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<p>(54) Title: USE OF N-ACETYL-L-CYSTEINE AND DERIVATIVES FOR REGULATING SKIN WRINKLES AND/OR SKIN ATROPHY</p> <p>(57) Abstract</p> <p>The present invention relates to a method for regulating wrinkles and/or atrophy in mammalian skin comprising treating the skin with a safe and effective amount of N-acetyl-L-cysteine and/or a derivative thereof.</p>		

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USE OF N-ACETYL-L-CYSTEINE AND DERIVATIVES
FOR REGULATING SKIN WRINKLES AND/OR SKIN ATROPHY

Technical Field

The present invention relates to the field of anti-aging of skin. Specifically, the invention relates to novel compositions and methods of using the compositions for effacing and preventing wrinkles in mammalian skin.

Background of the Invention

Skin is subject to abuse by many extrinsic (environmental) factors as well as intrinsic (chronoaging) factors. A common extrinsic factor is exposure to ultraviolet radiation. Whether extrinsic or intrinsic, the abuse results in wrinkling of the skin. To many people, skin wrinkles are a reminder of the disappearance of youth. As a result, the elimination of wrinkles has become a booming business in youth-conscious societies. Treatments range from cosmetic creams and moisturizers to various forms of cosmetic surgery.

Chronoaging results in the thinning and general degradation of skin. As the skin naturally ages, there is a reduction in the cells and blood vessels that supply the skin. There is also a flattening of the dermal-epidermal junction which results in weaker mechanical resistance of this junction. As a consequence, older persons are more susceptible to blister formation in cases of mechanical trauma or disease processes. (See Oikarinen, (1990) "The Aging of Skin: Chronoaging Versus Photoaging", Photodermatal. Photoimmunol. Photomed., Vol. 7, pp 3-4).

N-acetyl-L-cysteine, a preferred active of the present invention, has been used as a mucolytic, corneal vulnerary and an antidote to acetaminophen poisoning (The Merck Index, (1989) 11th Edition, p.14). European Patent Application 219 455, Fabbro,

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published April 22, 1987, discloses a dermatological and skin cosmetic, topical, cosmetic composition containing N-acetyl-L-cysteine as the active constituent. The composition is disclosed as being useful for the prevention and treatment of sunburn and for increasing the speed of skin pigmentation bronzing.

Objects of the Present Invention

It is an object of the present invention to provide a method of regulating wrinkles and/or atrophy in mammalian skin which comprises treating mammalian skin with a safe and effective amount of an anti-wrinkle/anti-atrophy agent.

Summary of the Invention

The present invention relates to a method for regulating wrinkles and/or atrophy in mammalian skin comprising chronic treatment of the skin with a safe and effective amount of N-acetyl-L-cysteine and/or a derivative thereof.

Detailed Description of the Invention

As used herein, "alkyl" means an unsubstituted carbon-containing chain which may be straight, branched or cyclic, preferably straight or branched, more preferably straight; saturated, monounsaturated (i.e., one double or triple bond in the chain), or polyunsaturated (i.e., two or more double bonds in the chain; two or more triple bonds in the chain; one or more double and one or more triple bonds in the chain), preferably saturated.

As used herein, "topical application" means directly laying on or spreading on outer skin.

As used herein, "cosmetically-acceptable" means that drugs, medicaments or inert ingredients which the term describes are suitable for use in contact with the tissues of humans and lower animals without undue toxicity, incompatibility, instability, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio.

As used herein, "regulating wrinkles" means preventing, retarding, arresting, or reversing the process of wrinkle formation in mammalian skin.

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As used herein, "skin atrophy" means the thinning and/or general degradation of the dermis often characterized by a decrease in collagen and/or elastin as well as decreased number, size and doubling potential of fibroblast cells. Skin atrophy is a natural result of aging. Skin atrophy is often an undesirable side effect resulting from treatment with corticosteroids.

As used herein, "regulating skin atrophy" means preventing, retarding, arresting, or reversing the process of atrophy in mammalian skin.

As used herein, "safe and effective amount" means an amount of compound or composition sufficient to significantly induce a positive modification in the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. The safe and effective amount of the compound or composition will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the specific compound or composition employed, the particular cosmetically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician.

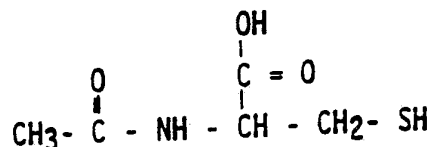
As used herein, "chronic treatment" means continued treatment with an active agent over an extended period during a subject's lifetime, preferably for at least about one month, more preferably from about three months to about twenty years, more preferably from about six months to about ten years, more preferably still from about one year to about five years.

As used herein, all percentages are by weight unless otherwise specified.

Active Compound

The present invention relates to a method for regulating wrinkles and/or atrophy in mammalian skin comprising treating the skin with a safe and effective amount of a composition comprising an active compound. As used herein, "active compound" means a compound having the structure

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Compositions of the present invention comprise from about 0.01% to about 50% of the active compound, preferably from about 0.1% to about 20%, more preferably from about 2% to about 5%.

