(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 2 311 452 B9**

(12) **CORRECTED EUROPEAN PATENT SPECIFICATION**

(15) Correction information:
Corrected version no 1 (W1 B1)
Corrections, see
Description Paragraph(s) 1, 13, 58

(48) Corrigendum issued on:
24.12.2014 Bulletin 2014/52

(45) Date of publication and mention of the grant of the patent:
02.04.2014 Bulletin 2014/14

(21) Application number: **10006974.9**

(22) Date of filing: **07.01.2000**

(51) Int Cl.:
A61K 31/401 *(2006.01)* ***A61K 31/198*** *(2006.01)*
A61K 31/7008 *(2006.01)* ***A61K 31/405*** *(2006.01)*
A61K 9/06 *(2006.01)* ***A61P 17/04*** *(2006.01)*
A61P 17/10 *(2006.01)* ***A61P 31/10*** *(2006.01)*
A61K 8/73 *(2006.01)* ***A61Q 19/00*** *(2006.01)*
A61K 8/60 *(2006.01)* ***A61K 8/44*** *(2006.01)*
A61K 8/49 *(2006.01)* ***A61Q 3/00*** *(2006.01)*
A61Q 5/02 *(2006.01)* ***A61Q 19/02*** *(2006.01)*
A61Q 19/08 *(2006.01)* ***A61K 9/00*** *(2006.01)*
A61K 45/06 *(2006.01)* ***A61K 31/4045*** *(2006.01)*
A61Q 5/00 *(2006.01)*

(54) **Topical composition comprising n-acetyl glucosamine**

Topische Zusammensetzung mit N-acetylglucosamin

Composition topique contenant du N-acétylglucosamine

(84) Designated Contracting States:
DE ES FR GB IT

(30) Priority: **08.01.1999 US 227213**

(43) Date of publication of application:
20.04.2011 Bulletin 2011/16

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
09001844.1 / 2 080 504
04029094.2 / 1 570 840
00902347.4 / 1 143 925

(73) Proprietors:
- **Yu, Ruey J.**
  Chalfont, PA 18914 (US)
- **Van Scott, Eugene J.**
  Abington, PA 19001 (US)

(72) Inventors:
- **Yu, Ruey J.**
  Chalfont, PA 18914 (US)
- **Van Scott, Eugene J.**
  Abington, PA 19001 (US)

(74) Representative: **Grünecker, Kinkeldey,**
Stockmair & Schwanhäusser
Leopoldstrasse 4
80802 München (DE)

(56) References cited:
EP-A1- 0 281 812 **EP-A2- 0 852 946**
WO-A1-87/02244 **WO-A1-98/52576**
GB-A- 1 503 564 **JP-A- 59 013 708**
US-A- 3 697 652 **US-A- 4 870 061**
US-A- 5 650 166

- **YANO H ET AL: "Effects of N-Acetyl-D-Glucosamine on Wound Healing in Rats", MIE MEDICAL JOURNAL, TSU, JP, vol. XXXV, no. 1, 1 January 1985 (1985-01-01), pages 53-56, XP002997084, ISSN: 0026-3532**

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

EP 2 311 452 B9

Description

Field of the Invention

[0001] This application relates to topical compositions containing N-acetyl-glucosamine or isomeric forms thereof, and their use in alleviating or improving various cosmetic conditions of the skin associated with aging.

Brief Description of the Prior Art

[0002] In our U.S. Pat. No. 5,091,171 we described and claimed preventive as well as therapeutic treatment to alleviate cosmetic conditions and symptoms of dermatologic disorders with amphoteric compositions containing alpha hydroxy-acids, alpha ketoacids, polymeric forms of hydroxyacids, and related compounds or. In U.S. Pat. No. 5,547,988, and related patents, we described the use of topical compositions comprising a 2-hydroxycarboxylic acid or related compound to alleviate or improve signs of skin, nail and hair changes associated with intrinsic or extrinsic aging. In our U.S. Pat. No. 5,385,938, and related patents, we described preventive and therapeutic treatment to alleviate cosmetic conditions and symptoms of dermatologic disorders with amphoteric compositions containing alpha hydroxy acids, alpha ketoacids, polymeric forms of hydroxy acids, and related compounds or. In our U.S. Pat. No. 5,258,391 entitled "Phenyl Alpha Acyloxyalkanoic Acids. Derivatives and Their Therapeutic Use" we described and claimed the use of topical compositions containing phenyl alpha acyloxyalkanoic acids and derivatives to enhance the keratization of nails, skin, lips and other mucous membranes. In our U.S. Pat. No. 5,665,776 entitled "Additives Enhancing Topical Actions of Therapeutic Agents" we described and claimed the use of hydroxycarboxylic acids or related compounds to increase the cosmetic or therapeutic effect of cosmetic or pharmaceutical agents. In our U.S. Pat. No. 5,641,475 we described and claimed the use of topical compositions containing a bioactive cosmetic, dermatologic or preservative agent and aryl 2-acetoxyethanoic acid effective as a synergist or amplifier. In our U.S. Pat. No. 5,643,949 also entitled "Phenyl Alpha Acyloxyalkanoic Acids, Derivatives and Their Therapeutic Use" we described and claimed the use of topical compositions containing a cosmetic or dermatologic drug for topical administration to nails, skin and lips and an amount of a phenyl alpha acyloxy-alkanoic acid or derivatives effective to enhance the cosmetic or therapeutic effect of the dermatologic drug. In U.S. Pat. No. 4,603,146 to Albert M. Kligman, disclosure is made of the use of vitamin A (tretionoin) to reduced and prevent epithelial growths and aid the skin in regaining and maintaining firmness, turgor and elasticity.

