A method is disclosed for the utilization of topically applied melatonin for the prevention of oxidative damage in human skin induced by sunlight; i.e., a method for preparing formulations containing melatonin for use as moisturizers, sunblocks, and sunscreens. In addition the formulations will contain one or more proteins that will preserve the melatonin from degradation while in storage, but will allow its controlled release for penetration into cells of the skin when topically applied to the skin, in such a manner that serum melatonin concentration is not raised to supra-physiological levels that may induce adverse effects. In addition the formulation may optionally contain other antioxidants and cosmetic agents.
Abstract

A method is disclosed for the utilization of topically applied melatonin for the prevention of oxidative damage in human skin induced by sunlight; i.e., a method for preparing formulations containing melatonin for use as moisturizers, sunblocks, and sunscreens. In addition the formulations will contain one or more proteins that will preserve the melatonin from degradation while in storage, but will allow its controlled release for penetration into cells of the skin when topically applied to the skin, in such a manner that serum melatonin concentration is not raised to supra-physiological levels that may induce adverse effects. In addition the formulation may optionally contain other antioxidants and cosmetic agents.
Field of the invention.

This invention relates to the incorporation of melatonin into topically applied formulations for the purpose of preventing oxidative damage to the skin, in a manner that:
1) the melatonin is preserved in a stable form that maintains the anti-oxidative capability of the melatonin while it is in storage in the container for extended periods of time, and while it is exposed to the elements and sunlight for the period that it is applied to the skin, and;
2) the release of melatonin into the skin is restricted, so that the application to the skin of the formulations containing the melatonin does not induce an elevation of the concentration of melatonin in the serum to supra-physiological levels which might have adverse physiological effects.

Background

In recent years, the awareness that oxidation contributes to damage to cells in the skin resulting in wrinkles, dryness and inelasticity, has led to the incorporation of many ingredients with known or presumed antioxidant effects. These include Vitamin A, Vitamin C, Vitamin E, and related compounds with similar chemical structures, as well as other organic materials such as tea, algae, and seaweeds.

It has recently been demonstrated that melatonin is a powerful antioxidant that can protect living mammalian cells from the toxic and damaging effects of oxidation (Reiter et al., 1997). An added advantage of melatonin over other antioxidants is that it readily passes through cell membranes, enters cells and penetrates the nuclear membrane. Melatonin administration has been shown to reduce free radical induced damage to DNA associated with ionizing radiation in laboratory rodents (Vijayalaxmi et al., 1995 a, b). This ability of melatonin to reduce oxidative damage to DNA enhances natural repair mechanisms in the cells and may protect DNA in cells of the skin from mutations induced by solar radiation or other factors which may cause the cells to become malignant (Tan et al., 1994).

Because of the benefits which melatonin provides as an antioxidant, its use as a food supplement has been proposed. Also important is the consideration that an antioxidant effect of melatonin could have an inhibitory effect on the incidence of development of melanomas. Previous studies have reported an inhibitory effect of orally administered melatonin on the growth of melanomas already established in mice (Narita and Kudo, 1985) and in humans (McElhinney et al, 1994).

There are several factors that must be taken into account in order to incorporate melatonin into topically applied preparations/formulations. Firstly, it is important to maintain the melatonin in a stable state so that it will be effective as an antioxidant over the entire period of time that it is applied to the skin. Therefore, it is necessary that the formulation contain materials that prevent the degradation of melatonin while it is in storage in the container for extended periods of time, at least months, and also for the period of time that it is exposed to the elements after being applied topically on the skin, which may be several hours.