Zinc Salts

In a preferred embodiment, the compositions of the present invention are rendered substantially odorless by additionally comprising a zinc salt. Without being bound by theory, zinc most likely removes odor by complexing with malodorous H_2 which may be formed as trace amounts of the active compound decomposes. Zinc salts useful in the present invention include, but are not limited to, the following:

<u>Name</u>	<u>Formula</u>
Zinc acetate	$\text{Zn}(\text{C}_2\text{H}_3\text{O}_2)_2$
Zinc acetate-2-water	$\text{Zn}(\text{C}_2\text{H}_3\text{O}_2)_2 \cdot \text{H}_2\text{O}$
Zinc aluminum oxide (1/1)(gahnite)	$\text{Al}_2\text{O}_3 \cdot \text{ZnO}$
Zinc di-amide	$\text{Zn}(\text{NH}_2)_2$
Zinc antimonide	Zn_3Sb_2
Zinc arsenate(V)-8-water (koettigite)	$\text{Zn}_3(\text{AsO}_4)_2 \cdot 8\text{H}_2\text{O}$
Zinc arsenate(III)	$\text{Zn}_3(\text{AsO}_2)_2$
Zinc arsenate(V)-hydroxide (1/1)(adamite)	$\text{Zn}_3(\text{AsO}_4)_2 \cdot \text{Zn}(\text{OH})_2$
Zinc arsenide	Zn_3As_2
Zinc bromate-6-water	$\text{Zn}(\text{BrO}_3)_2 \cdot 6\text{H}_2\text{O}$
Zinc bromide	ZnBr_2
Zinc carbonate (zincspar, smithsonite)	ZnCO_3
Zinc chlorate-4-water	$\text{Zn}(\text{ClO}_3)_2 \cdot 4\text{H}_2\text{O}$
Zinc chloride	ZnCl_2
Zinc -diammine chloride	$(\text{Zn}(\text{NH}_3)_2)\text{Cl}_2$
Zinc chromate(VI)	ZnCrO_4
Zinc cyanide	$\text{Zn}(\text{CN})_2$
Zinc dichromate(VI)-3-water	$\text{ZnCr}_2 \text{ I. } \text{O}_7 \cdot 3\text{H}_2\text{O}$
Zinc diphosphate	$\text{Zn}_2\text{P}_2\text{O}_7$

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Zinc hexacyanofluoride ferrate(II)	$Zn_2(Fe(CN)_6)$
Zinc fluoride	ZnF_2
Zinc fluoride-4-water	$ZnF_2 \cdot 4H_2O$
Zinc formate	$Zn(HCO_2)_2$
Zinc formate-2-water	$Zn(HCO_2)_2 \cdot 2H_2O$
Zinc hydroxide	$Zn(OH)_2$
Zinc iodate	$Zn(IO_3)_2$
Zinc iodate-2-water	$Zn(IO_3)_2 \cdot 2H_2O$
Zinc iodide	ZnI_2
Zinc iron oxide (1/1)	$Fe_2O_3 \cdot ZnO$
Zinc nitrate-6-water	$Zn(NO_3)_2 \cdot 6H_2O$
Zinc nitride	Zn_3N_2
Zinc oxalate-2-water	$ZnC_2O_4 \cdot 2H_2O$
Zinc oxide (zincite)	ZnO
Zinc perchlorate-6-water	$Zn(ClO_4)_2 \cdot 6H_2O$
Zinc permanganate-6-water	$Zn(MnO_4)_2 \cdot 6H_2O$
Zinc peroxide	ZnO_2
Zinc <i>p</i> -phenolsulfonate-8-water	$Zn(C_6H_4(OH)SO_3)_2 \cdot 8H_2O$
Zinc phosphate(V)	$Zn_3(PO_4)_2$
Zinc phosphate-4-water (hopeite)	$Zn_3(PO_4)_2 \cdot 4H_2O$
Zinc phosphide	Zn_3P_2
Zinc propionate	$Zn(C_2H_5O_2)_2$
Zinc selenate(VI)-5-water	$ZnSeO_4 \cdot 5H_2O$
Zinc selenide	$ZnSe$
Zinc silicate(2-)	$ZnSiO_3$
Zinc silicate (4-) (willemite)	Zn_2SiO_4
Zinc silicon oxide-water (2/1/1) (hemimorphite)	$2ZnO \cdot SiO_2 \cdot H_2O$
Zinc hexafluoro-silicate-6-water	$Zn(SiF_6) \cdot 6H_2O$
Zinc stearate	$Zn(C_{18}H_{35}O_2)_2$
Zinc sulfate (zincosite)	$ZnSO_4$
Zinc sulfate-7-water (goslarite)	$ZnSO_4 \cdot 7H_2O$
Zinc sulfide (α) (wurtzite)	ZnS
Zinc sulfite-2-water	$ZnSO_3 \cdot 2H_2O$
Zinc telluride	$ZnTe$

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Zinc thiocyanate	Zn(SCN) ₂
Zinc salt of the active compound	(Zn ⁺²)(anti-wrinkle agent)

Preferably, the zinc salt is selected from the group consisting of zinc oxide, zinc chloride, zinc acetate, zinc stearate, and zinc sulfate; more preferably zinc oxide and zinc chloride; more preferably still, zinc oxide.

Compositions of the present invention preferably comprise from about .001% to about 10% of a zinc salt, more preferably from about 0.01% to about 5%, more preferably still from about 0.1% to about 0.5%.

Compositions of the present invention may comprise a zinc salt of the active compound such as the zinc mercaptide N-acetylcysteine carboxylate salts disclosed in U.S. 3,749,770, Martin, issued July 31, 1973, incorporated herein by reference.

Zinc complexes which may be formed by zinc and the active compound are useful in the compositions and methods of the present invention.

In addition to its wrinkle and skin atrophy regulating benefits, the active compound is also useful as a photoprotection agent.

Cosmetic Compositions

In a preferred embodiment, treatment will employ the use of a topical cosmetic composition comprising the active compound and a cosmetically-acceptable carrier. The term "cosmetically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or microencapsulating substances which are suitable for administration to a human or lower animal. Cosmetically-acceptable carriers must be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the human or lower animal being treated. A safe and effective amount of carrier is from about 50% to about 99.99%, preferably from about 99.9% to about 80%, more preferably from about 98% to about 95%, of the composition.

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Variations in formulation of these carriers will result in a wide variety of products which fall within the scope of the present invention.

The topical cosmetic compositions of the present invention may be made into a wide variety of product types. These include, but are not limited to lotions, creams, beach oils, gels, sticks, sprays, ointments, pastes, mousses and cosmetics. These product types may comprise several types of carrier systems including, but not limited to solutions, emulsions, gels and solids.

