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(54) **COMBINATION OF MONOSACCHARIDES AND ADENOSINE AND USE THEREOF**

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(57) **ABSTRACT**

The present invention relates to a composition, especially a cosmetic and/or dermatological composition, containing, in a physiologically acceptable medium, a combination of at least one monosaccharide chosen from mannose, rhamnose and a mixture thereof, and of at least one additional compound chosen from adenosine, an analogue thereof and a mixture thereof.

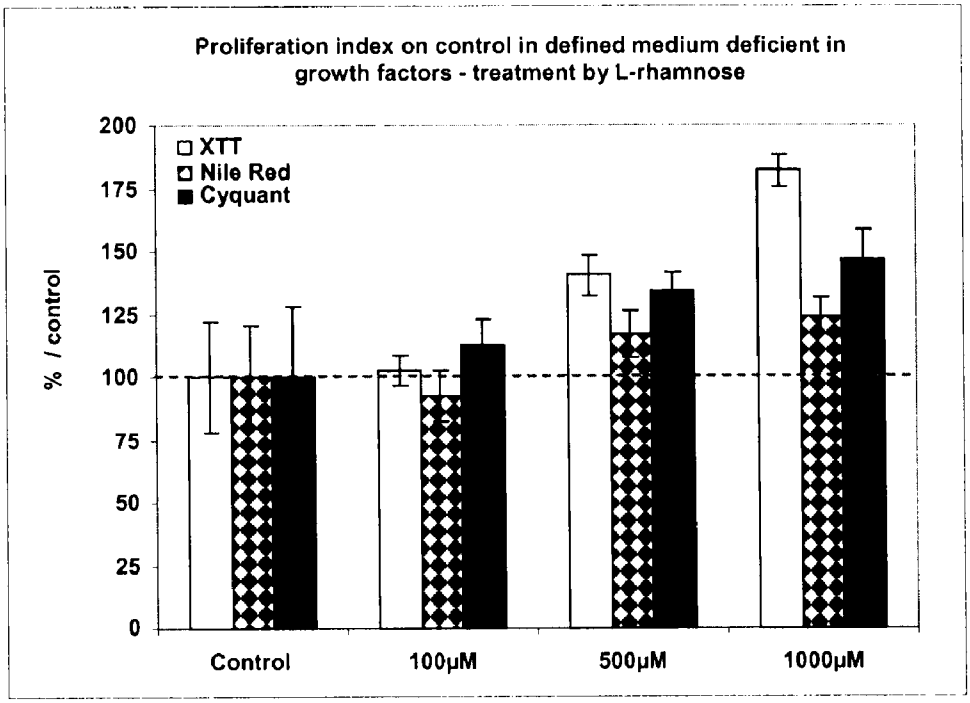


FIGURE 1

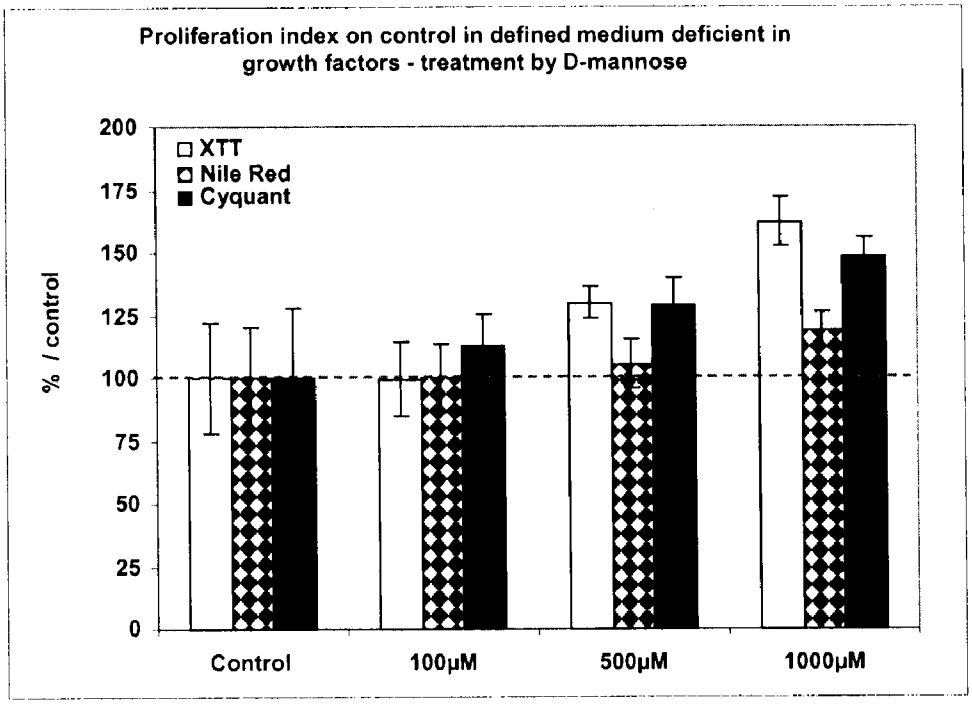


FIGURE 2

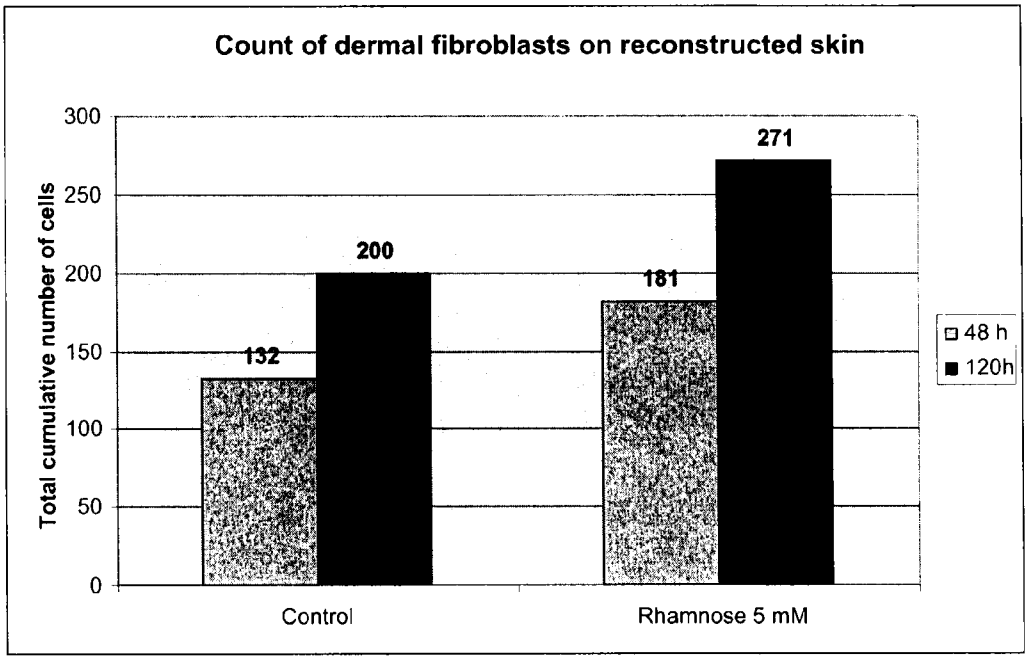


FIGURE 3

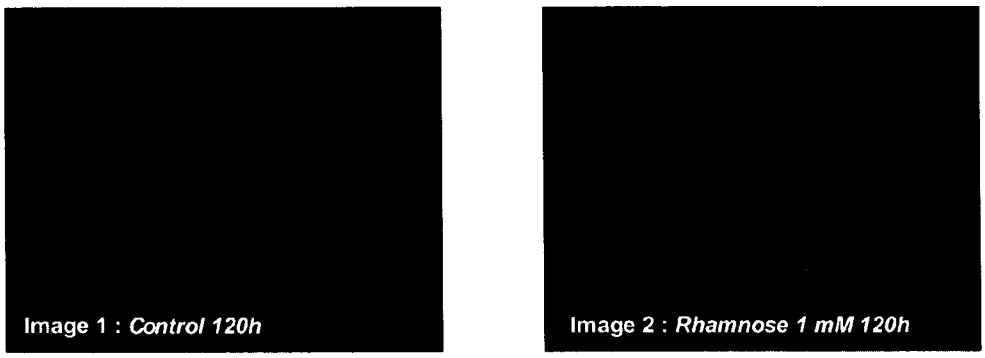


FIGURE 4

COMBINATION OF MONOSACCHARIDES AND ADENOSINE AND USE THEREOF

REFERENCE TO PRIOR APPLICATIONS

[0001] This application claims priority to U.S. provisional application Ser. No. 61/144,756, filed Jan. 15, 2009; and to French patent application 08 59151, filed Dec. 30, 2008, both incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] The present invention relates to a composition, especially a cosmetic and/or dermatological composition, comprising, in a physiologically acceptable medium, a combination of at least one monosaccharide selected from mannose, rhamnose and a mixture thereof, and of at least one additional compound selected from adenosine, an analogue thereof and a mixture thereof.

[0003] Additional advantages and other features of the present invention will be set forth in part in the description that follows and in part will become apparent to those having ordinary skill in the art upon examination of the following or may be learned from the practice of the present invention. The advantages of the present invention may be realized and obtained as particularly pointed out in the appended claims. As will be realized, the present invention is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the present invention. The description is to be regarded as illustrative in nature, and not as restrictive.

