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(54) Title: PRODUCT AGAINST DEFICIENCY

(57) Abstract

The invention relates to a substance intended to be administered in a deficiency condition resulting in collagen insufficiency in the mesodermal, ectodermal and endodermal tissue, or for the purpose of preventing the aforementioned deficiency condition, and intended to undergo further development as a drug to be used for appropriate indications. The amino acid Lysine, preferably L-Lysine, is present in the aforementioned substance, and the substance also contains Glycine, preferably L-Glycine, and Proline, preferably L-Proline, as a mixture.
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Product against deficiency

The present application relates to a patent for Lysine, preferably L-Lysine, as a substance to be administered in a deficiency condition resulting in collagen insufficiency in the mesodermal, ectodermal and endodermal tissue, and intended to undergo further development as a drug to be used for appropriate indications.

The substance also contains Glycine, preferably L-Glycine, and Proline, preferably L-Proline, and is intended to provide the essential basic building block in collagen, i.e. the amino acid Lysine, preferably L-Lysine, in a mixture with other building blocks Glycine, preferably L-Glycine, and Proline, preferably L-Proline, in order to substitute/repair deficiency conditions which predispose towards or establish generation in the collagen through the deficient reconstruction of, for example, mesodermal tissue systems consisting of or containing collagen. These tissue systems are encountered mainly in, for example, the cartilage, skeleton, tendons and muscle fasciae. Collagen is present in all supportive tissue, for example connective tissue in the skin and other ectodermal tissue. Apart from collagen fibres, connective tissue also contains thinner reticular fibrils and thinner elastic fibres, all with the same chemical building blocks Lysine, preferably L-Lysine, Proline, preferably L-Proline, and Glycine, preferably L-Glycine. Connective tissue/collagen is present not only in the mesoderm, endoderm and ectoderm, but also in the further development of the basic tissues into, for example neural grove, and its further differentiation into self-developing facial and cranial structures, the brain, the nervous system and the sensory organs of the skin, as well as maxillary-dental structures (periodontal and gingival structures). Collagen also occurs in mucous membranes and other endodermal tissues, for example the liver, lungs, airways and vessels, etc. A lack of
collagen in the skeleton is probably a not insignificant component of osteoporosis (brittle bones).

An adequate supplement of the other 18 essential and non-essential amino acids should also be provided in L-form in order to establish a positive N-balance and to optimize matrix formation and sulphonation. Other nutrition in respect of vitamins (note vitamin C for hydroxylation) fats and carbohydrates and salts and minerals, especially calcium, shall be optimized.

Previously disclosed in WO 89/12441 is a “cosmetic and skin treatment compound, intended through external treatment a) to improve and maintain the health of the skin, and b) to increase the subcutaneous fat in warm-blooded animals”.

Certain of the peptides that are recommended contain both lysine, proline, glycine and other amino acids, although these are bonded as peptides and in compounds, including with fatty acids intended to increase their fat solubility and in so doing to make them more appealing in pharmaceutical or cosmetic creams and gels for application via the skin.

According to the present invention, the method of administration of free L-acids is via the mouth or via the blood, which has an effect on the skin by building up the fibrils and fibres of the connective tissue from within, from the basic substrate administered via the mouth or the blood.

The invention previously disclosed in DE-A1-4243362 A and DE-A-1-4243633 is intended in the first instance to make available a preparation that is capable of successfully treating ‘Hauttrockenheit’ = dryness of the skin.

The preparation contains Quencetin esters of the amino acids Lysine, Proline and ascorbic acid and Quencetin esters of Valine, Isoleucine and Leucine in varying proportions up to a maximum of 100 per cent by weight. No glycine is present, however.
The preparation can be administered via the mouth, parenterally or locally. Oral application is preferred.

The description makes reference to the fact that the previously disclosed substance has also been found to be suitable for strengthening and stabilizing collagen in humans and animals. The aforementioned uses include as treatment for sprained muscles, muscle rupture and intervertebral disc pain and intervertebral disc protrusion.

In the course of our research we have thus observed the effect on collagen, but we have applied our observations to muscle injuries and intervertebral disc pain and intervertebral disc protrusion. We have taken no account of the essential collagen tissue with its so dominant function outside the muscle cells and the discs, and we have made no mention of the fundamental significance of the thread functions of collagen for stabilizing, supporting and attaching the body’s tissues, not least the musculo-skeletal tissues from the mesoderm, for example sinews which transfer muscular power or ligaments which stabilize limbs, for example between the vertebrae where the disk is enclosed. We do not describe or do not require the common building blocks lysine, proline and glycine, which in the present invention are administered as free amino acids and serve as a specific substrate for the formation of collagen fibre in endodermal, mesodermal and ectodermal tissues. The chemistry in the previously disclosed method is different because of the absence of glycine, an important building block in collagen.