[0003] In a report entitled "Topical Tretinoin for Photoaged Skin" by Kligman et al., J. American Academy of Dermatology, Vol. 15, pages 836-859, 886-887 (1986), daily topical application of 0.05% tretinoin (also known as all-transretinoic acid) in a cream has been found to improve photodamaged skin. In another report entitled "Topical Tretinoin Improves Photoaged Skin: A Double-blind Vehicle-controlled Study" by Weiss et al., J. American Medical Association, Vol. 259 pages 527-532 (1988), daily topical application of 0.1% tretinoin as compared to vehicle alone application for 16 weeks has been shown to improve photoaged skin. One side-effect has been a dermatitis encountered by 92% of the patients participating in this study. The dermatitis was characterized by a patchy erythema, localized swelling, dry skin, and mild scaling. Patients complained about burning, tingling, or pruritus. In yet another report entitled "Topical Tretinoin in the Treatment of Aging Skin" by Weiss et al., J. American Academy of Dermatology Vol. 19, pages 169-175 (1988), topical application of 0.1% tretinoin cream for 8 to 12 months has been found to improve clinical signs of aging skin. The side effects have been burning sensation in the eyes and mild skin irritations.

[0004] In PCT Application No. PCT/US96/16534, filed October 16, 1996, entitled "Topical Compositions Containing N-Acetylcysteine and Odor Masking Materials," topical compositions comprising from 0.01% to 50% of N-acetylcysteine or a derivative of N-acetylcysteine, from 0.01% to 0.5% of an odor masking material, and a topical carrier are disclosed to improve the appearance of skin.

[0005] N-Acetylcysteine is N-acetylated cysteine which is a thiol containing amino acid, also called a-acetamido-β-mercaptopropanoic acid. Topical compositions containing N-acetylcyseine have been claimed to improve physical appearance of the skin including cosmetic wrinkles. N-acetylcysteine contains a free thiol group, thus, is known as an antioxidant. The affect of N-acetylcysteine is claimed to be due to its antioxidant property. N-Acetylcysteine, as an antioxidant substance, also has been indicated as protective against pulmonary oxygen toxicity (Eur. Respir. J. 2, 116-126, 1989).

[0006] N-acetylcysteine, however, is also associated with a number of significant drawbacks. N-acetyleysteine is known to degrade under ordinary storage conditions and result in a malodorous smell. The malodor is suggested to be caused by the release of thiol compounds and hydrogen sulfide upon degradation. Thus, topical compositions containing N-acetylcysteine have little or no commercial use due to the strong malodor of N-acetylcysteine.

[0007] PCT/US96/16534 claimed that the malodor could be masked by addition of certain perfume chemicals at concentrations ranging from 0.01 to 0.5% by weight. The perfume chemicals include aromatic esters, aliphatic esters, aromatic alcohol, aliphatic alcohols, aliphatic ketones, aromatic aldehydes, aliphatic aldehydes, aromatic ethers and aliphatic ethers. Because the malodorous thiol compounds and hydrogen sulfide have not been chemically neutralized

or destroyed, however, the transient masking effect is not a satisfactory solution for most consumers, and therefore is not a viable approach for commercialization of N-acetylcysteine in cosmetic industry.

[0008] JP 59013708 discloses the topical use of amino sugars including N-acetyl glucosamine as a moisturiser, emollient, activator for the skin which gives a smooth feeling, springiness and luster to the skin.

[0009] We have now discovered that N-aldosamines, N-acetylated amino acids and related compounds are topically effective for various cosmetic conditions including the signs of skin changes associated with intrinsic and/or extrinsic aging.

Summary of the Invention

[0010] Accordingly, it is an object of this invention to provide methods and compositions which can alleviate various cosmetic conditions including the signs of skin changes associated with intrinsic and/or extrinsic aging.

[0011] We have now discovered that N-acetyl aldosamines, N-acetylamino acids and related N-acetyl compounds have unexpected properties. Topical applications of compositions comprising N-acetyl aldosamines, N-acetylamino acids and related N-acetyl compounds have been found to improve cosmetic conditions and dermatological disorders including cosmetic as well as clinical signs of changes in skin, nails and hair associated with intrinsic and/or extrinsic aging, or the damages caused by extrinsic factors such as sunlight, radiation, air pollution, wind, cold, dampness, heat, chemicals, smoke, and cigarette smoking.

[0012] The signs of skin changes associated with intrinsic and/or extrinsic aging and the skin damages caused by extrinsic factors include thinning of skin; fragile skin; deepening of skin lines and fine lines; wrinkles, including fine and course wrinkles; blemishes; atrophy; pigmented spots, blotches and mottles, nodules and mottled skin; elastotic changes characterized by leathery, lusterless, uneven, coarse, rough, dry and/or yellowish skin; loss of skin elasticity and recoilability; loss of skin lubricating substances; changes in qualities and quantities of glycosaminoglycans and proteoglycans and collagen and elastic fibers; solar elastosis; decrease in collagen fibers; diminution in the number and diameter of elasitic fibers in the papillary dermis; atrophy; stretch marks; reduction in subcutaneous adipose tissue; deposition of abnormal elastic materials in the dermis leading to thickening of the dermis; older-looking skin; and telangiectatic skin.

[0013] In accordance with the objects of the invention a use of a water-containing composition consisting of N-acetyl glucosamine or an isomeric form thereof, present in a therapeutically effective amount and in a pharmaceutically acceptable vehicle for topical treatment of cosmetic conditions or dermatological disorders is provided. In one option, the composition further comprises a cosmetic, pharmaceutical, or other topical agent.

[0014] Also disclosed is a method for treating cosmetic conditions and dermatological disorders (not claimed) comprising topically applying a therapeutically effective amount of a composition comprising at least one compound selected from the group consisting of N-acetyl aldosamines, N-acetylamino acids and related compounds, in a pharmaceutically acceptable vehicle is provided. In one option, the method comprises topically applying a therapeutically effective amount of a composition comprising at least one compound selected from the group consisting of N-acetyl aldosamines, N-acetylamino acids and related compounds, and at least one cosmetic, pharmaceutical, or other topical agent, in a pharmaceutically acceptable vehicle.

