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Gibson

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[54] **COSMETIC COMPOSITION**

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[30] **Foreign Application Priority Data**

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[51] **Int. Cl.**[5] **A61K 7/06**

[52] **U.S. Cl.** **424/70;** 514/2; 424/603; 424/660; 424/673; 424/663; 424/709; 424/711; 435/200

[58] **Field of Search** 424/70, 603, 660, 673, 424/663, 709, 711; 514/880, 881; 435/200

[56] **References Cited**

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[57] **ABSTRACT**

A composition suitable for topical application to mammalian skin or hair for inducing, maintaining or increasing hair growth comprises:

(i) a first chemical inhibitor chosen from proteoglycanase inhibitors, glycosaminoglycanase inhibitors, glycosaminoglycan chain cellular uptake inhibitors or mixtures thereof; and

(ii) a cosmetically acceptable vehicle for the chemical inhibitor;

provided that when the first chemical inhibitor is a weak inhibitor, such that a 1 mM aqueous solution of the inhibitor reduces proteoglycanase activity, glycosaminoglycanase activity or cellular uptake of glycosaminoglycan chains, by from 5 to 50%, in accordance with at least one of the assay tests as herein described, then there is also present in the composition a second chemical inhibitor and/or an activity enhancer. When minoxidil is the sole chemical inhibitor, then the activity enhancer is a penetration enhancer chosen from a limited number of materials, including certain esters and cationic polymers.

The total amount of chemical inhibitor present in the composition is sufficient to increase hair growth in the rat, when said composition is applied topically thereto, by at least 10% more than that obtainable using a control composition from which the said inhibitors have been omitted.

31 Claims, No Drawings

COSMETIC COMPOSITION

FIELD OF THE INVENTION

The invention relates to cosmetic and pharmaceutical compositions for topical application to mammalian skin or hair, containing an enzyme inhibitor which is capable of promoting hair growth, especially terminal hair growth on the human scalp.

BACKGROUND

The Hair Growth Cycle

It should be explained that in most mammals, hair does not grow continuously, but undergoes a cycle of activity involving alternate periods of growth and rest. The hair growth cycle can be divided into three main stages, namely:

(i) the growth phase known as anagen, during which the hair follicle penetrates deep into the dermis with the cells of the bulb dividing rapidly and differentiating to form the hair,

(ii) the transitional stage known as catagen, which is heralded by the cessation of mitosis, and during which the follicle regresses upwards through the dermis and hair growth ceases,

(iii) the resting stage known as telogen, in which the regressed follicle contains a small secondary germ with an underlying ball of tightly packed dermal papilla cells.

The initiation of a new anagen phase is revealed by rapid proliferation in the germ, expansion of the dermal papilla and elaboration of basement membrane components. The hair cycle is then repeated many times until, as a consequence of the onset of male pattern baldness, most of the hair follicles spend an increasing proportion of their time in the telogen stage, and the hairs produced become finer, shorter, and less visible; this is known as terminal to vellus transformation.

PRIOR ART

Alleged Baldness Cures

Although there have been many claims in the scientific literature to the promotion or maintenance of hair growth by the topical application of hair tonics and the like, with the possible exception of minoxidil, none has been shown to be sufficiently free from disadvantageous clinical side effects, whether administered topically, orally or systemically, to warrant commercial exploitation as an ethical pharmaceutical, proprietary medicine, or as a cosmetic product. Possibly, the only means which has met with partial success for growing hair on the bald or balding human head is by transplantation of hair to the bald areas. This is, however, an extremely painful operation and is not always successful. Furthermore, it is immediately apparent to the casual observer that the subject has received a hair transplant and it may take many months or even years before hair regrowth, following this operation, assumes an appearance which resembles that of the original naturally growing hair.

Among the many hair regrowth studies that have been reported in the literature, there is included the work of Bazzano as described in PCT International Publication No. WO 85/04577. This publication describes a composition which is useful for increasing the rates of hair growth on mammalian skin, prolonging the anagen phase of the hair growth cycle and for treating various types of alopecias. The composition in question comprises a pyrimidine carbamate.

It has also been reported in US patent no. 4 139 619 to Chidsey assigned to the Upjohn Company, that a topical composition comprising minoxidil as the free base or acid addition salt thereof, or certain specified related iminopyrimidines, is useful in stimulating the conversion of vellus hair to growth as terminal hair, as well as increasing the rate of growth of terminal hair.