Secondly, it is desirable to avoid rapid transdermal penetration in order to avoid greatly increasing circulating levels of melatonin in the serum, when applied over large areas of the skin. Unbound melatonin, when applied to the scalp or the forearm can increase circulating levels of melatonin in a dose dependent manner (Bangha et al., 1997).
Summary

We have determined that melatonin can be stabilized, and that its penetration into the skin can be restricted, by including albumin and/or α-1-acid glycoprotein in topically applied formulations. We propose to patent formulations that contain melatonin as an ingredient, including lotions, ointments, oils and creams and other topically applied substances used in cosmetics, for the purpose of moisturizing and/or preserving and maintaining skin texture. As well we propose to patent formulations that contain melatonin as an ingredient, including lotions, ointments, oils and creams, used for the purpose of protecting the skin from the effects of exposure to sunlight, commonly referred to as sun lotions, sun-screens or sun-blocks, which through a process of absorption by ingredients or by reflection by particles of substances such as titanium dioxide embedded in the lotions, ointments, oils, and creams, inhibit the ability of ultraviolet light (UV-A and/or UV-B) from reaching the skin.

Description of the invention

We have determined that melatonin, because of its anti-oxidative properties, would provide two forms of protection to the skin when topically applied in a cream, lotion, ointment or oil. It would protect the skin by preserving the properties of skin from the effects commonly observed when people age, such as loss of elasticity and wrinkling. It would also reduce skin damage induced by exposure to sunlight.

Because of the nature of melatonin as a naturally occurring hormone, it must be protected during storage and must remain stable for the time that the product will remain on the skin. Additionally, the release of melatonin from the topically applied formulation into the skin must be restricted so that the concentration in the skin does not significantly increase serum levels to a point where they might adversely influence normal physiological activity in the body.

We have determined that melatonin can be stabilized in a formulation, (oil, cream, lotion, ointment) in which it is dissolved by incorporating the proteins albumin and/or alpha-1-acid glycoprotein as components of the formulation. Utilizing the proteins albumin and alpha-1-acid glycoprotein as stabilizing agents to which melatonin can bind will help maintain the integrity of the anti-oxidizing properties of melatonin during storage. Because the binding of these proteins and melatonin is reversible, this will allow melatonin to be released in a controlled manner into the epidermis and dermis of the skin. For example, a phosphate buffer with 40% propylene glycol can be used to enhance release of melatonin from proteins. This buffer has been shown to enhance the penetration into the skin of melatonin (Lee et al., 1994).
The embodiments of this invention would consist of:

Topically applied formulations, including lotions, creams, ointments or oils, that claim to protect the skin against oxidative damage and that contain melatonin as an ingredient.

Topically applied formulations, including lotions, creams, ointments or oils, that claim to protect the skin against oxidative damage and that contain melatonin, and a protein that reversibly binds to melatonin so as to stabilize and preserve it from degradation while in storage, but that will release the melatonin for penetration into cells of the skin when topically applied.

Topically applied formulations, including lotions, creams, ointments or oils, that claim to protect the skin against oxidative damage and that contain melatonin and albumin as ingredients.

Topically applied formulations, including lotions, creams, ointments or oils, that claim to protect the skin against oxidative damage and that contain melatonin and α-1-acid glycoprotein as ingredients.

Topically applied formulations, including lotions, creams, ointments or oils, that claim to protect the skin against oxidative damage and that contain melatonin and a protein that reversibly binds to melatonin so as to stabilize it and preserve it from degradation, and an ingredient that will reverse the binding of melatonin from that protein during the time the formulation is applied to the skin.

Formulations, including lotions, creams, ointments or oils, that are topically applied for the purpose of moisturizing the skin and that contain melatonin as an ingredient. i.e. moisturizing cosmetics containing melatonin.

Formulations, including lotions, creams, ointments or oils, that are topically applied for the purpose of moisturizing the skin and that contain melatonin and a protein that reversibly binds to melatonin so as to stabilize and preserve it from degradation while in storage, but will allow its release for penetration into cells of the skin when topically applied. i.e. moisturizing cosmetics that contain melatonin and a protein that reversibly binds to melatonin so as to stabilize and preserve it from degradation while in storage, but will release the melatonin for penetration into cells of the skin when topically applied.