[0015] N-Acetyl aldosamines, N-acerylamino acids and related N-acetyl compounds which are useful for topical treatment of skin, nail and hair changes associated with intrinsic and/or extrinsic aging and extrinsic factors include, *inter alia*, N-acetyl-aidosamines which are derivatives of aminosugars and include N-aceryl-ribosamine, N-acetyl-arabinosamine, N-acetyl-glucosamine, N-acetyl-galactosamine and N-acetyl-mannosamine, and N-acetylamino acids which are N-acetyl derivatives of amino acids and include N-acetyl-glucine, N-acetyl-proline. N-acetyl-lysine, N-acetyl-arginine and N-acetyl-tryptophan.

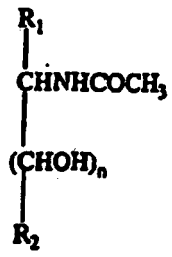
[0016] Additional objects and advantages of the invention will be set forth in part in the description that follows, and in part will be obvious from the description, or may be learned by practice of the invention. The objects and the advantages of this invention may be realized and obtained by means of the compositions and methods particularly pointed out in the appended claims.

Detailed Description

1. N-Acetyl-aldosamines, N-Acetylamino acids and Related N-Acetyl Compounds

(i) *N-Acetyl-aldosamines*

[0017] One aspect of the present disclosure pertains to compositions comprising N-acetyl-aldosamines and related compounds. N-acetyl-aldosamines are N-acetylated aminosugars in which the acetylamino group is preferably located at position 2 of the carbon chain. In accordance with the present disclosure, the generic structure or formula of N-aceryl-aldosamines which are topically beneficial for various cosmetic and dermatologic indications may be represented as follows:



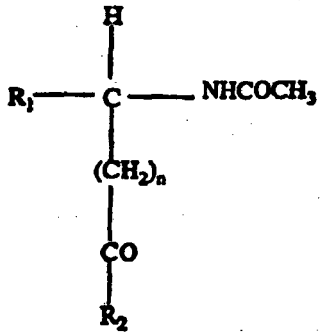
$R_2(CHOH)_3(CHNHCOCH_3)R_1$

where n is an integer, preferably 1-19; R_1 is selected from the group consisting of CHO, $CONH_2$, and $COOR_3$; R_2 is selected from the group consisting of H. I, F. Cl, Br, and an alkyl, alkoxyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 19 carbon atoms; and R^3 is selected from the group consisting of H, an alkyl, aralkyl or aryl group having 1 to 9 carbon atoms. N-Acetyl-aldosaroines may be present as saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form. A typical cyclic form of an N-acetyl-aldosarnine is a five member ring (furanose form) or a six member ring (pyranose form).

[0018] The following are some representative N-acetyl-aldosamines and related compounds: N-acetyl-glycerosamine, N-acetyl-erythrosamine, N-acetyl-threosamine, N-acetyl-ribosamine. N-acetyl-arabinosamine. N-acetyl-xylosamine, N-acetyl-lyxosamine, N-acetyl-allosamine, N-acetyl-altrosamine, N-acetyl-glucosamine, N-acetyl-mannosamine, N-acetyl-gulosamine. N-acetyl-idosamine, N-acetyl-galactosamine, N-acetyl-talosamine, N-acetyl-glucoheptosamine, N-acetyl-galactoheptosamine, N-acetyl-mannoheptosamine, N-acetyllactosamine, N-acetylmuramic acid, N-acetylneuramine, N-acetylneuramin Lactose. N-acetylglyceraminic acid, N-acetyl-erythmsaminic acid, N-acetyl-threosaminic acid, N-acetyl-ribosaminic acid, N-acetyl-arabinosaminic acid, N-acetyl-xylosaminic acid, N-acetyl-lyxosaminic acid, N-acetyl-allosaminic acid, N-acetyl-altrosaminic acid, N-acetyl-glucosaminic acid, N-acetyl-mannosaminic acid, N-acetyl-gulosaminic acid, N-acetyl-idosaminic acid, N-acetyl-galactosaminic acid, N-acetyl-talosaminic acid, N-acetyl-heptoglucosaminic acid, N-acetyl-heptogalactosaminic acid, N-acetyl-heptomannosaminic acid, and N-acetyl-N-acetylncuraminic. The amides and esters of the foregoing acid compounds also are contemplated by the present invention. Examples of five and six member ring forms are 2-acetamido-2-deoxy-D-ribofuranoside, 2-acetamido-2-deoxy-D-ribopyranoside, 2-acetamido-2-deoxy-D-glacofuranoside, 2-acetamido-2-deoxy-D-glucopyranoside, 2-acetamido-2-deoxy-D-galactofuranoside and 2-acemido-2-deoxy-D-galactopyranoside.

(ii) *N-Acetylamino acids*

[0019] Another aspect of the disclosure pertains to compositions comprising N-acetylamino acids and related compounds. N-acetylamino acids are N-acetyl derivatives of amino acids. In accordance with the present disclosure the generic structure or formula of N-acetylamino acids and related compounds which are topically beneficial for various cosmetic and dermatologic indications may be represented as follows:



$R_1CH(NHCOCH_3)(CH_2)_nCOR_2$

where R_1 is H, or an alkyl or aralkyl group having 1 to 14 carbon atoms; n is an integer, preferably from 0 to 5; R_2 is OH, NH_2 or OR_3; and R_3 is an alkyl, aralkyl or aryl group having 1 to 9 carbon atoms; the alkyl, aralkyl or aryl group may be saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form; and in addition R_1 may carry OH, SH, SCH_3, COOH, $CONH_2$, guanidine or heterocyclic group; the H attached to a carbon atom may be substituted

by I, F, Cl, Br or alkoxyl group having 1 to 9 carbons. N-Acetylamino acids may be present as isomeric or non-isomeric, as a free acid, salt, lactone, amide or ester form.