The topical cosmetic compositions of the present invention formulated as solutions typically include a cosmetically-acceptable aqueous or organic solvent. The terms "cosmetically-acceptable aqueous solvent" and "cosmetically-acceptable organic solvent" refer to a solvent which is capable of having dispersed or dissolved therein the active compound, and possesses acceptable safety properties (e.g., irritation and sensitization characteristics). Water is a typical aqueous solvent. Examples of suitable organic solvents include: propylene glycol, butylene glycol, polyethylene glycol (200-600), polypropylene glycol (425-2025), glycerol, 1,2,4-butanetriol, sorbitol esters, 1,2,6-hexanetriol, ethanol, isopropanol, butanediol, and mixtures thereof. Preferably, these solutions contain from about 0.01% to about 50% of the active compound, more preferably from about 0.1% to about 20%; and from about 1% to about 10% of an acceptable aqueous or organic solvent, more preferably from about 1% to about 5%.

If the topical cosmetic compositions of the present invention are formulated as an aerosol and applied to the skin as a spray-on, a propellant is added to a solution composition. Examples of propellants useful herein include, but are not limited to, the chlorinated, fluorinated and chloro-fluorinated lower molecular weight hydrocarbons. A more complete disclosure of propellants useful herein can be found in Sagarin, Cosmetics Science and Technology, 2nd Edition, Vol. 2, pp. 443-465 (1972).

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Topical cosmetic compositions of the present invention may be formulated as a solution comprising an emollient. An example of a composition formulated in this way would be a beach oil product. Preferably, such compositions contain from about 0.1% to about 50% of the active compound and from about 2% to about 50% of a topical cosmetically-acceptable emollient.

As used herein, "emollients" refer to materials used for the prevention or 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, Cosmetics, Science and Technology, 2nd Edition, Vol. 1, pp. 32-43 (1972), incorporated herein by reference, contains numerous examples of suitable materials.

A lotion can be made from a solution carrier system. Lotions preferably comprise from about 0.1% to about 20%, more preferably from about 2% to about 5%, of the active compound; from about 1% to about 20%, preferably from about 5% to about 10%, of an emollient; and from about 50% to about 90%, preferably from about 60% to about 80%, water.

Another type of product that may be formulated from a solution carrier system is a cream. A cream of the present invention would preferably comprise from about .1% to about 20%, more preferably from about 2% to about 5%, of the active compound; from about 5% to about 50%, preferably from about 10% to about 20%, of an emollient, and from about 45% to about 85%, preferably from about 50% to about 75%, water.

Yet another type of product that may be formulated from a solution carrier system is an ointment. An ointment may comprise a simple base of animal or vegetable oils or semi-solid hydrocarbons (oleaginous). Ointments may also comprise absorption ointment bases which absorb water to form emulsions. Ointment carriers may also be water soluble. An ointment may also comprise from about 2% to about 10% of an emollient plus from about 0.1% to about 2% of a thickening agent. A more complete disclosure of thickening agents useful herein can be found in Segarin,

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Cosmetics, Science and Technology, 2nd Edition, Vol. 1, pp. 72-73 (1972).

If the carrier is formulated as an emulsion, from about 1% to about 10%, preferably from about 2% to about 5%, of the carrier system comprises an emulsifier. Emulsifiers may be nonionic, anionic or cationic. Suitable emulsifiers are disclosed in, for example, U.S. Patent 3,755,560, issued August 28, 1973, Dickert et al.; U.S. Patent 4,421,769, issued December 20, 1983, Dixon et al.; and McCutcheon's Detergents and Emulsifiers, North American Edition, pages 317-324 (1986); the disclosures of which are incorporated herein by reference. Preferred emulsifiers are anionic or nonionic, although the other types may also be used.

Lotions and creams can be formulated as emulsions as well as solutions. Preferably such lotions comprise from about 0.1% to about 20%, more preferably from about 2% to about 5%, of the active compound; from about 1% to about 20%, preferably from about 5% to about 10%, of an emollient; from about 25% to about 75%, preferably from about 45% to about 95%, water; and from about 0.1% to about 10%, preferably from about 0.5% to about 5%, of an emulsifier. Such creams would preferably comprise from about 0.1% to about 20%, more preferably from about 2% to about 5%, of the active compound; from about 1% to about 20%, preferably from about 5% to about 10%, of an emollient; from about 20% to about 80%, preferably from about 30% to about 70%, water; and from about 1% to about 10%, preferably from about 2% to about 5%, of an emulsifier.

Single emulsion skin care preparations, such as lotions and creams, of the oil-in-water type and water-in-oil type are well-known in the cosmetic art and are useful in the present invention. Multiphase emulsion compositions, such as the water-in-oil-in-water type, as disclosed in U.S. Patent No. 4,254,105, Fakuda et al., issued March 3, 1981, incorporated herein by reference, are also useful in the present invention. In general, such single or multiphase emulsions contain water, emollients and emulsifiers as essential ingredients.

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Triple emulsion carrier systems comprising an oil-in-water-in-silicone fluid emulsion composition as disclosed in U.S. Patent No. 4,960,764, Figueroa, issued October 2, 1990, are also useful in the present invention. Preferably, this triple emulsion carrier system can be combined with from about 0.1% to about 20%, more preferably from about 2% to about 5%, of the active compound to yield the topical cosmetic composition of the present invention.

Another emulsion carrier system useful in the topical cosmetic compositions of the present invention is a micro-emulsion carrier system. Such a system comprises from about 9% to about 15% squalane; from about 25% to about 40% silicone oil; from about 8% to about 20% of a fatty alcohol; from about 15% to about 30% of polyoxyethylene sorbitan mono-fatty acid (commercially available under the trade name Tweens) or other nonionics; and from about 7% to about 20% water. This carrier system is preferably combined with from about 2% to about 5% of the active compound.