The muscle tissue lies entirely outside, and the disk lies largely outside the scope of the present invention.

On the other hand, the present invention includes sinews and ligaments, for example, including in the back surrounding the discs.
Case 1.

A male aged 63 years was given approx. 50-150 mg of 1-Lysine daily for a period of 6 months, plus ample substitution of all essential amino acids. The basic illness was pronounced chondroma in one knee, which had been diagnosed by arthroscopy in the spring of 1994. There was a significant improvement after 3 months. After 6 months, the patient's walking distance increased from 20-100 m to 6-8 km. Stability was restored in the knee and in the quadriceps sinew.

Case 2.

A male aged 32 years. Previously in good health. He suffered a clavicle fracture following moderate trauma at the age of 30 years.

He engages in a lot of sport, including jogging and indoor bandy (a form of ice hockey played with a ball) in a number of leagues.

In the autumn of 1993 he noticed pains in his knees, ankles, sinews and muscles after training, which showed a tendency to increase and caused him to cease training.

There was a significant improvement after treatment with 1-Lysine for approx. 3 months at a dose of approx. 50-100 mg, which had been noticed subjectively after only one month or thereabouts; after 3-4 months' treatment, the condition was felt to be better than during the months preceding the start of treatment.

Case 3.

A male aged 64 years. He was suffering from wrinkled, dry skin, especially on the face and neck. He had been receiving treatment with a moisturizing cream for 3 years, with insignificant results.
A significant improvement in the wrinkling was noted after 8 months' treatment with approx. 50-150 mg of l-Lysine. The man has been told that he looks 10 or even 20 years younger.

The appropriate dose of Lysine, preferably l-Lysine, is 50-5000 mg/day;
Glycine, preferably l-Glycine, 50-5000 mg/day;
Proline, preferably l-Proline, 50-5000 mg/day.

The appropriate dose for children, persons with low body weight and pregnant women is approx. 5-300 mg/day respectively for Lysine, preferably l-Lysine, Glycine, preferably l-Glycine, and Proline, preferably l-Proline.

In the case of pronounced malnutrition (under-nutrition) and malabsorption (poor absorption of nutrients in the intestine), the appropriate dose is 300 - 3 000 mg/day, or even as much as 20 000 - 30 000 mg/day. Form: tablets, powder, food additive or food modification (powder), liquid form.

Preferably administered via the mouth.

In the event of serious disorders of the absorption capability of the intestine, the substance may be administered parenterally, e.g. via the blood, or it may be injected locally particularly where certain indications are present.

The reason why Lysine, preferably l-Lysine, has become the critical deficiency factor can be explained by changed habits over centuries rather than decades, and by the physico-chemical properties and the occurrence of Lysine, preferably l-Lysine. Proline, preferably l-Proline, can become a critical factor in certain situations.
As far as the degree of inventiveness is concerned, the patent represents a novel concept in the sense that fibrosis is regarded as a shrinking process involving organs/connective tissue/collagen.

The present invention and the facts that have emerged in case studies support the view that tissue shrinkage - fibrosis - also appears to be subject to a reversible deficiency in the building substrate of the collagen, Lysine, preferably L-Lysine, Proline, preferably L-Proline, and Glycine, preferably L-Glycine. A deficiency in Lysine, preferably L-Lysine, Proline, preferably L-Proline, and Glycine, preferably L-Glycine, can also restrict capsule formation, for example around foreign bodies, tumours or other tissue formations.