[0020] The following are some representative N-acetylamino acids and related compounds: N-acetyl-glycine, N-aceryl-alanine, N-acetyl-valine, N-acetyl-leucine, N-aceryl-isoleucine. N-acetyl-serine, N-acetyl-threonine. N-acetyl-tyrosine, N-acetyl-cysteine, N-acetyl-methionine, N-acetyl-aspartic acid, N-acetyl-asparagine, N-acetyl-glutamic acid, N-acetyl-glutamine, N-acetyl-arginine, N-acetyl-lysine, N-aceryl-histidine, N-acetyl-phenytatanine. N-acetyl-tyrosine, N-acetyl-tryptophan, N-acetyl-proline, N-acetyl-β-alanine, N-acetyl-taurine, N-acetyl-r-aminobutanoic acid, N-acetyl-hydroxyproline. N-acetyl-canavanine, N-aceryl-hydroxylysine, N-acetyl-cycloserine, N-acetyl-homoarginine, N-acetyl-norleucine, N-acetyl-norvaline, N-acetyl-homoserine, N-acetyl-methylserine, N-acetyl-hydroxyvaline, N-acetyl-ethionine, N-acetyl-mahoxinie, N-acetyl-β-aminoisobutanoic acid, N-acetyl-homocysteine, N-acetyl-cysteine sulfinic acid, N-acetyl-homophenylalanine. N-acetyl-homotryptophan, N-acetyl-5-hydroxytryptamine (N-acetylserotonin), N-acetyltryptamine, N-acetyl-omithine, N-acetyl-citrulline, N-acetyl-argininosuccinic acid, N-acetyl-dopa, N-actyl-3-iodotyrosine, N-acetyl-3,5-diiodotyrosine, N-acetyl-3,5,3'-triiodothyronine, N-acetyl-thyroxine, N-acetyl-creatine, N-acetyl-creatinine, N-acetyl-cystine and N-acetyl-homocystine.

[0021] The above N-acetylamino acids and related N-acetyl compounds may be present as a free acid, salt, lactone, amide or ester form. Examples of these compounds include N-acetyl-cysteine ammonium salt, N-acetyl-homocysteine thiolactone, N-acetyl-L-cystine methyl ester, N-acetyl-L-tryosinamide, N-acetyl-L-tryosine ethyl ester, N-acetyl-serine amide, N-acetylglycine methyl ester, N-acetylglycinamide, and N-acetyl-tryptophan methyl, ethyl, propyl or isopropyl esters.

[0022] The related N-acetyl compounds may also include dimers and oligomers formed from N-acetylamino acids with 2 to 5 monomer units. Examples include N-acetylglycylglycine and its amide and esters, N-acetylglycyl-leucine its amide and esters, N-acetylglycyltryptophan, N-acetylglycy!-glutamic acid and its amide and esters, N-acetyltryosyl-phenylalanine and its amide and esters, N-acetylglycyllysine and its amide and esters, N-acetyllaicyl-glycine and its amide and esters, N-acetylglycyl-glycyl-glycine and its amide and esters, N-acerylglycyl-lysyl-hydroxyproline and its amide and esters.

[0023] A preferred group N-Acetylamino acids and related compounds are the group of compounds represented by the generic structure or formula above, but excluding N-acetylcysteine and derivatives of N-acetylcysteine. N-acetylcysteine is known to degrade under ordinary storage conditions and result in a malodorous smell. The malodor is suggested to be caused by the release of thiol compounds and hydrogen sulfide upon degradation. Because N-acetylcysteine and its derivatives are malodorous, they are less preferred for use in the present invention.

2. Topical Uses of N-Acetyl-aldosamines , N-Acetylamino acids and Related N-Acetyl Compounds

(i) *N-Acetyl-aldosamines, N-Acelylamino acids and Related N-Aceryl Compounds*

[0024] Compositions comprising the N-acetyl-aldosamine, N-acetylamino acid or related N-acetyl compounds described herein are topically beneficial for various cosmetic conditions and dermatologic disorders, including those associated with intrinsic and/or extrinsic aging, as well as with changes or damage caused by extrinsic factors. These compositions can comprise one or more than one N-aceryl-aidosamine, N-acetylamino acid or related N-acetyl compound. In a preferred option, the compositions may be used for skin, hair and nail changes associated with intrinsic and/or extrinsic aging, and changes or damage caused by extrinsic factors.

[0025] With respect to age associated skin changes, the underlying bases of these changes is described in US Patent No. 4,603,146 (Kligman). In particular, the underlying causes of skin changes associated with aging can be more easily understood in view of the following summary of the changes in the epidermis and dermis as aging progresses.

[0026] With increasing age and exposure of a human to sun and other environmental traumas, cells divide at a slower rate (decreased capacity to renew themselves). They show marked irregularities in size, shape and staining properties; orderliness (polarity) from below to above is lost. The thickness of the epidermis decreases (atrophy). The horny layer which comprises the barrier against water loss and penetration of chemicals becomes abnormal due to the shedding (exfoliation) of cells in large group or clusters instead of as individual cells, resulting in roughness, scaling and dryness. There is loss of the orderly transformation of living epithelial cells into cornified dead cells which are shed at the surface, that is, differentiation is impaired. Aberrant differentiation results in numerous foci of abnormal epithelial growths or tumors, the most frequent and important of which are actinic keratoses. After many years these can transform into frank skin cancers called basal cell and squamous cell cancers. Pigment producing cells (melanocytes) can also become altered forming flat, dark growths (lentigo melanoma) which may progress to malignant melanoms.