If the topical cosmetic compositions of the present invention are formulated as a gel or a cosmetic stick, a suitable amount of a thickening agent, as disclosed supra, is added to a cream or lotion formulation.

The topical cosmetic compositions of the present invention may also be formulated as makeup products such as foundations.

The topical cosmetic compositions of the present invention may contain, in addition to the aforementioned components, a wide variety of additional oil-soluble materials and/or water-soluble materials conventionally used in topical compositions, at their art-established levels.

Various water-soluble materials may also be present in the compositions of this invention. These include humectants, proteins and polypeptides, preservatives and an alkaline agent. In addition, the topical compositions herein can contain conventional cosmetic adjuvants, such as dyes, opacifiers (e.g., titanium dioxide), pigments and perfumes.

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The topical cosmetic compositions of the present invention may also include a safe and effective amount of a penetration enhancing agent. A preferred amount of penetration enhancing agent is from about 1% to about 5% of the composition. Examples of useful penetration enhancers, among others, are disclosed in U.S. Patents 4,537,776, Cooper, issued August 27, 1985; 4,552,872, Cooper et al., issued November 12, 1985; 4,557,934, Cooper, issued December 10, 1985; 4,130,667, Smith, issued December 19, 1978; 3,989,816, Rhaadhyaksha, issued November 2, 1976; 4,017,641, DiGiulio, issued April 12, 1977; and European Patent Application 0043738, Cooper et al., published January 13, 1982.

Other conventional skin care product additives may also be included in the compositions of the present invention. For example, collagen, hyaluronic acid, elastin, hydrolysates, primrose oil, jojoba oil, epidermal growth factor, soybean saponins, mucopolysaccharides, and mixtures thereof may be used.

Various vitamins may also be included in the compositions of the present invention. For example, vitamin A, and derivatives thereof, vitamin B₂, biotin, pantothenic, vitamin D, vitamin E, and mixtures thereof may be used.

Cleaning Compositions

The skin cleaning compositions of the present invention comprise, in addition to the active compound, a cosmetically-acceptable surfactant. The term "cosmetically-acceptable surfactant" refers to a surfactant which is not only an effective skin cleanser, but also can be used without undue toxicity, irritation, allergic response, and the like. Furthermore, the surfactant must be capable of being commingled with the active compound in a manner such that there is no interaction which would substantially reduce the efficacy of the composition for regulating skin wrinkles and/or skin atrophy.

The skin cleaning compositions of the present invention preferably contain from about 0.1% to about 20%, preferably from about 2% to about 5%, of the active compound and from about 1% to

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about 90%, more preferably from about 5% to about 10%, of a cosmetically-acceptable surfactant.

The physical form of the skin cleansing compositions is not critical. The compositions can be, for example, formulated as toilet bars, liquids, pastes, or mousses. Toilet bars are most preferred since this is the form of cleansing agent most commonly used to wash the skin.

The surfactant component of the compositions of the present invention are 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.

The cleaning compositions of the present invention can optionally contain, at their art-established levels, materials which are conventionally used in skin cleansing compositions.

Combination Actives

A. Sunscreens and Sunblocks

Optimum regulation of skin wrinkling resulting from exposure to U.V. light can be obtained by using a combination of the active compound of the present invention together with sunscreens or sunblocks. Useful sunblocks include, for example, zinc oxide and titanium dioxide.

Photodamage is a predominant cause of skin wrinkling. Thus, for purposes of wrinkle prevention, the combination of the active compound with a UVA and/or UVB sunscreen would be most desirable. The inclusion of sunscreens in compositions of the present invention will provide immediate protection against acute UV damage. Thus, the sunscreen will prevent further wrinkle formation caused by UV radiation, while the active compound regulates existing wrinkles and skin atrophy.

A wide variety of conventional suncreening agents are suitable for use in combination with the active compound. Segarin, et al., at Chapter VIII, pages 189 et seq., of Cosmetics Science and Technology, disclose numerous suitable agents. Specific suitable suncreening agents include, for example:

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p-aminobenzoic acid, its salts and its derivatives (ethyl, iso-butyl, glyceryl esters; p-dimethylaminobenzoic acid); anthranilates (i.e., o-aminobenzoates; methyl, menthyl, phenyl, benzyl, phenylethyl, linalyl, terpinyl, and cyclohexenyl esters); salicylates (amyl, phenyl, benzyl, menthyl, glyceryl, and dipropylene glycol esters); cinnamic acid derivatives (methyl and benzyl esters, α -phenyl cinnamitrile; butyl cinnamoyl pyruvate); Dihydroxycinnamic acid derivatives (umbelliferone, methylumbelliferone, methylaceto-umbelliferone); trihydroxycinnamic acid derivatives (esculetin, methylesculetin, daphnetin, and the glucosides, esculin and daphnin); hydrocarbons (diphenylbutadiene, stilbene); dibenzalacetone and benzalacetophenone; Naphthol-sulfonates (sodium salts of 2-naphthol-3,6-disulfonic and of 2-naphthol-6,8-disulfonic acids); Dihydroxy-naphthoic 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 vilouric acids; Tannic acid and its derivatives (e.g., hexaethylether); (Butyl carbotol) (6-propyl piperonyl ether; Hydroquinone; Benzophenones (Oxybenzene, Sulisobenzene, Dioxycbenzone, Benzoresorcinol, 2,2',4,4'-Tetrahydroxybenzophenone, 2,2'-Dihydroxy-4,4'-dimethoxybenzophenone, Octabenzene; 4-Isopropyl dibenzoylmethane; Butylmethoxydibenzoylmethane; Etocrylene; and 4-isopropyl-di-benzoylmethane.