In spite of the apparent stimulation of hair growth or regrowth reported independently by Bazzano and Chidsey, following topical application of minoxidil or related compounds, there is general concern that systemic side-effects can result, particularly following topical application of minoxidil. Thus it is generally recognised in the medical literature that the side effects of orally administered minoxidil are very serious, and include fluid retention, tachycardia, dyspnea, gynecomastia, fatigue, nausea and cardiotoxicity. There is also evidence that certain side effects have been experienced following topical application of minoxidil.

In addition to the alleged benefits of employing the pyrimidine carbamates of Bazzano or minoxidil of Upjohn, many other hair regrowth studies have been reported in the literature. In particular, the work of Meyer et al (1961) in the Proceedings of the Society of Experimental and Biological Medicine, 108, 59–61, is worthy of mention. Meyer and his co-workers repeatedly injected acid mucopolysaccharides into the skin of shaved rabbits and reported observing the initiation of the hair growth cycle with stimulation of hair growth which in some instances appeared to be thicker than usual. They found that heparan sulphate was particularly active, while dermatan sulphate and chondroitin-6-sulphate were also active in this respect, but to a lesser extent.

It has also been reported by Frajdenrajch in EP-A-O 035 919 to include chondroitin sulphate in a hair composition in order to prevent loss and encourage growth of the hair.

Also, Shansho Seigaku in JA-59/186911 describes a shampoo containing a mucopolysaccharide such as chondroitin sulphate.

There are also other references, mainly of Japanese origin, which claim the use of chondroitin sulphate in preparations for topical application to human skin, particularly as hair tonics.

Kohler in DE OLS 24 38 534 reports that D-glucuronic acid and glucuronic acid γ-lactone (also known as glucurono-6,3-lactone) can be applied externally to the skin, together with vitamin C and water, ethanol or aqueous ethanol as a vehicle, as a scalp care agent. In a particular experiment, Kohler reports regrowth of hair following daily application for six months of a 1% solution of D-glucuronic acid.

Kohler et al in DE OLS 26 19 100 also claims the use of glucuronic acid or glucuronic acid γ-lactone as inhibitors in agents for inhibiting the activity of γ-glucuronidase, particularly in combination with vitamin B_{12}. Whereas Kohler et al are concerned with γ-blucuronidase as found in unusually high concentrations in healing wounds and cancer tissues, they do state that the agents also have a beneficial effect on the loss of hair.

In experiments to be described later in this specification, we have found that both glucuronic acid and glucurono-6,3-lactone are weak inhibitors of γ-glucuronidase activity and require the presence of a second inhibitor and/or a special activity enhancer, as

hereinafter defined, to provide significant hair growth or regrowth. The weak inhibition by glucuronic acid in this respect has also been confirmed by Levvy and Snaith (1972) in "Advances in Enzymology" 36 where, at page 156 they state that:

"Both β-glucuronidase and α-glucuronidase are feebly inhibited by glucuronic acid . . . "

BACKGROUND OF THE INVENTION

The above review of the most relevant references concerning the alleged promotion of hair growth following topical or systemic application of specified molecules, has prompted the study in greater detail, of the biological and biochemical mechanisms involved in the control of the hair growth cycle. The reported role of the dermal papilla which is situated at the base of the hair follicle, and the closely related cells of the connective tissue sheath which surrounds the hair follicle are alleged to be of key importance in governing the cyclic behaviour of hair follicles. This has been shown, for example, directly by Oliver R F (1970) J Embryol Exp Morphol., 23, 219–236, and the changes in the dermal papilla during the hair cycle are consistent with these observations. At the end of anagen, there is a sudden loss of fibronectin [Couchman J R and Gibson W T, (1985) Dev Biol , 108, 290–298]and metachromatic (glycosaminoglycan) staining [Montagna W et al, (1952) Q J Microsc Sci., 93, 241–245]from the connective tissue matrix of the dermal papilla which then undergoes condensation.

Conversely, expansion and elaboration of new matrix is associated with the onset of anagen. A direct role of matrix components in stimulating hair growth was suggested by the work of Meyer et al (1961), [supra].

It is accordingly apparent that glycosaminoglycan breakdown is an important early change in catagen, and since there is already evidence for a link between the presence of intact glycosaminoglycans and hair growth, we have suggested that prevention of proteoglycan and glycosaminoglycan breakdown may lead to earlier onset and/or prolongation of anagen. This would effectively retard hair loss and reverse baldness.

