effects summarized above: alkanolamines advantageously treat and prevent skin damage and aging (U.S. Pat. No. 5,554,647 to Perricone), increase subcutaneous muscle tone (*ibid.*), prevent and treat acne scars and other disfigurements, and cause visible contraction of skin
20 pores, often within 10 to 15 minutes after application, resulting in a clearer, smoother appearing complexion, firmer skin tone, and a healthier look. The results are cumulative. With continued applications, skin tone increases and pores become smaller and tighter over time, enhancing the appearance of skin, especially in patients with acne or scars, where lesions and scars simultaneously diminish. -
25 Beneficial effects are immediate, and formulations of the invention are well-tolerated by the skin and scalp. It is another advantage of the invention already discussed that alkanolamines are anti-inflammatories, and decrease erythema in both lesions and perilesional areas of persons with acne. Since compositions of the invention are both anti-inflammatory and anti-acne, their use in combination
30 with conventional acne medications, particularly those requiring a prescription, reduce the need for frequent application of these products and high concentrations

- 27 -

of irritating ingredients in these products. Use of combination treatments thus provides superior acne therapies. Taken together, all these effects increase the smoothness and surface uniformity of the skin.

Where a muscle stimulating device is used together with alkanolamine compositions of the invention, an important advantage is the synergy provided by using electronic subcutaneous muscle stimulation together with biochemical subcutaneous muscle stimulation caused by topical application of the composition. Simultaneously providing neurotransmitter precursors and electrical pulses results in greater muscle tightening and toning than what is achieved by using either electronic or biochemical stimulation alone or by using electronic or biochemical stimulation sequentially. The result is a more youthful appearance to the skin and the body areas to which the treatment is applied, shaping and toning. This is particularly true of the face. The combination treatment decreases wrinkles, and firms nasolabial folds, the mandibular region, and sagging around the eyes, resulting in a smoother, tighter, more youthful appearance. Patients benefit not only from favorable cosmetic effects using the treatment, *e.g.*, reduced pore size, diminished scars, and, where present, diminished acne lesions, but also find the treatment contributes to an overall relaxed and refreshed feeling. Over time, the muscles actually appear to shorten so that persons using the treatment look as though they've had a facelift or other cosmetic surgery. And the therapy can be easily managed by an individual alone at home or at a health club or gym, and the like, without cumbersome equipment, prescription drugs, or surgery. No assistance from a physician or other technical person is required to operate the equipment, and the composition ingredients are safe. Insofar as has been determined to date, no adverse side effects are encountered.

Treatment of hair with compositions of the invention, typically used as a shampoo or rinse, render hair softer, more manageable, and shiny, and the effect is pronounced in the treatment of sun- or chemically bleached hair, including chlorine-bleached hair. Magnification of individual treated hairs show visibly more intact keratin and smoother, less fragmented shanks than untreated controls.

- 28 -

Application of alkanolamine compositions to nails results in their becoming more lustrous and considerably less brittle. While not wishing to be bound by any theory, preferred compositions containing lipid penetrants seem to drive active ingredients into the hair shaft and nail surface, softening the keratin matrix, providing emolliency to the keratin and making it more elastic. And, as illustrated in the examples that follow, the effect is cumulative. Successive applications enhance the appearance of both hair and nails.

EXAMPLES

The following examples are presented to further illustrate and explain the present invention and should not be taken as limiting in any regard. Unless otherwise indicated, all percentages are by weight of the total composition.

Example 1

A phospholipid-based lotion containing 5% DMAE, 5% tyrosine, and 1 to 3% lipoic acid was applied to facial skin of test subjects. Pore size was visibly reduced in all subjects within an hour. In an open, unblinded study involving twice daily application of the composition over 2 to 3 months to subjects presenting with uneven skin having enlarged pores and a few blemishes resulted in a very pronounced smoother, more porcelain-like complexion of treated subjects when compared to the uneven, ruddy complexion of control subjects.

Example 2

This example summarizes trials using alkanolamine compositions of the invention for treating scars.

A double-blind, placebo-controlled study was conducted on 15 children who had just undergone surgery for a cleft palate. A formulation containing 3% DMAE, 5% tyrosine, and 3% lipoic acid was applied twice daily post-operatively

- 29 -

to the lips of patients by their parents for a period of one year. At the end of the year, test patients had less scarring and no observable lip deformity, a considerable improvement over the control, untreated patients who all showed more evidence of the surgery.

5 An open, unblinded study of 8 to 10 patients presenting with acne atrophic scars were treated twice daily with a formulation containing 5% DMAE, 5% tyrosine and 5% lipoic acid for a period of 8 months. Patients in the test group showed an 80% reduction in the scars.

10 Silicone gel bandages saturated either with a 5% DMAE solution and 5% tyrosine, or a 5% DMAE solution containing 5% tyrosine and 0.1% to 2% lipoic acid both resulted in significant improvement in wound healing over control bandages containing no alkanolamines used to dress the same type of wound.