Of these, 2-ethylhexyl-p-methoxycinnamate, 4,4'-t-butyl methoxydibenzoylmethane, 2-hydroxy-4-methoxybenzophenone, octyl-dimethyl-p-aminobenzoic acid, digalloyltriolate, 2,2-dihydroxy-4-methoxybenzophenone, ethyl-4-[bis(hydroxypropyl)]aminobenzoate, 2-ethylhexyl-2-cyano-3,3-diphenylacrylate, 2-ethylhexylsalicylate, glyceryl-p-aminobenzoate, 3,3,5-trimethylcyclohexylsalicylate, methylanthranilate, p-dimethylamino-benzoic acid or aminobenzoate, 2-ethylhexyl-p-dimethylamino-benzoate, 2-phenylbenzimidazole-5-

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sulfonic acid, 2-(p-dimethylaminophenyl)-5-sulfonicbenzoxazoic acid and mixtures of these compounds, are particularly useful.

Preferred sunscreens useful in the compositions of the present invention are 2-ethylhexyl-p-methoxycinnamate, butyl-methoxydibenzoylmethane, 2-hydroxy-4-methoxybenzophenone, octyl-dimethyl-p-aminobenzoic acid and mixtures thereof.

A safe and effective amount of sunscreen may be used in the compositions of the present invention. The suncreening agent must be compatible with the active compound. Generally the composition may comprise from about 1% to about 20%, preferably from about 2% to about 10%, of a suncreening agent. Exact amounts will vary depending upon the sunscreen chosen and the desired Sun Protection Factor (SPF).

Also particularly useful in the present invention are suncreens such as those disclosed in Sabatelli, U.S. Patent Application Serial No. 054,085 * (filed June 2, 1987) and Sabatelli et al., U.S. Patent Application Serial No 054,046* (filed June 2, 1987). The suncreening 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.

Preferred members of this class of suncreening agents are 4-N,N-(2-ethylhexyl)methylaminobenzoic acid ester of 2,4-dihydroxybenzophenone; N,N-di-(2-ethylhexyl)-4-aminobenzoic acid ester with 4-hydroxydibenzoylmethane; 4-N,N-(2-ethylhexyl) methylaminobenzoic acid ester with 4-hydroxydibenzoylmethane; 4-N,N-(2-ethylhexyl)methylaminobenzoic acid ester 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.

(* equivalent to EP Patent 0251398 granted 12 August 1992 and EP Patent 0255157 published 03 February 1988)

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An agent may also be added to any of the compositions of the present invention to improve the skin substantivity of those compositions, particularly to enhance their resistance to being washed off by water, or rubbed off. A preferred agent which will provide this benefit is a copolymer of ethylene and acrylic acid. Compositions comprising this copolymer are disclosed in U.S. Patent 4,663,157, Brock, issued May 5, 1987, which is incorporated herein by reference.

B. Anti-Inflammatory Agents

In a preferred wrinkle and atrophy regulating composition of the present invention, an anti-inflammatory agent is included as an active agent along with the active compound. The inclusion of an anti-inflammatory agent enhances the wrinkle regulating benefits of the compositions. The anti-inflammatory agent protects strongly in the UVA radiation range (though it also provides some UVB protection as well) thereby preventing further wrinkle formation caused by UV radiation, while the active compound regulates existing wrinkles and skin atrophy. Thus the combination provides broad protection. The topical use of anti-inflammatory agents reduces photo-aging of the skin resulting from chronic exposure to UV radiation. (See U.S. Patent 4,847,071, Bissett, Bush, and Chatterjee, issued July 11, 1989, incorporated herein by reference; and U.S. Patent 4,847,069, Bissett and Chatterjee, issued July 11, 1989, incorporated herein by reference.)

A safe and effective amount of an anti-inflammatory agent may be added to the compositions 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 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.

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

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beclomethasone dipropionate, clobetasol valerate, desonide, desoxymethasone, desoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, difluocortolone valerate, fluadrenolone, fluclorolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylester, fluocortolone, fluprednidene (fluprednylidene) acetate, flurandrenolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters, chloroprednisone, chlorprednisone acetate, clocortelone, clescicolone, dichlorisone, difluprednate, flucloronide, flunisolide, 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 in the present invention is hydrocortisone.

A second class of anti-inflammatory agents which is useful in the compositions of the present invention 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, reference may be had 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).

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

- 1) the oxicams, such as piroxicam, isoxicam, tenoxicam, sudoxicam, and CP-14,304;

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- 2) the salicylates, such as aspirin, disalcid, benorylate, trilisate, safapryn, solprin, diflunisal, and fendosal;
- 3) the acetic acid derivatives, such as diclofenac, fenclufenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepiract, clidanac, oxepinac, and felbinac;
- 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, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, and tiaprofenic; and
- 6) the pyrazoles, such as phenybutazone, oxyphenbutazone, feprazone, azapropazone, and trimethazone.

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

Another class of anti-inflammatory agents which are useful in the present invention are the anti-inflammatory agents disclosed in U.S. Patent No. 4,708,966, Loomans et al., issued November 24, 1987. This patent discloses a class of nonsteroidal anti-inflammatory compounds which comprise specifically substituted phenyl compounds, especially substituted 2,6-di-tert-butyl phenol derivatives. For example, compounds selected from 4-(4'-pentyn-3'-one)-2,6-di-t-butylphenol; 4-(5'-hexynoyl)-2,6-di-t-butylphenol; 4-((S)-(-)-3'-methyl-5'-hexynoyl)-2,6-di-t-butylphenol; 4-((R)-(+)-3'-methyl-5'-hexynoyl)-2,6-di-t-butylphenol; and 4-(3',3'-dimethoxypropionyl)-2,6-di-t-butylphenol are useful in the present invention.

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Yet another class of anti-inflammatory agents which are useful in the present invention are those disclosed in U.S. Patent No. 4,912,248, Mueller, issued March 27, 1990. This patent discloses compounds and diastereomeric mixtures of specific 2-naphthyl- containing ester compounds, especially naproxen ester and naproxol ester compounds, having two or more chiral centers. For example, compounds selected from (S)-naproxen-(S)-2-butyl ester, (S)-naproxen-(R)-2-butylester, (S)-naproxol-(R)-2-methyl butyrate, (S)-naproxol-(S)-2-methyl butyrate, diasteromeric mixtures of (S)-naproxen-(S)-2-butyl ester and (S)-naproxen-(R)-2-butyl ester, and diasteromeric mixtures of (S)-naproxol-(R)-2-methyl butyrate and (S)-naproxol-(S)-2-methyl butyrate are useful in the present invention.