BACKGROUND OF THE INVENTION

[0004] Human skin is made up of two main layers, namely the dermis and the epidermis that superficially covers the dermis. Natural human epidermis is composed mainly of three types of cells, namely keratinocytes, which form the vast majority, melanocytes and Langerhans cells. Each of these three types of cells contributes, via its intrinsic functions, to the essential role played in the body by the skin, especially the role of protecting the body against external attacking factors (the climate, ultraviolet rays, tobacco, etc.), which is also known as the "barrier function".

[0005] The epidermis is a keratinized, stratified pavement epithelium 90% made up of keratinocytes. The gradual differentiation of the cells of the basal membrane, which separates the dermis from the epidermis, towards the surface of the epidermis especially includes the differentiation of keratinocytes, which migrate towards the surface of the skin, where they desquamate.

[0006] Ageing of the epidermis is manifested mainly by a reduction in its thickness. Atrophy of the epidermis is the consequence of the slowing down of keratinocyte proliferation and of the accumulation of senescent keratinocytes. The horny layer becomes dull.

[0007] The dermis provides the epidermis with a solid support. It is also its nourishing element. It is made up mainly of fibroblasts and an extracellular matrix composed mainly of collagen, elastin and a substance known as ground substance. These components are synthesized by the fibroblasts. The cohesion between the epidermis and the dermis is provided by the dermo-epidermal junction. This is a complex region about 100 nm thick, which comprises the basal pole of the basal keratinocytes, the epidermal membrane and the sub-basal zone of the superficial dermis.

[0008] Collagens are the major proteins of the extracellular [illegible] dominantly present throughout the epidermis are collagens of the type I and III that form the extracellular matrix of the entire dermis (these collagens constitute 70-80% of the dry weight of the dermis). Moreover, collagens are not all synthesized by the same cell types: collagens of type I and III are essentially produced by the dermal fibroblasts, whereas type VII collagen is produced by two categories of cell, keratinocytes and fibroblasts. Regulation of their expression differs from one collagen to another, for example collagens I and VII are not regulated in the same way by certain cytokines; specifically, TNF-α and leukoregulin stimulate collagen VII and negatively regulate collagen I. Finally, all collagen molecules are variants of a common precursor, which is the α chain of procollagen.

[0009] With age, collagen becomes thinner and wrinkles appear on the surface of the skin. Cutaneous ageing is a genetically programmed mechanism.

[0010] Moreover, certain environmental factors such as smoking and above all exposure to sunlight accelerate it. The skin thus has a much more aged appearance on the areas exposed to sunlight, such as the back of the hands or the face. Thus, these other factors also have a negative impact on the natural collagen of the skin.

[0011] Consequently, given the important role of collagen in the integrity of the skin and in its resistance to external attacking factors of mechanical type, stimulation of the synthesis of these collagens, and in particular of type I collagen, appears to be an effective means for overcoming the signs of ageing of the skin. During chronological and/or actinic ageing, the epidermis also undergoes many changes and degradations that are reflected, with age, by an impairment in the microrelief, impairment in the barrier function of the skin, the appearance of wrinkles and fine lines, an impairment in the mechanical properties of the skin, especially lack of elasticity of the skin, and loss of radiance of the complexion.

[0012] Expression wrinkles are the result of mechanisms different from those that generate the wrinkles caused by ageing. Specifically, they are produced due to the effect of the strain exerted on the skin by the skin muscles that allow facial expressions. Depending on the shape of the face, the frequency of facial expressions and possible tics, they may appear even from childhood. Expression wrinkles are characterized by the presence of grooves around the orifices formed by the nose (nasal grooves), the mouth (perioral wrinkles and "sour-face" wrinkles) and the eyes (crow's-feet wrinkles), around which are the skin muscles, and also between the eyebrows (glabella wrinkles or lion wrinkles) and on the forehead.

[0013] Hitherto, the only means commonly used for acting on expression wrinkles are, firstly, botulinum toxin, which is especially injected into the wrinkles of the glabella which are wrinkles between the eyebrows (see J. D. Carruters et al., *J. Dermatol. Sum. Oncol.,* 1992, 18, pp. 17-21), and, secondly, degradable implants based on collagen, hyaluronic acid or polylactic acid.

[0014] The importance of having available compositions whose effects are directed towards regenerating skin tissue via increasing keratinocyte proliferation and stimulating fibroblast proliferation and/or metabolism, and especially stimulating the synthesis of procollagens and collagens, and also for combating cutaneous contractions that are responsible for the formation of expression wrinkles, may thus be appreciated.

[0015] It is known practice from the literature to use agents such as retinol, which promote keratinocyte proliferation and [illegible]

as a direct biological effect. However, retinol has a certain number of drawbacks when it is used in a cosmetic composition. Specifically, it has low stability towards oxidation and gives rise to adverse side effects on consumers, especially such as skin irritation. There is thus a need to find other compounds with a direct biological effect, which are readily available and whose efficacy is acceptable for optimal use in cosmetics.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] FIG. **1** shows the results obtained for the keratinocyte proliferation under certain conditions, described in detail below.