Example 3

15 This example describes clinical trials illustrating the efficacy of using compositions and methods of the invention for the treatment of acne.

 A cream composition containing 2% dimethylaminoethanol, 0.5% tyrosine, 2% lipoic acid, and 2% glycolic acid was applied to affected skin areas of acne patients twice daily during an eight-week trial. Both inflammatory and noninflammatory lesions were significantly diminished.

20 A cover-up composition containing 3% dimethylaminoethanol, 0.5% tyrosine, and 10% glutathione in a tinted base was applied as needed to inflammatory papules and nodules in skin areas affected by acne. Not only was a reduction in the severity of the lesions observed, but also there was an observable decrease in the length of lesion healing time during the duration of a two-week trial.

25 Another successful cover-up composition contained 2% dimethylaminoethanol, 2% lipoic acid, 10% glutathione, and 0.2% tyrosine in a similar study; it was noted by the patients that this composition was especially efficacious in drying the lesions.

30 A cleanser composition containing 2% dimethylaminoethanol, 0.2% tyrosine, and 0.2% lipoic acid was tested by washing affected skin areas of acne

- 30 -

patients twice daily with the formulation. The patients showed improvement over the four weeks of the test. Improvement was also observed in patients washing with a cleanser containing 0.5% ascorbyl palmitate and the same amounts of DMAE, tyrosine, and lipoic acid.

5 A pad saturated with a solution containing 3% dimethylaminoethanol, 0.5% tyrosine, 1% salicylic acid, and 0.1% lipoic acid was used as a face wipe twice daily on affected skin areas of acne patients. Improvement was observed during the course of the several week trial.

 A double-blind, placebo-controlled study involving 50 acne patients
10 underwent an intensive treatment involving the sequential application, twice daily, of the DMAE products described above. Test patients prepared their faces by first cleansing them with the DMAE cleanser, then using a pad saturated with DMAE, and then applying a cover-up composition containing 10% DMAE, 2% lipoic acid, and 5% tyrosine. The control group followed the same regimen with the same
15 bases of the products containing no active ingredients. Significant ($p < .05$) improvement was observed in the resolution of lesions in the treated patient group.

Example 4

 This example illustrates the efficacy of using compositions of the
20 invention with conventional acne treatments to reduce skin irritation observed with conventional treatments and to maximize the therapy.

 In one trial, affected skin areas of acne patients were wiped with a pad saturated with a solution containing 3% dimethylaminoethanol, 0.5% tyrosine, and 2% lipoic acid. Afterwards, a commercial 2% benzoyl peroxide gel product was
25 applied to the same areas following instructions on the product's label. Less skin irritation was observed with this sequential treatment than that observed when the same patients used the benzoyl peroxide gel alone on another day. The same results were obtained when pads saturated with the same composition containing DMAE, tyrosine, and lipoic acid were used as a wipe before applying a commer-
30 cial 2% salicylic acid acne treatment composition. Significantly less skin irritation

- 31 -

was observed when the therapy involved pretreatment with compositions of the invention.

Another trial compared skin irritation observed when a commercial Retin A[®] was used on acne lesions and irritation observed when skin areas were
5 treated with compositions of the invention beforehand. In this test, patients wiped affected skin areas with pads saturated with 3% dimethylaminoethanol, 0.2 % tyrosine, and 2% lipoic acid and then applied 0.1% Retin-A[®]. Pretreatment according to the invention resulted in significantly less skin irritation than that observed when tretinoin alone was applied, and patients who could not tolerate
10 Retin-A[®] could use it if they wiped their acne with pads of the invention before applying tretinoin. Moreover, acne skin regions on all patients using the combination therapy was considerably improved over regions treated with the Retin-A[®] product alone.

Example 5

15 A formulation containing 5% DMAE and 5% tyrosine was applied to the faces of subjects, who then underwent a standard 20 to 30-minute treatment of electronic muscle stimulation using the commercial Derma-Tone[™] facial massager once a day for a week. A significantly more youthful facial appearance, with fewer eye and mouth lines, was observed in the group using DMAE pretreatment
20 and the facial massager when compared with a control group using the facial massager only after 5 or 6 days.

Example 6

Hair rinses formulated to contain 0.1% to 3% DMAE either in a phospholipid base, a cationic hair conditioner base, or a nonionic shampoo all out-
25 performed the same hair care products without active ingredients in an open-ended, unblinded comparison of overall hair manageability, softness, and shininess. The effect was more pronounced in subjects with sun- and chlorine-bleached hair.

- 32 -

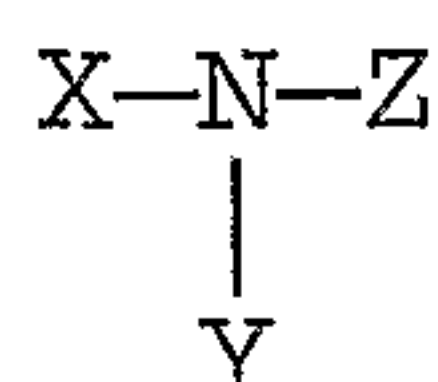
Fingernails of subjects who soaked the tips of one hand in a solution containing 3% DMAE and 5% tyrosine in a phospholipid base were less brittle and smoother than the fingernails of the other hand soaked in base only. The same effect was seen when the solution was applied topically to the nails or with a
5 brush.