Finally, so-called "natural" anti-inflammatory agents are useful in the present invention. For example, candelilla wax, alpha bisabolol, aloe vera, Manjistha (extracted from plants in the genus Rubia, particularly Rubia Cordifolia), and Guggal (extracted from plants in the genus Commiphora, particularly Commiphora Mukul), may be used.

Another preferred composition of the present invention comprises the active compound, a sunscreen, and an anti-inflammatory agent together for wrinkle and/or atrophy regulation in the amounts disclosed for each individually hereinabove.

C. Anti-Oxidants/Radical Scavengers

In a preferred wrinkle and atrophy regulating composition of the present invention, an anti-oxidant/radical scavenger is included as an active agent along with the active compound. The inclusion of an anti-oxidant/radical scavenger increases the wrinkle regulating benefits of the composition.

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

Anti-oxidants/radical scavengers such as ascorbic acid (vitamin C) and its salts, tocopherol (vitamin E), tocopherol

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sorbate, 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 tradename Trolox®), gallic acid and its alkyl esters, especially propyl gallate, uric acid and its salts and alkyl esters, sorbic acid and its salts, the ascorbyl esters of fatty acids, amines (e.g., N,N-diethylhydroxylamine, amino-guanidine), sulfhydryl compounds (e.g., glutathione), and dihydroxy fumaric acid and its salts may be used.

In a preferred wrinkle regulating composition of the present invention, compositions comprise one, any two, or all three of a sunscreensing agent, anti-inflammatory agent, and/or an anti-oxidant/radical scavenging agent included as actives along with the active compound. The inclusion of two or all three of these agents with the active compound increases the wrinkle regulating benefits of the composition.

D. Chelators

In a preferred wrinkle and atrophy regulating composition of the present invention, a chelating agent is included as an active agent along with the active compound. As used herein, "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 increases the wrinkle regulating benefits of the composition.

A safe and effective amount of a chelating agent may be added to the compositions of the present invention, preferably from about 0.1% to about 10%, more preferably from about 1% to about 5%, of the composition. Chelators useful in compositions of the present invention are disclosed in U.S. Patent Application Serial No. 251,910,* Bissett, Bush & Chatterjee, filed October 4, 1988, incorporated herein by reference. Preferred chelators useful in compositions of the present invention are furildioxime and derivatives thereof, more preferably amphi-2-furildioxime.

(* equivalent to EP Patent 0313305 published 26 April 1989)

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In a preferred wrinkle and atrophy regulating composition of the present invention, compositions comprise one, any two, any three, or all four of a sunscreensing agent, anti-inflammatory agent, anti-oxidant/radical scavenging agent, and/or chelating agent included as actives along with the active compound. The inclusion of two, three, or all four of these agents with the active compound increases the wrinkle regulating benefits of the composition.

E. Retinoids

In a preferred wrinkle and atrophy regulating composition of the present invention, a retinoid, preferably retinoic acid, is included as an active agent along with the active compound. The inclusion of a retinoid increases the wrinkle regulating benefits of the composition. A safe and effective amount of a retinoid may be added to the compositions of the present invention, preferably from about 0.001% to about 2%, more preferably from about 0.01% to about 1% of the composition. 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, such as all-trans retinoic acid and 13-cis-retinoic acid.

F. Benzofuran Derivatives

In a preferred wrinkle and atrophy regulating composition of the present invention, a benzofuran derivative, preferably amiodarone, is included as an active agent along with the active compound. The inclusion of a benzofuran derivative increases the wrinkle regulating benefits of the composition.

A safe and effective amount of a benzofuran derivative may be added to the compositions of the present invention, preferably from about 0.01% to about 20%, more preferably from about 0.1% to about 10%, of the composition. Benzofuran derivatives useful in the present invention are disclosed in U.S. Patent Application Serial No. 674,628,* Chatterjee and Kapoor, filed March 25, 1991, incorporated herein by reference.

(*equivalent to US Patent 5,118,707 granted 02 June 1992)

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In a preferred wrinkle regulating composition of the present invention, compositions comprise one, any two, any three, any four, any five, and or all six of a sunscreensing agent, anti-inflammatory agent, anti-oxidant/radical scavenging agent, chelating agent, retinoid, and/or benzofuran derivative included as actives along with the active compound. The inclusion of two, three, four, five or all six of these agents with the active compound increases the wrinkle regulating benefits of the composition.

Methods for Regulating Wrinkles and/or Skin Atrophy in Mammalian Skin

The present invention relates to a method for regulating wrinkles and/or atrophy in mammalian skin. Such a method comprises treating the skin with a safe and effective amount of the active compound. The amount of active compound and frequency of treatment will vary widely depending upon the level of wrinkling and/or skin atrophy already in existence in the subject, the rate of further wrinkle formation and/or atrophy, and the level of regulation desired.

A preferred method of treating the skin is via chronic topical application of a safe and effective amount of the active compound to regulate wrinkles and/or atrophy in mammalian skin. The amount of active compound and frequency of topical application to the skin can vary widely, depending upon personal needs, but it is suggested as an example that topical application range from about once per week to about 10 times daily, preferably from about twice per week to about 4 times daily, more preferably from about 3 times a week to about 3 times daily, most preferably about once or twice per day. The composition for topical application will comprise from about 0.01% to about 50%, preferably from about 0.1% to about 20%, more preferably from about 1% to about 10% of the active compound. By "chronic" application, it is meant herein that the period of topical application may be over the lifetime of the subject, preferably for a period of at least about one month, more preferably from about three months to about twenty years, more preferably from about six months to about ten years, more

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preferably still from about one year to about five years, thereby resulting in regulation of wrinkles and/or atrophy in mammalian skin.