When considering the breakdown of glycosaminoglycans, it must be remembered that these are complex polysaccharides built up from alternating hexosamine and uronic acid units. Modification of these units by N-and/or and/or O-sulphation, and by N-acetylation provides further scope for diversity, which necessitates the concerted, sequential action of a range of enzymes for complete degradation to occur. Furthermore, glycosaminoglycans normally exist in the form of a proteoglycan, in which glycosaminoglycan chains are attached to a protein core. Degradation can therefore occur by the action of proteolytic enzymes ("proteoglycanases") on the protein core, causing release of intact glycosaminoglycan chains which are taken up by cells or removed in the circulation, or by the action of endoglycosidases, exoglycosidases and sulphatases ("glycosaminoglycanases") which cleave the glycosaminoglycan molecule at specific sites. It follows that glycosaminoglycan breakdown may be prevented in a number of ways, viz by inhibiting proteoglycanase activity, by blocking cellular uptake of intact glycosaminoglycan chains, and/or by inhibiting

We have now identified chemical inhibitors of key enzymes and other cellular events involved respectively in the breakdown of proteoglycan or glycosaminoglycan chains, and in the blocking of cellular uptake of intact glycosaminoglycan chains.

It should be explained by "chemical inhibitor" is meant a substance that is physiologically suitable and safe for topical application to human skin, and which is capable of inhibiting proteolytic breakdown of the proteoglycans or inhibiting glycosidase or sulphatase enzymes involved in the breakdown or modification of glycosaminoglycan side chains by direct, enzyme inhibition or by protecting the substrate so that the enzyme does not recognise it, or inhibiting cellular events involved in the recognition and uptake of glycosaminoglycans.

We have accordingly found that these inhibitors will indeed stimulate hair growth as predicted on the basis of the theory outlined above.

DEFINITION OF THE INVENTION

Accordingly, the invention provides a composition suitable for topical application to mammalian skin or hair for inducing, maintaining or increasing hair growth which comprises:

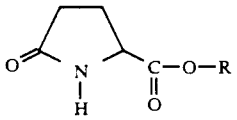
(i) a first chemical inhibitor chosen from proteoglycanase inhibitors, glycosaminoglycanase inhibitors, glycosamincglycan chain cellular uptake inhibitors or mixtures thereof; and

(ii) a cosmetically acceptable vehicle for the chemical inhibitor;

provided that when the first chemical inhibitor is a weak inhibitor, such that a 1mM aqueous solution of the inhibitor reduces proteoglycanase activity, glycosaminoglycanase activity or cellular uptake of glycosaminoglycan chains, by from 5 to 50%, in accordance with at least one of the assay tests as herein described, then there is also present in the composition a second chemical inhibitor and/or an activity enhancer; provided also that when minoxidil is the sole chemical inhibitor then the activity enhancer is a penetration enhancer chosen from:

Dioctyl adipate
Dicapryl adipate
Diisopropyl adipate
Diisopropyl sebacate
Dibutyl sebacate
Diethyl sebacate
Dimethyl sebacate
Dioctyl sebacate
Dibutyl suberate
Dioctyl azelate
Debenzyl sebacate
Dibutyl phthalate
Dibutyl azelate
Ethyl myristate
Dimethyl azelate
Butyl myristate
Dibutyl succinate
Didecyl phthalate
Decyl oleate
Ethyl caproate
Ethyl salicylate
Isopropyl palmitate
Ethyl laurate
2-ethyl-hexyl pelargonate
Isopropyl isostearate

Benzyl benzoate
Butyl benzoate
Hexyl laurate
L- Ethyl caprate
Ethyl caprylate
Butyl stearate
Benzyl salicylate
2-hydroxypropanoic acid
2-hyroxyoctanoic acid,
esters of pyroglutamic acid having the structure:



(1)

where R is C_1 to C_{30} alkyl, or

and where R′ and R″ are the same or different and are each represented by H or the grouping:

$$(CH_3)_u, (CH_2OH)_v, (CH_2)_w, (CH_3CH_2)_x, (CH{=}CH)_z]- \quad (2)$$

where
u is zero or 1
v is zero, or the integer 1 or 2,
w is zero, or an integer of from 1 to 21
x is zero, or an integer of from 1 to 4,
y is zero, or the integer 1 or 2,
z is zero, or an integer of from 1 to 22, and
u+v+w+x+y+z is an integer of from 1 to 22;
provided that when the subgrouping (CH=CH) is present, then the total number of carbon atoms in said grouping is from 10 to 22; and/or
a cationic polymer chosen from:
Guar Hydroxypropyltrimonium chloride
Quaternium-19
Quaternium-23
Quaternium-40
Quaternium-57
Poly(dipropyldiallylammonium chloride)
Poly(methyl-β-propaniodiallylammonium chloride)
Poly(diallylpiperidinium chloride)
Poly(vinyl pyrinium chloride)
Quaternised poly (vinyl alcohol) and
Quaternised poly-(dimethylaminoethylmethacrylate);
the total amount of chemical inhibitor present in the composition being sufficient to increase hair growth in the rat, when said composition is applied topically thereto, by at least 10% more than that obtainable using a control composition from which the said inhibitors have been omitted.

DISCLOSURE OF THE INVENTION

The Chemical Inhibitor

As has already been stated, a "chemical inhibitor" is a substance which is not only physiologically suitable and safe for topical application to skin, but which is capable of inhibiting in some way proteoglycanase activity, and/or glycosaminoglycanase activity and/or cellular uptake of glycosaminoglycan chains.

It is preferred that the chemical inhibitor is one which is significantly effective in at least one of these respects, that is, it is a strong inhibitor which is normally capable at a concentration of 1mM of reducing said activity or cellular uptake by more than 50%. For less effective inhibitors, ie., weak inhibitors, which are only capable, at this concentration, of reducing said activity or cellular uptake by from 5 to 50%, then it is necessary to include in the composition according to the invention a second chemical inhibitor and/or an activity enhancer.

In view of the complexity of the proteoglycan and glycosaminoglycan chain which can be degraded in different ways with a variety of enzymes, it is necessary to screen a potential chemical inhibitor in at least one of several different assay systems. Suitable assays which can be employed for endoglycosidases, exoglycosidases, sulphatases, sulphamatases are described in "Lysosomes—A Laboratory Handbook", Second Edition (1977) edited by J. T. Dingle. Proteoglycanase inhibitors may be conveniently assayed by the method described by Nagase & Woessner (1980) in Analyst. Biochem. 107, 385. Cellular uptake inhibition may be assessed by using radioactively labelled glycosaminoglycans according to the method described by Eskild W, et al., (1986) in Int. J. Biochem. 18, 647.

Suitable assay methods for each of the relevant enzymes and their inhibition by chemical inhibitors will be described and illustrated later in this specification.

The Proteoglycanase Inhibitors

According to one embodiment of the invention, the composition comprises a direct proteoglycanase inhibitor, that is a substance which will suppress the activity of proteinase enzymes present in or in the region of the dermal papilla, and/or the connective tissue sheath of the hair follicle.

An example of a direct proteoglycanase inhibitor of this type is 1,10-phenanthroline, also identified by Galloway et al, (1983) in Biochem. J. 209, 741–742, as a bone proteoglycanas inhibitor.

Further examples of direct proteoglycanase inhibitors include various thiol, carboxyalkyl and hydrcxamic peptide inhibitors, such as those described by Caputo et al., (1987) in Biochemical Pharmacology 36, 995-1002 as effective inhibitors of the action of a metalloproteinase on proteoglycan core protein. These inhibitors include:
Thiols, such as
AcetylPhe-LeuSH
AcetylSer-LeuSH
AcetylTrp-LeuSH
AcetylPhe-Phe-LeuSH
$HSCH_2CH(i\text{-Butyl})COPheNH_2$
$HSCH_2CH(i\text{-Butyl})COLeu\text{-}PheNH_2$
AcetylTrp-IleSH
AcetylPhe-IleSH
Carboxylic acids, such as
$HOOCCH(i\text{-Butyl})Leu\text{-}Leu\text{-}LeuOCH_3$
$HOOCCH(i\text{-Butyl})Leu\text{-}Leu\text{-}AlaNH_2$
$HOOCCH(i\text{-Butyl})Leu\text{-}Leu\text{-}PheNH_2$
$HOOCCH(i\text{-Butyl})Leu\text{-}Leu\text{-}Leu\text{-}AlaNH_2$
Hydroxamic acids, such as
$HONHCOCH_2CH(n\text{-Pentyl})COLeu\text{-}PheNH_2$
$HONHCOCH_2CH(n\text{-Pentyl})COLeu\text{-}AlaNH$
$HONHCOCH_2CH(i\text{-Butyl})COLeu\text{-}PheNH_2$
HONHCOCH CH(n-Pentyl)COVal-AlaNH$_2$

According to a further embodiment of the invention, the composition can comprise an indirect proteoglycanase inhibitor, that is a substance which modifies the

proteoglycan substrate so that the proteoglycanase does not recognise it. An example of an indirect proteoglycanase inhibitor of this type is the class of compounds defined as cationic oligomers.

