Neova® Intense Brightening Complex™ Targets Hyperpigmentation with a Combination of Four Active Ingredients.

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Abstract
Various dermatological disorders, such as melasma, age spots, and sites of actinic damage, arise from the accumulation of an excessive level of epidermal pigmentation. Neova Intense Brightening Complex targets this hyperpigmentation with a combination of four active ingredients (Undecylenoyl Phenylalanine, Manganese Tripeptide-1, Glycyrrhiza Glabra (Licorice) Root Extract, and Tetrahexyldecyl Ascorbate) all known for their skin lightening activity.

Introduction

Skin pigments or melanins are produced in specialized cells in the skin termed melanocytes. Two forms of melanin are produced by the melanocytes, pheomelanin, which is red to yellow in color, and eumelanin which is dark brown to black. The relative proportions of these melanins influence general skin color and hyperpigmentation effects. In addition, individuals differ in the number and size of melanin particles. Melanin biosynthesis (melanogenesis) is influenced by genetics, environmental factors, diet and medication.

The rate-limiting step in melanogenesis is the multistep conversion of L-tyrosine to melanin through the action of tyrosinase. Melanogenesis is under hormonal control also through the action of Alpha Melanocyte Stimulationg Hormone (α-MSH). The α-MSH interacts with the melanocyte through a series of biochemical events to initiate the melanin production process. Melanin is synthesized in a series of steps from tyrosine through the action of the enzyme tyrosinase. Subsequent steps include the polymerization of the melanin and assembly into melanosomes and transport from the melanocyte to the keratinocytes.

The variation in skin pigmentation is related to the levels of melanin produced and the number of melanocytes present. Localized increased melanin production (hyperpigmentation or uneven pigmentation) is often referred to as melasma, chloasma or solar lentigenes.

Melasma is a general term describing darkening of the skin.

Chloasma is generally used to describe skin discolorations caused by hormones. These hormonal changes are usually the result of pregnancy, birth control pills or estrogen replacement therapy.

Solar lentigenes is the technical term for darkened spots on the skin caused by the sun. Solar refers to sunlight and lentigene describes a darkened area of skin. These spots are quite common in adults with a long history of unprotected sun exposure and are a marker of photoaging. Aside from sun exposure and hormones, hyperpigmentation can be caused by skin damage, such as remnants of blemishes, wounds or rashes.

Concern about and treatment of uneven and hyperpigmentation dates to ancient times when plant extracts and minerals were used to facilitate skin lightening. Early skin bleaching products were based on phenolic compounds such as hydroquinone and derivatives. Hydroquinone remains one of the most effective skin lightening pharmaceutical agents.

Numerous non-pharmaceutical skin lightening agents derived from plants are currently in use including arbutin, kojic acid, and azelaic acid. These, in addition to ascorbic acid and derivatives, are common cosmetic actives used in skin lightening and brightening formulation.

Intense Brightening Complex has been formulated to contain a cocktail of complimentary cosmetic actives to treat the appearance of hyperpigmentation associated with the common causes.

Undecylenoyl Phenylalanine

Undecylenoyl phenylalanine (U.Phenylalanine) works as an α-MSH (alphs melanin stimulating hormone or melanotropin) antagonist, bind-

ing to the α-MSH cellular receptor and preventing the melanin synthesis from starting. Melanotropin controls all stages of melanin production, tyrosinase activity, subsequent melanin (eumalanin) synthesis and melanosome transfer to keratinocytes. Experimental in vitro model testing shows that U.Phenylalanine[2,3] works differently than other common topical ingredients for hyperpigmentation reduction. The U.Phenylalanine works to prevent the action of the melanotropin and thus all subsequent steps in the formation of the melanin pigments.

This proposed mechanism is unique compared to that described for other lightening agents, such as hydroquinone, arbutin, kojic acid or Magnesium Ascorbyl Phosphate, which do not involve the receptor of α-MSH. In vitro tests have shown the enhanced effectiveness of the active ingredient compared to these active reference lightening agents.

The activity of U.Phenylalanine has been shown on B16 melanocytes to encompass the following.