A preferred method of the present invention for regulating wrinkles and/or atrophy in mammalian skin involves applying both a safe and effective amount of the active compound and a safe and effective amount of one or more of a sunscreensing agent, an anti-inflammatory agent, an anti-oxidant/radical scavenging agent, a chelating agent, a retinoid and/or a benzofuran derivative to the skin simultaneously. As used herein, "simultaneous application" or "simultaneously" means applying the agents to the skin at the same situs on the body at about the same time. Though this can be accomplished by applying the agents separately to the skin, preferably a composition comprising all the desired agents commingled is applied to the skin. The amount of sunscreensing agent applied is generally from about 0.02 mg to about 1.0 mg per cm^2 skin. The amount of anti-inflammatory agent applied is generally from about 0.005 mg to about 0.5 mg, preferably from about 0.01 mg to about 0.1 mg per cm^2 skin. The amount of anti-oxidant/radical scavenging agent generally applied is from about 0.001 mg to about 1.0 mg, preferably from about 0.05 mg to about 0.5 mg per cm^2 skin. The amount of chelating agent generally applied is from about 0.001 mg to about 1.0 mg, preferably from about 0.01 mg to about 0.5 mg, more preferably from about 0.05 mg to about 0.1 mg per cm^2 skin. The amount of retinoid applied is generally from about 0.00001 mg to about 0.02 mg per cm^2 skin, preferably from about 0.001 mg to about 0.01 mg per cm^2 skin. The amount of benzofuran derivative applied is generally from about 0.001 mg to about 1.0 mg/ cm^2 skin per application, preferably from about 0.01 to about 0.5 mg/ cm^2 skin per application. The amount of active compound applied is generally from about 0.001 mg to about 1.0 mg per cm^2 skin per application, preferably from about 0.01 mg to about 0.5 mg per cm^2 , more preferably from about 0.05 to about 0.25 mg/ cm^2 skin per application.

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The following examples further describe and demonstrate the preferred embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration, and are not to be construed as limitations of the present invention since many variations thereof are possible without departing from its spirit and scope.

EXAMPLE I

A topical composition is prepared by combining the following components utilizing conventional mixing techniques.

<u>Component</u>	<u>Percent by Weight Of Composition</u>
Distilled water	71.98
Disodium ethylenediaminetetraacetic acid (EDTA)	0.03
Glycerin	3.00
C12-15 Alcohols Benzoate	6.00
Glycerol Stearate	2.50
Stearyl alcohol	0.75
Cetyl alcohol	1.00
DL-tocopherol	1.00
Polyoxyethylene (12) cetyl/stearyl ether (50:50)	0.50
Polyoxyethylene (20) cetyl/stearyl ether (50:50)	0.50
Talc 114 USP	0.50
Butylene glycol	1.50
DMDM hydantoin/3-Iodo-2-propynyl- butylcarbamate (95:5)	0.15
Sodium hydroxide (20% solution)	5.50
N-acetyl-L-cysteine	
5.00	
Fragrance - Palmarose oil	0.09

This composition is useful for topical application to regulate skin wrinkles and/or skin atrophy. Use of an amount of the composition to deposit about 2 mg/cm² of the active compound to the skin is appropriate.

EXAMPLE II

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A topical composition is prepared by combining the following components utilizing conventional mixing techniques.

<u>Component</u>	<u>Percent by Weight of Composition</u>
Distilled water	71.73
Disodium EDTA	0.03
Glycerin	3.00
C ₁₂₋₁₅ Alcohols Benzoate	6.00
Glycerol Stearate	2.50
Stearyl alcohol	0.75
Cetyl alcohol	1.00
DL-tocopherol	1.00
Polyoxyethylene (12) cetyl/stearyl ether (50:50)	0.50
Polyoxyethylene (20) cetyl/stearyl ether (50:50)	0.50
Talc 114 USP	0.50
Butylene glycol	1.50
DMDM hydantoin/3-Iodo-2-propynyl- butylcarbamate (95:5)	0.15
Sodium hydroxide (20% solution)	5.50
N-acetyl-L-cysteine	5.00
ZnCl ₂	0.25
Fragrance - Palmarose oil	0.09

This composition is useful for topical application to regulate skin wrinkles and/or skin atrophy. Use of an amount of the composition sufficient to deposit about 2 mg/cm² of the active compound to the skin is appropriate.

EXAMPLE III

A topical composition is prepared by combining the following components utilizing conventional mixing techniques.

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<u>Component</u>	<u>Percent by Weight of Composition</u>
Distilled water	69.98
Disodium EDTA	0.03
Glycerin	3.00
C12-15 Alcohols Benzoate	6.00
Glycerol Stearate	2.50
Stearyl alcohol	0.75
Cetyl alcohol	1.00
DL-tocopherol	1.00
Polyoxyethylene (12) cetyl/stearyl ether (50:50)	0.50
Polyoxyethylene (20) cetyl/stearyl ether (50:50)	0.50
Talc 114 USP	0.50
Butylene glycol	1.50
DMDM hydantoin/3-Iodo-2-propynyl- butylcarbamate (95:5)	0.15
Sodium hydroxide (20% solution)	5.50
N-acetyl-L-cysteine	5.00
Hydrocortisone	2.00
Fragrance - Palmarose oil	0.09

This composition is useful for topical application to regulate skin wrinkles and/or skin atrophy. Use of an amount of the composition sufficient to deposit about 2 mg/cm² of the active compound to the skin is appropriate.

EXAMPLE IV

A sunscreen composition is prepared by combining the following components utilizing conventional mixing techniques.