According to this embodiment of the invention, there is provided a composition which comprises one or more oligomeric molecules containing one or more cationic groups which will bind to negatively charged anionic proteoglycan molecules and protect them from enzymic attack. Preferred cationic oligomers may be chosen from those which are rich in arginine and/or lysine, containing up to 20, preferably 5 to 10 amino acids in sequences similar to or the same as those found in naturally occurring basic proteins such as protamines and histones.

Specific examples of cationic oligomers are:
Arg-Arg-Arg,
Cys-Arg-Arg-Arg-Lys-Arg-Arg,
Pro-Arg-Arg-Arg-Arg, and
Arg-Pro-Val-Arg-Arg-Arg-Arg-Arg-Pro-Val.

The Glycosaminoglycanase Inhibitors

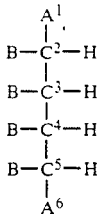
According to a further embodiment of the invention, the composition comprises a glycosaminoglycanase inhibitor chosen from endoglycosidase inhibitors, exoglycosidase inhibitors, sulphatase inhibitors, sulphamatase inhibitors and mixtures thereof.

Examples of these enzyme inhibitors, together with the relevant enzymes whose activity they inhibit, can be classified as follows:

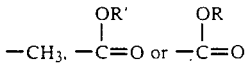
Chemical Class	Enzyme(s) Inhibited
(a) Anions (as soluble metal or ammonium salts)	
sulphate	idurono-sulphate sulphatase; sulphatases A and B; heparin sulphamatase; N-acetylglucosamine-6-sulphate sulphatase
sulphite	sulphatase A; heparin sulphamatase
pyrophosphate	sulphatase A; chondroitin-6-sulphatase; heparin sulphamatase
fluoride	sulphatase A; heparin sulphamatase
borate	- heparin sulphamatase
chloride	sulphatase B; chondroitin-6-sulphatase
gluconate	- sulphatase B

Of the above anion inhibitors of sulphatase A or B, particularly preferred examples are sulphate and gluconate, especially in the form of magnesium sulphate and zinc gluconate respectively.

(b) Aldonolactones and esterified aldonolactones



where
A^1 and A^6 are —H,



B is OR″ or a lactone linkage to position 1 or 6, or —$NHCOCH_3$
and where R is -H or C_2 to C_8 alkyl,
R′ is the remainder of the molecule joined through another C atom at positions 2 to 5 to form a lactone,
R″ is —H or C_2 (ie acetyl) to C_4 acyl of either configuration with respect to the backbone of this molecule.

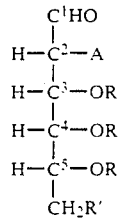
Preferred examples of aldonolactones which inhibit the exoglycosidases, as specified, are as follows:

	Enzyme(s) inhibited
L-Galactono-1,4-lactone	β-galactosidase; β-N-acetylhexosaminidase
L-Arabino-1,5-lactone	β-galactosidase
D-Fucono-1,5-lactone	β-galactosidase
D-Glucaro-1,4-lactone	β-glucuronidase; α-L-iduronidase
D-Glucurono-6,3-lactone	β-glucuronidase
Galactaric acid lactone	β-glucuronidase; α-L-iduronidase
2-Acetamido-2-deoxygluconolactone	β-N-acetylhexosaminidase
2-Acetamido-2-deoxygalactonolactone	β-N-acetylhexosaminidase
D-Glucaro-1,4:6,3-dilactone	β-glucuronidase; α-L-iduronidase
L-Idaro-1,4-lactone	α-L-iduronidase

Preferred examples of esterified forms of aldonolactones which give a more sustained inhibitory effect are:

2,3,5-Tri-O-acetyl-D-glucaro-1,4-lactone	β-glucuronidase; α-L-iduronidase
2,5-Di-O-acetyl-D-glucaro-1,4:6,3-dilactone	β-glucuronidase; α-L-iduronidase

(c) Monosaccharides and esterified monosaccharides having the structure:



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