1. It has a spontaneous lightening action through an inhibition of basal melanogenesis.
2. The results in Figure 1 show that U.Phenylalanine inhibits the melanogenesis stimulated by α-MSH (antagonist effect towards melanotropin) binding to the α-MSH receptor on melanocytes and the subsequent increase in cAMP (cyclic AMP) the secondary messenger to trigger the initiation of melanogenesis. In this aspect, the U.Phenylalanine is more effective than Arbutin, Kojic Acid, Magnesium Ascorbyl Phosphate, and hydroquinone.

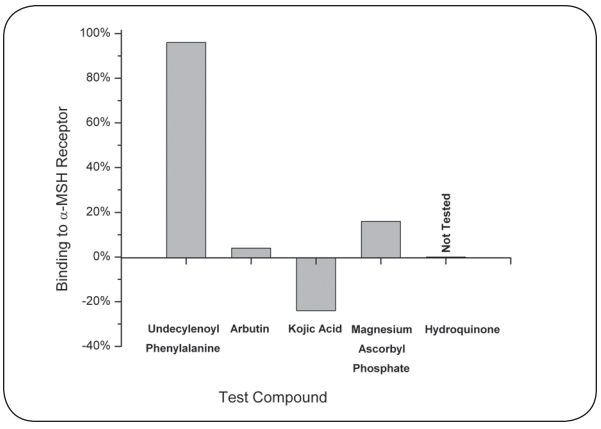

Figure 1. Binding of U.Phenylalanine to the α-MSH receptor.

3. The results in Figure 2 show that U.Phenylalanine is an inhibitor of tyrosinase comparable to Arbutin, Kojic Acid, Magnesium Ascorbyl Phosphate, and hydroquinone. Phenylanine is a precursor to tyrosine and may act as a false substrate for the tyrosinase enzyme.

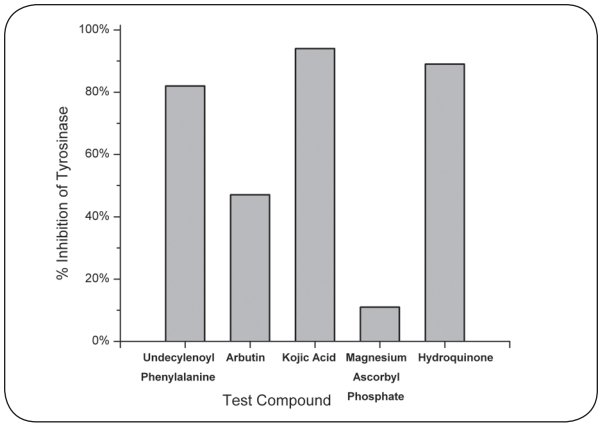

Figure 2. Inhibition of Tyrosinase by U.Phenylalanine.

4. The lightening action of U.Phenylalanine has been confirmed in three types of cell culture studies, basil melanogenesis in melanocytes, melanocytes stimulated by α-MSH, and melanocytes stimulated by UVB.
5. The lightening action of U.Phenylalanine has also been confirmed in a model of reconstituted epidermis.

Performance Evaluation — U.Phenylalanine

The clinical evaluation of U.Phenylalanine was performed on 30 Asian volunteers. The U.Phenylalanine was applied to the face twice a day for 3 months and the lightening effectiveness was assessed before treatment (after 2 and 3 months of treatment.

1. *Decrease of melanin pigments at the skin surface.* By the second month of treatment, there were fewer melanin pigments located in the corneocytes (surface cells of the stratum corneum). The skin was visibly clearer.
2. *Even skin tone effect.* By the second month of treatment, there were significant increases even skin tone.
3. *Lightening effect.* By the second month of treatment, the skin was significantly lightened (decrease of the melanin index). The pigmented areas faded away, the tone became more uniform.
4. *Lightening effect on pigmented areas.* By the second month of treatment, the hyper-pigmented areas were visibly and significantly lightened.
5. *Overall dermatologist assessment*. The test subjects showed that after three months of

treatment, 93% of the volunteers appreciated U.Phenylalanine for its effectiveness and comfort. Moreover, tolerance was excellent on all the persons tested. It shows excellent lightening effectiveness.