The above description is for the purpose of teaching the person of ordinary skill in the art how to practice the present invention, and it is not intended to detail all those obvious modifications and variations of it which will become apparent to the skilled worker upon reading the description. It is intend-
10 ed, however, that all such obvious modifications and variations be included within the scope of the present invention, which is defined by the following claims. The claims are intended to cover the claimed components and steps in any sequence which is effective to meet the objectives there intended, unless the context specifically indicates the contrary.

- 33 -

CLAIMS

1. A method for treating skin, hair or nails to render them more uniform and smoother comprising applying to the skin, hair or nails, a composition containing an effective amount of an alkanolamine of the formula



wherein X, Y and Z are selected from the group consisting of hydrogen, C₁-C₃ alkyl groups, C₂-C₄ alkanol group, wherein at least one of X, Y, or Z is a C₂-C₄ alkanol group bearing at least one hydroxyl group and optionally at least one carboxyl group.

2. A method according to claim 1 which is a method for visibly reducing pore size.

3. A method according to claim 1 which is a method for treating or preventing acne.

4. A method according to claim 3 wherein the composition further comprises tyrosine and an effective amount of a sulfur ingredient selected from the group consisting of lipoic acid, glutathione, sulfur, a combination of sulfur and resorcinol, a combination of sulfur and resorcinol monoacetate, sulfacetamide, and mixtures thereof.

5. A method according to claim 4 further comprising applying to the same skin areas a composition comprising an effective amount of a conventional acne medication containing an active anti-acne ingredient selected from the group consisting of benzoyl peroxide, lauroyl peroxide, carbamide peroxide, ethanol, phenoxy ethanol, propanol, phenoxy propanol, resorcinol, ethyl acetate, salicylic acid, azelaic acid, fuming acid, dehydroacetic acid, pyruvic acid, urea, cetyl betaine, scymnol sulfate, cholate, deoxycholate, adalpalene, tretinoin, tazarotene,

- 34 -

erythromycin, lincomycin, clindamycin, tetracycline and meclocycline before or after treatment with the alkanolamine composition, preferably before.

6. A method according to claim 5 wherein the conventional acne medicine is salicylic acid, tretinoin, or benzoyl peroxide.

7. A method according to claims 4, 5, or 6 wherein composition contains from about 0.1% to about 10% by weight alkanolamine, from about 0.01% to about 6% tyrosine, and from about 0.5% to about 15% sulfur ingredient.

8. A method according to claim 1 which is a method for treating or inhibiting cutaneous scar tissue.

9. A method according to claim 8 wherein silicone gel sheets impregnated with the composition are applied to the cutaneous scar tissue.

10. A method according to claim 1 wherein the alkanolamine composition is applied to skin prior to applying electrical pulses sufficient to contract subcutaneous muscles underlying the skin.

11. A method according to claim 10 wherein the alkanolamine composition further comprises a compound exhibiting catecholamine activity selected from the group consisting of dopamine, norepinephrine, epinephrine, dopa, serotonin, tyrosine, phenylalanine, tyramine, ephedrine, amphetamine, tetrahydrobiopterin, pyridoxine, and mixtures thereof.

12. A method according to claims 10 or 11 wherein the electrical pulses are delivered by electrodes in the fingertips of a muscle stimulating device that fits on the hand.

13. A method according to claims 10, 11, or 12 wherein the electrical pulses having a relatively high voltage-to-width ratio and a steep waveform.

- 35 -

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14. A method according to any of the above claims wherein the alkanolamine is selected from the group consisting of ethylaminoethanol, methylaminoethanol, dimethylaminoethanol, isopropanolamine, triethanolamine, isopropanoldimethylamine, ethylethanolamine, 2-butanolamine, choline, serine, and mixtures thereof.

15. A method according to claim 14 wherein the alkanolamine is dimethylaminoethanol.

16. A method according to any of the above claims wherein the alkanolamine is present in the composition in an amount ranging from about 0.1% to about 10% by weight of the composition.

17. A method according to claim 16 wherein the alkanolamine is present in the composition in an amount ranging from about 1% to about 3% by weight of the composition.

18. A method according to any of the above claims wherein the composition further comprises at least one adjunct ingredient selected from the group consisting of lipoic acid, tyrosine, an α -hydroxy acid, a fatty acid ester of ascorbic acid, and mixtures of any of these.

19. A method according to claim 18 wherein the adjunct ingredient is tyrosine.

20. A method according to claim 18 wherein the α -hydroxy acid is glycolic acid and the fatty acid ester of ascorbic acid is ascorbyl palmitate.