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LIPOCHROMAN-6 AS NO-SYNTASE INHIBITOR AND USES

The present invention relates to the use of an effective amount of lipochroman-6, in a physiologically acceptable medium, in a composition or for preparing a composition, the lipochroman-6 or the composition being intended to inhibit NO-synthase.

The term "NO-synthase" covers a family of enzymes which carry out the enzymatic catalysis of L-arginine to citrulline, during which catalysis a gaseous medium with multiple functions, nitric oxide, or NO, is produced.

NO-synthases exist in three forms, two constitutive forms, nomenclature including neuronal NO-synthase (or NOS 1) and endothelial NO-synthase (or NOS 3), and the inducible form (or NOS 2) (Medicine/Sciences, 1992, 8, pp. 843-845). It is understood elsewhere in the text that, unless otherwise indicated, the term "NO-synthase" covers all the isoforms of the enzyme.

Thus, according to the invention, the term, "NO-synthase inhibitors" is intended to mean any product which, ultimately, notwithstanding the NO-synthase isoform, leads to a decrease in the concentration of NO. Mention may be made, by way of example, of products which reduce the amount of active NO-synthase, which block the enzymatic activity of NO-synthase or its induction, or which inhibit the activity of the NO produced.

By virtue of its structure, nitric oxide has an additional electron which makes it extremely chemically reactive. It is of note that such compounds are harmful, and the intention is to limit the production thereof as much as possible. Thus, in the case of nitric oxide, NO-synthase inhibitors have been widely studied.

NO is a multifunctional signal molecule which is active in a large variety of systems and of tissues of the body. Besides its damaging effects for cells, which are linked to its hyperreactivity due to its structure comprising an additional electron, it is acknowledged, inter alia, as being particularly involved in the cardiovascular system (regulator of blood pressure with vasodilator effect, inhibitor of platelet aggregation with anticlotting effect), in the nervous system (memory, modulation of neurotransmitter release), and in the immune system (modulation of immune defenses, inflammation, involvement in autoimmune pathological conditions).

It is now well accepted that NO plays a predominant role in the skin. NO can be synthesized by all the varieties of cells which make up the skin and, therefore, it is involved in multiple and complex processes of regulation, such as regulation of cellular differentiation and/or proliferation, of vasodilation, of melanogenesis, or of the response to environmental variations (homeostasis).

Its involvement in cellular differentiation and proliferation (stimulatory effect), particularly of keratinocytes, associates it both with growth of the epidermis and cicatrization and with hyperproliferative disorders (psoriasis).

Due to its electron hyperreactivity possibly leading to degradation, or even destruction, of cells, NO is involved in apoptotic processes and in intrinsic and/or extrinsic aging of the skin. It is involved in immunological and inflammatory processes of the skin. It is in fact commonly accepted that NO plays a role in contact hypersensitivity reactions, in allergic manifestations of the skin, and in the immune response of the skin. Similarly, besides its direct pro-inflammatory role, it is the mediator between neuropeptides such as substance P and/or the calcitonin gene-related peptide

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(CGRP) in neurogenic inflammatory processes of the skin, hence its involvement in the phenomena of "sensitive" skin.

The involvement of NO in vasodilation means that it is associated with erythemas of the skin, particularly erythemas induced by ultraviolet radiation, localized or diffuse erythematous eruptions of the skin, such as those caused by drugs, toxins and/or viral or bacterial infections, and with acne rosacea.

NO is acknowledged to be an intermediate in the melanogenesis induced by ultraviolet radiation type B (UVB). It is also thought to be one of the factors involved in disorders of the hypermelanosis type.

NO also appears to be involved in the control of sweating and also in that of lipolysis (inhibitory effect), or in hair loss.

Finally, NO is known to have an influence on the barrier function of the skin and therefore on the moisturization thereof (inhibitory effect).

The advantage which exists in having NO-synthase inhibitors can therefore be understood.

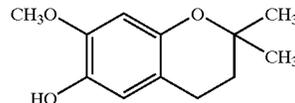
In this regard, many inhibitors have already been proposed in the prior art. Mention may be made more particularly of N^G-monomethyl-L-arginine (NMMA), N^G-nitro-L-arginine methyl ester (NAME), N^G-nitro-L-arginine (NNA), N^G-amino-L-arginine (NAA), N^G,N^G-dimethylarginine (asymmetric dimethylarginine, called ADMA), diphenylethylidimidazole-1-oxy 3-oxide, 7-nitroindazole, N(5)-(1-iminoethyl)-L-ornithine, aminoguanidine, canavanine and ebselen.

Without casting doubt on the effectiveness of these products, it is noted that they are chemical compounds which may induce problems, or even harmful side effects, in users, who generally prefer using natural products.

The aim of the present invention is to provide a novel NO-synthase inhibitor which is also a natural NO-synthase inhibitor.

Surprisingly and unexpectedly, the applicant has demonstrated that lipochroman-6 has the property of being an NO-synthase inhibitor, particularly an inhibitor of inducible NO synthase (NOS 2), which makes it a good candidate for uses in applications in which it proves to be advantageous to use an NO-synthase inhibitor, particularly in cosmetics.

Lipochroman-6 is a compound corresponding to the general formula:



This compound is described in the prior art as an antioxidant, as a free-radical scavenger, as an inhibitor of lipid peroxidation and as an agent protecting cells against peroxynitrite-induced damage. However, it is not described as an NO-synthase inhibitor.

The first subject of the invention is therefore the use of an effective amount of lipochroman-6, in a physiologically acceptable medium, in a composition or for preparing a composition, the lipochroman-6 or the composition being intended to inhibit NO-synthase.

The expression "physiologically acceptable medium" is understood to mean a medium compatible with the skin, the mucous membranes, the nails and the hair.

The second subject of the invention is the use of an effective amount of lipochroman-6, in a physiologically