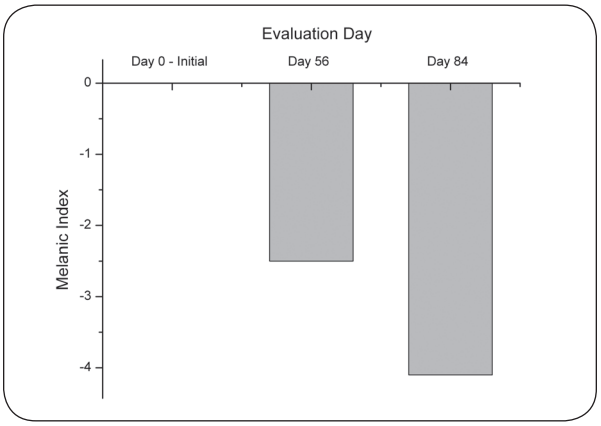

Figure 3. Decrease of melanin pigments at the skin surface.

Manganese Tripeptide-1 Complex

Procyte has been investigating the properties of manganese peptide complexes since the early 1990s. At that time, Procyte discovered and patented several manganese peptide complexes with enhanced superoxide dismutase properties. In a more recent set of experiments, the effect of manganese peptide complexes on pigmentation was studied by determining the amount of melanin produced by melanocytes in culture. Various amounts of Manganese Tripeptide-1 (the complex of glycyl-L-histidyl-l-lysine with Manganese) were added to the culture medium.

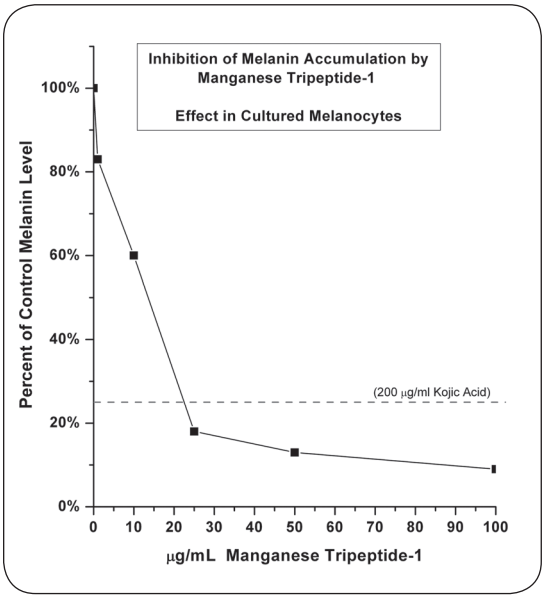

Figure 4. Inhibition of Melanin accumulation by Manganese Tripeptide-1.

After 5 days, the culture media was collected and analyzed for pigment content. The results in Figure 4 demonstrate that the addition of increasing doses of Manganese Tripeptide-1 inhibited the formation of melanin pigments in cultured melanocytes.

The inhibition observed at 25 to 100 µg/ml of the Manganese Tripeptide-1 was greater than that caused by 200 µg/ml of kojic acid, a known inhibitor of tyrosinase and melanin accumulation.

The experimental studies indicate that GHK-Manganese Complex is a not-toxic inhibitor of melanin accumulation through a mechanism that does not involve tyrosinase inhibition.

Performance Evaluation — Manganese Tripeptide-1

The experimental results with Manganese Tripeptide-1 have been confirmed in a dermatologist conducted clinical performance evaluation[1]. In this study, 14 patients were treated topically twice a day for 12 weeks with a serum formulation containing Manganese Tripeptide-1. At the end of the treatment, the subjects were evaluated for improvement in the appearance of hyperpigmentation and photoaging.

At the end of the treatment period, participants and investigators both noted significant improvements in the appearance of surface roughness, sallowness, mottled hyperpigmentation, and actinic lentigenes, Figure 5. Predominant among the parameters showing improvement were those associated with hyperpigmentation, in agreement with the research studies.

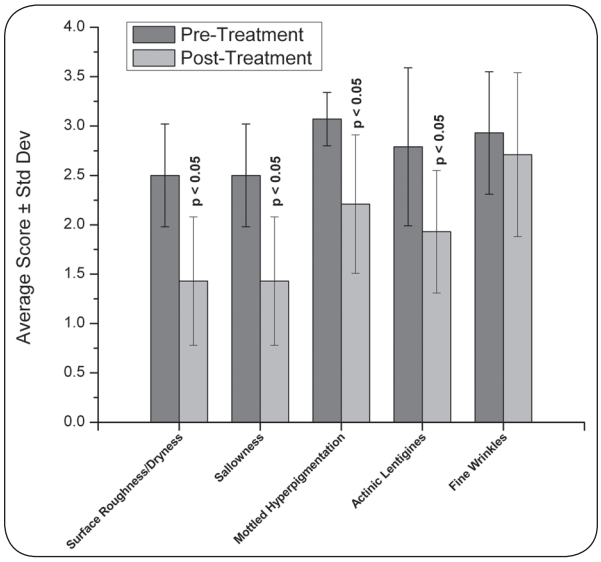

Figure 5. Effect of Manganese Tripeptide-1 on the clinical signs of photoaging and hyperpigmentation.