[0027] The cells which make the fibers of the dermis become smaller and spacer with increasing age, usually in sun-damaged facial skin. There is a great loss of collagen fibers resulting in looseness and easy stretchability of the skin; elastic fibers become abnormal so that the skin does not promptly snap back after being stretched. Since the fibrous components comprise more than 90% of the bulk of skin of which 95% is collagen, the degradation of these fibers,

especially collagen, is mainly responsible for wrinkling, laxness and loss of elasticity.

[0028] Additionally, small blood vessels become thin walled, dilated and often ruptured. Vascular supply thereby becomes compromised.

[0029] The signs of nail and hair changes associated with intrinsic aging and the damages caused by extrinsic factors include thinning of hair and nail plate; lack of lubricants and luster, and uneven surface of hair and nails; fragility and splitting of hair and nails; and reduction of flexibility, resiliency, and elasticity of hair and nails.

[0030] The conventional management of signs of aging skin has been the use of cosmetics, as well as medical procedures such as phenol, trichloroacetic acid, and other chemical peels, and plastic surgery, etc. Such medical procedures are costly and risky with serious side effects, and the treatments alter only the cosmetic appearance of the skin, without any significant modifications of the underlying aging process.

[0031] Topical application to the skin, hair or nails of a composition of the present disclosure is beneficial for various cosmetic conditions and dermatologic disorders including those associated with intrinsic and/or extrinsic aging and extrinsic factors, and also including those characterized by the foregoing changes to the skin, hair and nails. Exemplary indications are characterized as disturbed keratinization, defective syntheses of dermal components, and changes associated with aging of skin, nail and hair; and those indications which include dryness or loose of skin, nail and hair; xerosis; ichthyosis; palmar and plantar hyperkeratoses: uneven and rough surface of skin, nail and hair; dandruff: Darier's disease; lichen simplex chronicus; keratoses; acne; pseudofolliculitis barbae; eczema; psoriasis; itchy scalp and skin; pruritus; warts; herpes; age spots; lentigines; melasmas; blemished skin; hyperkeratoses; hyperpigmented skin; abnormal or diminished syntheses of collagen, glycosaminoglycans, proteoglycans and elastin as well as diminished levels of such components in the dermis; stretch marks; skin lines; fine lines; wrinkles; thinning of skin, nail plate and hair; skin thickening due to elastosis of photoaging, loss or reduction of skin, nail and hair resiliency, elasticity and recoilability; lack of skin, nail and hair lubricants and luster; dull and older-looking skin, nail and hair; fragility and splitting of nail and hair; and other topical conditions and indications.

(ii) *Combination Compositions*

[0032] In addition, compositions comprising one or more than one N-Acetyl-aldosamine, N-acetylamino acid and related N-acetyl compound may also be incorporated into a composition comprising a cosmetic, pharmaceutical or other topical agent to enhance or create synergetic effects.

[0033] In accordance with this aspect, the compositions of the present invention may contain one or more N-Acetyl-aldosamine, N-acetylamino acid and related N-acetyl compounds to magnify the therapeutic effect of an unrelated cosmetic or pharmaceutical agent. At least one compound selected from the group consisting of N-Acetyl-aldosamine, N-acetylamino acid and related N-acetyl compounds may be incorporated into composition containing a cosmetic or pharmaceutical agent for topical treatment to improve or alleviate signs of skin, nails or hair changes associated with intrinsic aging or the damages caused by extrinsic factors. It has been found that such incorporation results in magnified therapeutic efficacies which are not simply additive effects.

[0034] Most pharmaceutical drugs produce their therapeutic effects by first interacting with their receptors in the target tissues. Many drug receptors are functional macromolecules such as enzymes, cell membrane components or certain components of cells. The binding affinity or interacting property of a drug toward its specific receptor molecule is intimately governed by the chemical structure of the drug. Since most pharmaceutical agents are chemically different from N-acetyl compounds of the instant invention, the respective receptor molecule should be different and so are the pharmacological actions and the therapeutic effects. Under such conditions if N-Acetyl-aldosamine, N-acetylamino acid and/or a related N-acetyl compound is incorporated into a composition containing a pharmaceutical agent, one of the following two consequences may arise:

(a) No enhancement or any substantial changes in either effect. In this case, the overall clinical effect would be a mixed effect, i.e. the effect due to the pharmaceutical agent alone mixed with the effect due to N-Acetyl-aldosamine, N-acetylamino acid or related N-acetyl compound alone. Also in this case, the interaction between the pharmaceutical agent and its receptor molecule is not affected nor interfered by the presence of N-Acetyl-aidosaraine, N-acetylamino acid or related N-acetyl compound. Nor does the N-Acetyl-aldosamine, N-acetylamino acid or related N-acetyl compound assist in or enhance the binding affinity or the interaction of the pharmaceutical agent toward its receptor molecule. The clinical results from such combination composition would be just the mixed effects.

(b) Amplified therapeutic action or substantial loss of therapeutic action in either effect. In this case, the interaction between the pharmaceutical agent and its receptor molecule is affected either positively or negatively by the presence of a N-Acetyl-aldosamine, N-acetylamino acid or related N-acetyl compound. From the point of positive effect, N-Acetyl-aldosamine. N-acetylamino acid or the related N-acetyl compound may produce an amplified effect by either increasing the affinity of the receptor molecule toward the pharmaceutical agent; acting as a better and more efficient

coenzyme or as an activator by disrupting barriers and removing obstacles for better binding of the agent toward its receptor molecule; for example, enzyme activation by removal of natural inhibitors. In all these cases the overall clinical results would be due to magnified therapeutic effects which are not predictable from either effect alone.

[0035] From the point of negative effect, a N-Acetyl-aldosamine, N-acetylamino acid or related N-acetyl compound might interfere with or decrease the binding affinity of the pharmaceutical agent toward its receptor molecule; i.e. acting as an competitor or inhibitor. In such case, the overall clinical results should be due to substantial diminishment or completely loss of therapeutic effects, which is also unpredictable from either effect alone.