[0017] FIG. **2** shows the results obtained for the keratinocyte proliferation under certain conditions, described in detail below.

[0018] FIG. **3** shows the number of fibroblasts measured between an untreated control whole reconstructed skin, on the left, and a whole reconstructed skin treated with 5 mM of rhamnose, on the right.

[0019] FIG. **4** shows images of frozen sections of reconstructed skin 7 μm thick.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0020] The inventors have discovered, surprisingly and unexpectedly, that a combination of at least one monosaccharide selected from mannose, rhamnose and a mixture thereof, and of at least one additional compound selected from adenosine, an adenosine analogue and mixtures thereof, leads to a complementarity of action both on the microrelief of the skin, making it possible especially to combat the formation of expression wrinkles, and also on the stimulation of dermal and/or epidermal regeneration by stimulating the metabolism and the process of epidermal renewal, leading to a reduction in the appearance of the signs of chronological ageing and photoageing. Thus, the combination according to the invention causes relaxation, decontraction and a reduction in the differentiation of the dermal contractile cells involved in the generation of expression wrinkles, especially of the fibroblasts located along the tension lines created under the effect of contraction of the skin muscles. The combination according to the invention also makes it possible to synergistically stimulate the production of type I procollagen by the dermal fibroblasts.

[0021] As used herein the term "synergistic" and its derivatives means a greater than additive effect.

[0022] The present invention demonstrates the activation of keratinocyte and fibroblast proliferation and the stimulation of procollagen I synthesis by mannose or rhamnose. The use of compositions containing them thus makes it possible to counter the signs of ageing of the skin, and in particular age-related epidermal and/or dermal atrophy.

[0023] The use of these monosaccharides for the direct biological effects outlined above was hitherto unknown. Patent application WO 2007/128 939 mentions, however, anti-ageing activity obtained via a biomechanical effect of a tensioning agent in combination with saccharide compounds, which make it possible to increase the expression of the skin cell mechanoreceptors. This increase in the expression of mechanoreceptors is described as increasing the sensitization of skin cells to respond to the effects of tensioning agents. Similarly, patent application FR 2 900 572 describes the combined use of a cosmetic composition comprising saccha- thereof. As described previously, this is the combination of a biological action and a mechanical action, the latter being intended to tighten and constrain the skin.

[0024] Patent application WO 2005/063194 describes a galenical base with very high tolerance especially comprising mannose or rhamnose. It is specified that such a galenical base can function only in combination with an active agent of which it is only the vehicle. The dermal and/or cosmetic galenical bases disclosed are based essentially on the presence of the two polyols, namely mannitol and xylitol.

[0025] Moreover, the influence of adenosine and adenosine analogues on improving the appearance of the skin is described in patent applications EP 1 424 064 and EP 1 428 522. In particular, it is specified therein that adenosine makes it possible to relax or decontract the dermal contractile cells that are assumed to be involved in the generation of expression wrinkles.

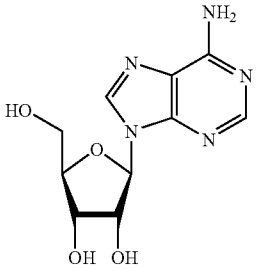
[0026] The present invention thus relates in one embodiment to a composition, especially a cosmetic and/or dermatological composition, comprising, in a physiologically acceptable medium, a combination of at least one monosaccharide chosen from mannose and rhamnose and of at least one additional compound chosen from adenosine and adenosine analogues.

[0027] The monosaccharides according to the invention are in the D or L form of mannose and/or rhamnose, each form itself possibly being the alpha and/or beta anomer. The forms that are preferred according to the invention are D-mannose and L-rhamnose.

[0028] D-Mannose is present in plants, in particular certain fruit, including cranberries, or in hardwood (beech and birch). Rhamnose is found in nature in L form. D-Mannose and L-rhamnose are commercially available, for example from the companies Danisco Sweeteners® and Symrise.

[0029] In the present invention, the monosaccharide is preferably present as a monomer.

[0030] For the purposes of the present invention, adenosine is the nucleoside derived from the condensation of adenine with ribose (in ribofuranose form) via β-N_9glucoside bond. Adenosine plays an important role in biochemical processes, such as energy transfer when it is, for example, in the form of adenosine triphosphate (ATP) and/or adenosine diphosphate (ADP); and also in signal transduction when it is, for example, in the form of cyclic adenosine monophosphate or cAMP. Adenosine has the following structural formula:



[0031] Among the adenosine analogues that may be used according to the invention, mention will be made especially of adenosine receptor agonists and compounds that increase the intracellular or extracellular levels of adenosine.

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