The invention is based on the principle that Lysine, preferably L-Lysine, Proline, preferably L-Proline, and Glycine, preferably L-Glycine, also act as building blocks not only in collagen as a product of the fibroblasts in the collagen fibre, but also in the thinner fibres such as reticular fibre and elastic fibre. The fibroblast can be differentiated as, for example, osteoblast, chondroblast, odontoblast (i.e. the one responsible for the formation of differentiated dental substance) and the fibroblast present in the peridontium and the gingiva.
Patent Claims

1. Substance to be administered in a deficiency condition resulting in collagen insufficiency in the mesodermal, ectodermal and endodermal tissue, or for the purpose of preventing the aforementioned deficiency condition, characterized in that the amino acid Lysine, preferably l-Lysine, is present in the aforementioned substance together with Glycine, preferably l-Glycine, and Proline, preferably l-Proline, as mixture, in that the substance is arranged in a form for taking orally or in a form to be administered parenterally in order to provide the essential building block in collagen, i.e. the amino acid Lysine, preferably l-Lysine, in a mixture with the other building blocks Glycine, preferably l-Glycine, and Proline, preferably l-Proline, in order to substitute/repair deficiency conditions which predispose towards or establish degeneration and the deficient reconstruction of mesodermal, ectodermal and endodermal tissue systems consisting of or containing collagen.

2. Substance as claimed in Patent Claim 2, characterized in that the drug includes an adequate supplement of other essential and non-essential amino acids in L-form.

3. Substance as claimed in one or other of Patent Claims 1-2, characterized in that it is in the form of tablets or in powder or liquid form.

4. Substance as claimed in one or other of the above Patent Claims 1-3, characterized in that the dose of Lysine, preferably l-Lysine, is 50-300 mg/day and that of Proline, preferably l-Proline, is 50-300 mg/day.

5. Substance as claimed in one or other of Patent Claims 1-3, characterized in that the dose of Lysine,
preferably L-Lysine, Glycine, preferably L-Glycine, and
Proline, preferably L-Proline, respectively is 5-300 mg/day
for children and for persons with low body weight.

6. Substance as claimed in one or other of Patent
Claims 1-3, characterized in that the dose of Lysine,
preferably L-Lysine, Glycine, preferably L-Glycine, and
Proline, preferably L-Proline, respectively is 300-3 000
mg/day in the event of severe malnutrition and malabsorption.

7. Substance as claimed in one or other of Patent
Claims 1-3, characterized in that the dose of Lysine,
preferably L-Lysine, Glycine, preferably L-Glycine, and
Proline, preferably L-Proline, respectively is up to 20 000 -
30 000 mg/day.
AMENDED CLAIMS

[received by the International Bureau on 29 July 1996 (29.07.96); original claims 1-7 replaced by amended claims 1-7 (2 pages)]

5 1. Substance to be administered in a deficiency condition resulting in collagen insufficiency in the mesodermal, ectodermal and endodermal tissue, or for the purpose of preventing the aforementioned deficiency condition, characterized in that the amino acid l-Lysine, is present in the aforementioned substance together with Glycine, and l-Proline, as mixture, in that the substance is arranged in a form for taking orally or in a form to be administered parenterally in order to provide the essential building block in collagen, i.e. the amino acid l-Lysine, in a mixture with the other building blocks Glycine, and l-Proline, in order to substitute/repair deficiency conditions which predispose towards or establish degeneration and the deficient reconstruction of mesodermal, ectodermal and endodermal tissue systems consisting of or containing collagen.

2. Substance as claimed in Patent Claim 2, characterized in that the drug includes an adequate supplement of other essential and non-essential amino acids in L-form.

3. Substance as claimed in one or other of Patent Claims 1-2, characterized in that it is in the form of tablets or in powder or liquid form.

4. Substance as claimed in one or other of the above Patent Claims 1-3, characterized in that the dose of l-Lysine, is 50-300 mg/day and that of l-Proline, is 50-300 mg/day.
5. Substance as claimed in one or other of Patent Claims 1-3, \textit{characterized in that} the dose of l-Lysine, Glycine, and l-Proline, respectively is 5-300 mg/day for children and for persons with low body weight.

6. Substance as claimed in one or other of Patent Claims 1-3, \textit{characterized in that} the dose of l-Lysine, Glycine, and l-Proline, respectively is 300-3 000 mg/day in the event of severe malnutrition and malabsorption.

7. Substance as claimed in one or other of Patent Claims 1-3, \textit{characterized in that} the dose of l-Lysine, Glycine, and l-Proline, respectively is up to 20 000 - 30 000 mg/day.
# INTERNATIONAL SEARCH REPORT

**International application No.**

PCT/SE 96/00305

## A. CLASSIFICATION OF SUBJECT MATTER

**IPC6: A61K 31/195, A61K 31/40**

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

**Minimum documentation searched (classification system followed by classification symbols)**

**IPC6: A61K**

**Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched**

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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**Date of the actual completion of the international search:** 23 May 1996

**Date of mailing of the international search report:** 29-05-1996

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