[0036] We have found that, in most cases, therapeutic effects of cosmetic and pharmaceutical agents are amplified when a N-acetyl-aldosamine, N-amtylamino acid or related N-acetyl compound is incorporated into the composition, i.e., consequence (b) above is observed.

[0037] The cosmetic and pharmaceutical agents which may be actuated by N-Acetyl-aldosamine, N-acetylamino acid or a related N-acetyl compound include those that improve or eradicate age spots, keratoses and wrinkles; local analgesics and anesthetics; antiacne agents; antibacterials; antiyeast agents; antifungal agents; antiviral agents; antidandruff agents; antidermatitis agents; antihistamine agents; antipruritic agents; antiemetics; antimotion sickness agents; antiinflammatory agents; antihyperkeratoiytic agents; antiperspirants; antipsoriatic agents; antiseborrheic agents; hair conditioners and hair treatment agents; antiaging and antiwrinkle agents; sunblock and sunscreen agents; skin lightening agents: depigmenting agents; vitamins; corticosteroids; tanning agents; hormones; retinoids; and other dermatologicals.

[0038] Some examples of cosmetic and pharmaceutical agents are clotrimazole, ketoconazole, miconazole, griseofulvin, econazole, metronidazole, hydroxyzine, diphenhydramine, pramoxine, lidocaine, procaine, mepivacaine, monobeazone, erythromycin, tetracycline, clindainycin, meclocycline, hydroquinone, hydroquinone monoether, minocycline, naproxen, ibuprofen, theophylline, cromolyn, albuterol, retinol, retinyl acetate, retinyl palmitate, retinal, retinoic acid, 13-cis retinoic acid, hydrocortisone, hydrocortisone 21-acetate, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, betamethasone valerate, betamethasone dipropionate, triamcinolone acetonide, fluocinonide, clobetasol, propionate, benzoyl peroxide, kojic acid, crotamiton, propranolol, promethazine, salicylic acid, vitamin E and vitamin E acetate.

[0039] Another example of cosmetic or other agents that may be combined with one or more N-acteyl-aidosainines, N-acetylamino acids or related N-acetyl compounds include hydroxyacids, ketoacids and related compounds. Examples of hydroxy acids include hydroxymonocarboxylic acids, hydroxydicarboxylic acids, 2-hydroxycarboxylic acids, other hydroxycarboxylic, 2-ketocarboxylic acids acids and related compounds. See, for example. US Patent Nos. 5,422,370, 5,547,988, 5,470,880, and 5,385,938. The hydroxy acids may exist as a free acid, an ester, a lactone, in salt form with an organic base or an inorganic alkali, and as stereoisomers. Representative examples of hydroxy acids and related compounds include glycolic acid, mandelic acid, lactic acid, tropic acid, methyllactic acid, lactobionic acid, tartaric acid, citric acid, glucuronic acid, ribonic acid, gluconolactone, ribonolactone, gycolyl glycollate, lactyl lactate, trilactic acid and polylactic acid.

[0040] Yet another example of cosmetic or other agents that may be combined with one or more N-actcyl-aldosomines, N-acetylamino acids or related N-acetyl compounds include phenyl alpha acyloxyalkanoic acids and derivatives thereof. These compounds may exist in a free acid, lactone or salt form, or as stereoisomers. See, for example, US Patent Nos. 5,258,391 and 5,643,949. Representative example of such compounds include diphenyl alpha acetoxyacetic acid, phenyl alpha acetoxyacetic acid, phenyl alpha methyl alpha acetoxyacetic acid, phenyl alpha acetoxypropanoic acid, and 2-phenyl beta acetoxypropanoic acid.

3. General Preparation of the Cosmetic and Therapeutic Compositions

[0041] Compositions comprising N-acetyl-aldosamine, N-acetylamino acid or related N-acetyl compounds may be formulated as solution, gel, lotion, cream, ointment, shampoo, spray, stick, powder, masque or other form topically acceptable for use on skin, nail and hair.

[0042] To prepare a solution composition, at least one N-acetyl compound of the instant invention is dissolved in a solution prepared from water, ethanol, propylene glycol, butylene glycol, diisopropyl adipate and/or other topically acceptable vehicle. The concentration of a single N-acetyl compound or the total concentration of all N-acetyl compounds, where the composition comprises more than one N-acetyl compound, may range from 0.01 to 99.9% by weight of the total composition, with preferred concentration of from 0.1 to 50% by weight of the total composition and with more preferred concentration of from 0.5 to 25% by weight of the total composition. Contemplated embodiments of the instant invention include ranges of 0.1 % to 0.2%, 0.2% to 0.3%, 0.3% to 0.4%, 0.4% to 0.5%, 0.5% to 0.6%, 0.6% to 0.7%, 0.7% to 0.8%, 0.8% to 0.9%. 0.9% to 1%, 1% to 2%, 2% to 3%, 3% to 4%, 4% to 5%, 5% to 6%, 6% to 7%, 7% to 8%, 8% to 9%, 9% to 10%, 10% to 14%, 14% to 18%. 18% to 22%, 22% to 26%. 26% to 30%, 30% to 35%, 35% to 40%, 40% to 45%, 45% to 50%, 50% to 60%, 60% to 70%, 70% to 80%, 80%n to 90%, and 90% to 99.9% by weight of the total composition.

[0043] To prepare a topical composition in lotion, cream or ointment form, the N-acetyl compound is first dissolved in water, ethanol, propylene glycol, diisopropyl adipate and/or another vehicle, and the solution thus obtained is mixed with a desired base or pharmaceutically acceptable vehicle to make lotion, cream or ointment. Concentrations of the N-acetyl compound are the same as described above for the solution form.