In general, at the end of 12 weeks of treatment, the rankings of photodamage moved from the moderate to the mild category.

The treatment was well tolerated with no cutaneous irritation associated with the manganese peptide complex. The lack of irritation is also confirmed by the results of a Repeat Insult Patch Test independently conducted that demonstrated the lack of irritation and sensitization of the serum.

Glycyrrhiza Glabra (Licorice) Root Extract

Licorice root extract (glycyrrhetinic acid) is widely used to inhibit tyrosinase activity. It also has anti-inflammatory properties. This inhibition is due to the presence of glabridin and other compounds with tyrosinase inhibitory activity in the extracts[4]. The glabridin inhibits tyrosinase activity of these cells at concentrations of 0.1 to 1.0 microg/ml and had no detectable effect on their DNA synthesis[5].

Tetrahexyldecyl Ascorbate

Tetrahexyldecyl Ascorbate is made by taking the natural Vitamin C molecule and attaching 4 extra molecules to the corners of the Vitamin C molecule. This new molecule, called Tetrahexyldecyl Ascorbate has a number of important advantages. It is lipid soluble which means that it easily penetrates into the skin. It does not require a low pH to get it to penetrate the skin so it does not sting. It possesses the lightening effects of ascorbic acid[6] with improved skin penetration and less irritation.

Summation of Activity

Intense Brightening Complex targets hyperpigmentation with a combination of four active ingredients U.Phenylalanine, Manganese Tripeptide-1, Glycyrrhiza Glabra (Licorice) Root Extract, and Tetrahexyldecyl Ascorbate, all known for their skin lightening activity.

U.Phenylalanine is an α-MSH antagonist and an inhibitor of the tyrosinase due to substrate substitution.

Manganese Tripeptide-1 inhibits melanogenesis by a presently unknown mechanism which does not involve tyrosinase.

Glycyrrhiza Glabra (Licorice) Root Extract, and Tetrahexyldecyl Ascorbate are inhibitors of the tyrosinase.

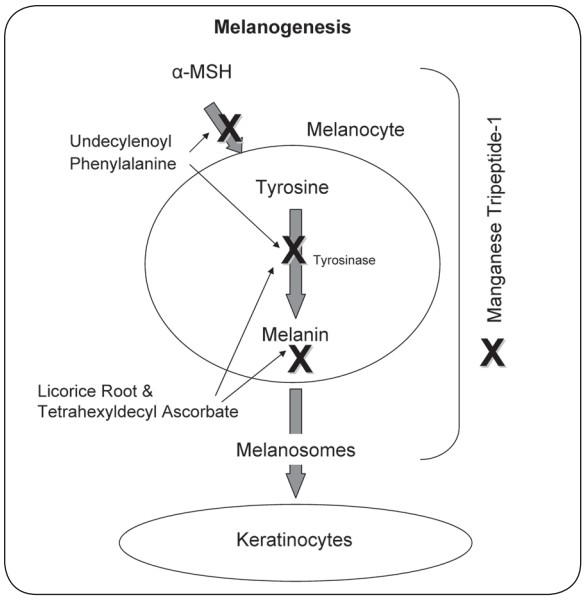

Figure 6. Sites of inhibition of hyperpigmentation and melanin accumulation by Intense Brightening Complex ingredients.

Additional Ingredients

The functionality of Intense Brightening Complex is enhanced by the presence of a mixture of Santalum Album (Sandalwood) Extract, Phellodendron Amurense Bark Extract, Hordeum Distichon (Barley) Extract. This mixture of extracts is composed of various polar and non-polar lipids which improves skin hydration and suppleness and reduces transepidermal water loss through repair of the barrier[7].

References

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