<u>Component</u>	<u>Percent by Weight of Composition</u>
Distilled water	61.73
Disodium EDTA	0.03
Glycerin	3.00
C12-15 Alcohols Benzoate	6.00
Glycerol Stearate	2.50
Stearyl alcohol	0.75

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Cetyl alcohol	1.00
DL-tocopherol	1.00
Polyoxyethylene (12) cetyl/stearyl ether (50:50)	0.50
Polyoxyethylene (20) cetyl/stearyl ether (50:50)	0.50
Talc 114 USP	0.50
Butylene glycol	1.50
DMDM hydantoin/3-Iodo-2-propynyl- butylcarbamate (95:5)	0.15
Sodium hydroxide (20% solution)	5.50
N-acetyl-L-cysteine	5.00
ZnO	0.25
Padimate O (octydimethyl p-aminobenzoic acid)	7.00
Butyldimethyldibenzoylmethane	3.00
Frangrance - Palmarose oil	0.09

This composition is useful for topical application to regulate skin wrinkles and/or skin atrophy. Use of an amount of the composition is sufficient to deposit about 2 mg/cm² of the active compound to the skin is appropriate.

N-acetyl-L-cysteine in the above Examples can be replaced with Zn-NAC or other active compounds of the structure provided herein.

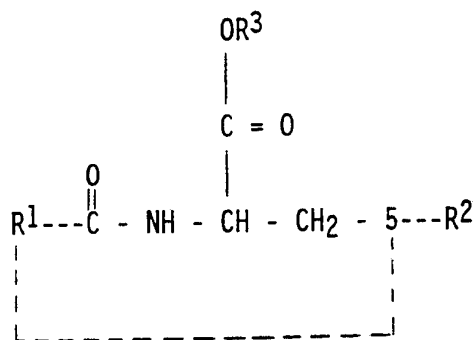
While particular embodiments of the subject invention have been described, it will be obvious to those skilled in the art that various changes and modifications of the subject invention can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of the invention.

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CLAIMS:

1. The use of:
 - a) a safe and effective amount, preferably from 0.01% to 50%, more preferably from 0.1% to 20%, of N-acetyl-L-cysteine or a cosmetically-acceptable salt thereof; and
 - b) a cosmetically-acceptable carrier, preferably a topical carrier, to make a cosmetic composition for regulating wrinkles or atrophy in mammalian skin.
2. The use of Claim 1 wherein the cosmetic composition is for chronic application, preferably for a period of at least six months comprising application of the composition from once per week to two times daily.
3. The use of any of Claims 1 and 2 wherein the cosmetic composition additionally comprises a safe and effective amount of a zinc salt, preferably the zinc salt is selected from the group consisting of zinc oxide, zinc stearate, zinc sulfate, zinc chloride and zinc acetate.
4. The use of any of Claims 1, 2 and 3 wherein the cosmetic composition additionally comprises a safe and effective amount of a sunscreensing agent.
5. The use of any of Claims 1, 2 and 3 wherein the cosmetic composition additionally comprises another active agent selected from the group consisting of a safe and effective amount of an anti-inflammatory agent, an anti-oxidant, a chelator, a retinoid, and a benzofuran derivative.
6. A composition useful for regulating wrinkles in mammalian skin which comprises a compound having the:

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wherein R¹ is selected from the group consisting of nil and a C₁-C₁₈ alkyl;

R² is selected from the group consisting of nil, -H,

C₁-C₁₈ alkyl and $-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}^4$;

R³ is selected from the group consisting of -H and C₁-C₁₈ alkyl;

R⁴ is a C₁-C₁₈ alkyl;

wherein R¹ and R² are either both nil or neither nil; if both R¹ and R² are nil, the carbonyl carbon and the sulfur adjacent R¹ and R², respectively, are covalently bonded to form a cyclic ring;

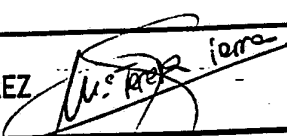
or a cosmetically-acceptable salt thereof, a zinc salt and a cosmetically-acceptable carrier.

7. A composition according to Claim 6 wherein said compound is N-acetyl-L-cysteine or a cosmetically-acceptable salt thereof.
8. A composition according to Claim 6 which comprises from 0.1 to 20% of N-acetyl-L-cysteine.
9. A composition according to Claim 6 wherein said zinc salt is zinc oxide, zinc stearate, zinc sulfate, zinc chloride, zinc acetate or a mixture of two or more of these.

INTERNATIONAL SEARCH REPORT

PCT/US 92/07287

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5. A61K7/48		
II. FIELDS SEARCHED Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ^o	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	US,A,4 711 780 (M.S. FAHIM) 8 December 1987 see column 1, line 1 - line 63 see column 2, line 42 - line 45 see claims 1,4,5,12,13 ---	1,3,5-9
Y	US,A,4 276 284 (S.I. BROWN) 30 June 1981 see the whole document ---	1,3,5-9
A	US,A,3 749 770 (T.A. MARTIN) 31 July 1973 cited in the application see the whole document ---	1-9
	-/--	
<p>^o Special categories of cited documents :¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document 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> <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</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>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 10 NOVEMBER 1992		Date of Mailing of this International Search Report 20. 11. 92
International Searching Authority EUROPEAN PATENT OFFICE		Signature of Authorized Officer SIERRA GONZALEZ 

Category ^a	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	FR,A,2 503 151 (J. MORELLE) 8 October 1982 see page 1 see page 2, line 34 see page 3, line 31 - line 39 see claims 1,2,5 -----	1-9

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. US 9207287
SA 64170**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 10/11/92. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4711780	08-12-87	EP-A- 0314835	10-05-89
US-A-4276284	30-06-81	None	
US-A-3749770	31-07-73	US-A- 3647834	07-03-72
FR-A-2503151	08-10-82	DE-A, C 3212448	11-11-82
		GB-A, B 2097256	03-11-82
		JP-C- 1624882	18-11-91
		JP-B- 2042805	26-09-90
		JP-A- 57183703	12-11-82
		US-A- 4859653	22-08-89