[0044] A topical composition may also be formulated in a gel or shampoo form. A typical gel composition is formulated by the addition of a gelling agent such as chitosan, methyl cellulose, ethyl cellulose, polyvinyl alcohol, polyquaterniums, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carbomer or ammoniated glycyrrhizinate to a solution comprising the N-acetyl compound The preferred concentration of the gelling agent may range from 0.1 to 4 percent by weight of the total composition. In the preparation of shampoo, the N-acetyl compound is first dissolved in water or propylene glycol, and the solution thus obtained is mixed with a shampoo base. Concentrations of the N-acetyl compound used in gel or shampoo form are the same as described above.

[0045] To prepare a combination composition for synergetic effects, a cosmetic, pharmaceutical or other topical agent is incorporated into any one of the above compositions by dissolving or mixing the agent into the formulation.

[0046] Other forms of compositions for topical delivery of N-acetyl compound of the instant invention are readily prepared or formulated by those skilled in the art.

[0047] The following are illustrative examples of formulations and uses. Although the examples utilize only selected compounds and formulations, it should be understood that the following examples are illustrative only.

Example 1

[0048] N-Acetyl-α-D-glucosamine 10 g was dissolved in 30 ml warm water, and the solution thus obtained was mixed uniformly with 60 g cream base or commercially available hydrophilic ointment. The white cream thus formulated contained 10% N-acetyl-glucosamine. N-Acetyl-glucosamine 1% or 5% cream was formulated in the same manner except that N-acetyl-α-D-glucosamine 1 g or 5 g was used, and was dissolved in 39 ml or 35 ml water.

Example 2

[0049] N-acetyl-α-D-glucosamine 0.5 g was dissolved in 99.5 ml solution prepared from water 40 ml, ethanol 40 ml and propylene glycol 20 ml. The composition thus prepared contained 0.5% N-acetyl-glucoaamine. N-Acetyl-glurosamine 5% in solution form was formulated in the same manner except that 5 g instead of 0.5 g active ingredient was dissolved in 95 ml solution.

Example 3

[0050] A typical combination composition comprising for example N-acetylaldosamine and an anti-itch agent may be formulated as follows.

[0051] N-Acetyl-α-D-glucosamine 2 g was dissolved in 10 ml water and the solution was mixed with diphenhydramine 2 g in 4 ml water containing 2 g gluconolactone. The above solution was mixed uniformly with 80 g cream base or commercially available hydrophilic ointment. The composition with pH 5.1 contained 2% N-acetyl-D-glucosamine and 2% diphenhydramine.

4. Application and Treatment Using N-Acetyl-Aldosamines. N-Acetylamino acids and Related N-Acetyl Compounds

[0052] The N-acetyl aldosamines, N-acetylamino acids and related N-acctyl compositions of the present invention may be applied to any area of the skin, hair, or nails. Exemplary areas of application include the hands, arms, neck, legs, feet, trunk, hair shaft, nails, including the nail plate and nail cuticle, and on and around the face. Exemplary areas of facial application include the nose, forehead, and areas around the eyes. The compositions may be applied with or without occlusion. Any suitable occlusive device may be used. In addition, it is within the knowledge of the skilled artisan how best to apply such occlusive devices to achieve the desired result.

[0053] The compositions of the present invention may be applied to these areas with varying frequency and for varying duration. In this regard, the skilled artisan will appreciate how to alter the frequency and duration of application to achieve the desired effect. For example, the compositions of the instant invention can be applied at varying frequencies including on a daily basis, 1 or more times daily, or 1 or more times weekly. When being applied on a daily basis, the instant invention can be applied 1, 2, 3 or more times a day. When being applied on a weekly basis the instant invention can be applied 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or more times a week. The duration of treatment with the compositions of the instant invention can also vary. For example, the compositions may be applied for 1, 2, 3, 4, 5, 6 or more weeks; or for 1, 2, 3, 4, 5, 6 or more months. The duration of treatment may also be continuous. Again, the skilled artisan will appreciate the interaction between frequency and duration of use in order to achieve and/or maintain the desired effect.

[0054] In addition, the skilled artisan will appreciate how to vary concentrations of the instant invention in conjunction with the frequency and duration of use to achieve the desired effect. For example, a composition of higher concentration might be applied with less frequency or for a shorter duration. In contrast, a composition of a lower concentration might be applied more frequently or for a longer duration.

Test Results

A Method of Measurement

[0055] In one of the studies related to skin changes associated with aging, skin thickness was measured by micrometer calipers as follows: The skin was grasped with a 2 X 6 cm metal hinge, the internal faces of the hinge were coated with emery cloth to prevent slippage, and manually squeezed to threshold subject discomfort. Combined thickness of two whole-skin layers including thickness of the two hinge leaves was measured with micrometer calipers. Thickness of the two hinge leaves was subtracted to determine the actual thickness of two whole-skin layers. Triplicate measurements on treated site were done and an average number was used for calculation of the skin thickness.

1. Xerosis and dry skin

[0056] A male subject, age 66, who had xerosis and dry skin on lower legs topically applied twice daily 5% N-acetyl-glucosamine cream for one week. After a few days of topical treatment, the skin became less rough and scaly, and felt smooth. The dry skin returned to normal- looking skin after one week of topical application. This result indicated that N-acetyl-glucosamine was therapeutically effective for topical treatment of xerosis and dry skin.

2. Effect of N-acetyl-glucosamine on skin

[0057] A female subject, age 74, applied topically twice daily 10% N-acetyl-glucosamine cream to her right forearm for three weeks. After three weeks her untreated left forearm was still loose, relatively thin and wrinkled when lifted. In contrast, her right forearm was more firm, smooth, plump and minimally wrinkled when lifted. While there was no change in skin thickness of her left forearm, her right forearm had increased 37% in skin thickness as measured by the micrometer calipers. This result indicated that N-acetyl-glucosamine would be therapeutically effective for topical treatment of wrinkles and changes of skin, nail or hair associated with aging.

3. Effect of combination composition on skin

[0058] A female subject, age 72, applied topically twice daily a combination cream formulated from 10% each of N-acetyl-α-D-glucosamine and gluconolactone to her right forearm for three weeks. After three weeks her untreated left forearm was still loose, relatively thin and wrinkled when lifted. In contrast, her right forearm was more firm, smooth, plump and minimally wrinkled when lifted. While there was no change in skin thickness of her left forearm, her right forearm had increased 118% in skin thickness as measured by the micrometer calipers. This result indicated that N-acetyl-glucosamine in combination with other topical agents would be topically effective for various cosmetic and dermatologic indications including wrinkles and changes of skin, nail and hair associated with intrinsic and extrinsic aging.

[0059] The invention described herein may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The specific embodiments previously described are therefore to be considered as illustrative of, and not limiting, the scope of the invention.

Claims

1. Use of a water-containing composition consisting of N-acetyl-glucosamine or an isomeric form thereof in a cosmetic formulation with water and a vehicle selected from a solution, cream and lotion for topically alleviating or improving a cosmetic condition of the skin, wherein the cosmetic condition is selected from changes associated with aging of skin.

2. The use of claim 1, wherein the vehicle is selected from a solution or cream.

3. The use of claim 1 or 2, wherein the changes associated with aging of skin are selected from the group consisting of, age spots, mottled skin, blotches, fine lines, wrinkles, older-looking skin, thinning of skin, loss or reduction of skin elasticity and recoilability; and lack of skin elasticity and recoilability.

4. The use of claim 3, wherein the changes associated with aging of skin are selected from the group consisting of age spots, mottled skin, wrinkles and older-looking skin.

5. The use of claim 3, wherein the changes associated with aging of skin are selected from the group consisting of age spots and wrinkles.

Patentansprüche

1. Verwendung einer Wasser enthaltende Zusammensetzung, bestehend aus N-acetyl-glukosamin oder einer isomeren Form davon in einer kosmetischen Formulierung mit Wasser und einem Vehikel, ausgewählt aus einer Lösung, Creme und Lotion zur topischen Linderung oder Verbesserung eines kosmetischen Zustands der Haut, wobei der kosmetische Zustand ausgewählt ist aus Veränderungen, assoziiert mit dem Altern der Haut.

2. Die Verwendung gemäß Anspruch 1, wobei das Vehikel ausgewählt ist aus einer Lösung oder Creme.

3. Die Verwendung gemäß Anspruch 1 oder 2, wobei die Veränderungen, assoziiert mit dem Altern der Haus, ausgewählt sind aus der Gruppe, bestehend aus Altersflecken, gesprenkelter Haut, Flecken, feinen Linien, Falten, alt aussehender Haut, Ausdünnung der Haut, Verlust oder Verminderung der Hautelastizität oder Rückformbarkeit und Fehlen von Hautelastizität und Rückformbarkeit.

4. Die Verwendung gemäß Anspruch 3, wobei die Veränderungen, assoziiert mit dem Altern der Haut, ausgewählt sind aus der Gruppe, bestehend aus Altersflecken, gesprenkelter Haut, Falten und alt aussehender Haut sind.

5. Die Verwendung gemäß Anspruch 3, wobei die Veränderungen, assoziiert mit dem Altern der Haut, ausgewählt sind aus der Gruppe, bestehend aus Altersflecken und Falten.

Revendications

1. Utilisation d'une composition aqueuse composée de N-acétylglucosamine ou d'une forme isomère de celui-ci dans une formulation cosmétique avec de l'eau et un véhicule sélectionné parmi une solution, une crème et une lotion pour soulager ou améliorer topiquement un état cosmétique de la peau, dans laquelle l'état cosmétique est sélectionné parmi des changements associés au vieillissement de la peau.

2. Utilisation selon la revendication 1, dans laquelle le véhicule est sélectionné parmi une solution ou une crème.

3. Utilisation selon la revendication 1 ou 2, dans laquelle les changements associés au vieillissement de la peau sont sélectionnés parmi le groupe comprenant les taches de vieillesse, la peau marbrée, les taches, les ridules, les rides, la peau mature, l'affinement de la peau, la perte ou la réduction de l'élasticité et du ressort de la peau ; et le manque d'élasticité et de ressort de la peau.

4. Utilisation selon la revendication 3, dans laquelle les changements associés au vieillissement de la peau sont sélectionnés parmi le groupe comprenant les taches de vieillesse, la peau marbrée, les rides et la peau mature.

5. Utilisation selon la revendication 3, dans laquelle les changements associés au vieillissement de la peau sont sélectionnés parmi le groupe comprenant les taches de vieillesse et les rides.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US 5091171 A **[0002]**
- US 5547988 A **[0002] [0039]**
- US 5385938 A **[0002] [0039]**
- US 5258391 A **[0002] [0040]**
- US 5665776 A **[0002]**
- US 5641475 A **[0002]**
- US 5643949 A **[0002] [0040]**
- US 4603146 A **[0002] [0025]**
- US 9616534 W **[0004] [0007]**
- JP 59013708 B **[0008]**
- US 5422370 A **[0039]**
- US 5470880 A **[0039]**

Non-patent literature cited in the description

- **KLIGMAN et al.** Topical Tretinoin for Photoaged Skin. *J. American Academy of Dermatology,* 1986, vol. 15, 836-859, 886-887 **[0003]**
- **WEISS et al.** Topical Tretinoin Improves Photoaged Skin: A Double-blind Vehicle-controlled Study. *J. American Medical Association,* 1988, vol. 259, 527-532 **[0003]**
- **WEISS et al.** Topical Tretinoin in the Treatment of Aging Skin. *J. American Academy of Dermatology,* 1988, vol. 19, 169-175 **[0003]**
- *Eur. Respir. J.,* 1989, vol. 2, 116-126 **[0005]**