Formulations, including lotions, creams, ointments or oils, that are topically applied for the purpose of moisturizing the skin and that contain melatonin and albumin as ingredients. i.e. moisturizing cosmetics containing melatonin and albumin.

Formulations, including lotions, creams, ointments or oils, that are topically applied for the purpose of moisturizing the skin and that contain melatonin and α-1-acid glycoprotein as ingredients. i.e. moisturizing cosmetics containing melatonin and α-1-acid glycoprotein.
Formulations, including lotions, creams, ointments or oils, that are topically applied for the purpose of moisturizing the skin and contain melatonin and a protein that reversibly binds to melatonin so as to stabilize and preserve it from degradation, and an ingredient that will reverse the binding of melatonin from that protein during the time the formulation is applied to the skin. i.e. moisturizing cosmetics containing contains melatonin and a protein that reversibly binds to melatonin so as to stabilize and preserve it from degradation while in storage and an ingredient that will reverse the binding of melatonin from that protein during the time the formulation is applied to the skin.

Formulations commonly referred to as sunscreens or sunblocks, including lotions, creams, ointments or oils, that are topically applied for the purpose of inhibiting, or preventing, or providing relief from, the effects of sunlight on the skin, (including sunburn, dryness, itching, and physical damage to the cells of the skin), that contain melatonin as an ingredient. i.e. cosmetics used as sunscreens or sunblocks that contain melatonin.

Formulations commonly referred to as sunscreens or sunblocks, including lotions, creams, ointments or oils, that are topically applied for the purpose of inhibiting, or preventing, or providing relief from, the effects of sunlight on the skin, (including sunburn, dryness, itching, and physical damage to the cells of the skin), that contain melatonin and a protein that reversibly binds to melatonin so as to stabilize it and preserve it from degradation while in storage, but that will allow its release for penetration into cells of the skin when topically applied. i.e. cosmetics used as sunscreens or sunblocks that contain melatonin and a protein that reversibly binds to melatonin so as to stabilize and preserve it from degradation while in storage, but that will release the melatonin for penetration into cells of the skin when topically applied.

Formulations, commonly referred to as sunscreens or sunblocks, including lotions, creams, ointments or oils, that are topically applied for the purpose of inhibiting, or preventing, or providing relief from, the effects of sunlight on the skin, (including sunburn, dryness, itching, and physical damage to the cells of the skin), that contain melatonin and albumin as ingredients. i.e. cosmetics used as sunscreens or sunblocks that contain melatonin and albumin.

Formulations commonly referred to as sunscreens or sunblocks, including lotions, creams, ointments or oils, that are topically applied for the purpose of inhibiting, or preventing, or providing relief from, the effects of sunlight on the skin, (including sunburn, dryness, itching, and physical damage to the cells of the skin), that contain melatonin and α-1-acid glycoprotein as ingredients. i.e. cosmetics used as sunscreens or sunblocks that contain melatonin and α-1-acid glycoprotein.

Formulations commonly referred to as sunscreens or sunblocks, including lotions, creams, ointments or oils, that are topically applied for the purpose of inhibiting, or preventing, or providing relief from, the effects of sunlight on the skin, (including sunburn, dryness, itching, and physical damage to the cells of the skin), that contain melatonin and a protein that reversibly binds to melatonin so as to stabilize it and preserve it from degradation, and an ingredient that will reverse the binding of melatonin from that protein during the time the formulation is applied to the skin. i.e. cosmetics used as sunscreens or sunblocks that contain melatonin and a protein that reversibly binds to melatonin so as to stabilize it and preserve it from degradation, and an ingredient that will reverse the binding of melatonin from that protein during the time the formulation is applied to the skin.
References


Claims:

The embodiments of the invention in which an exclusive property or privilege is claimed are as follows:

1. Cosmetic formulations, including lotions, creams, ointments or oils, and including preparations commonly termed moisturizers consisting of products topically applied to human skin for the purpose of moisturizing and preserving the skin from the effects commonly observed when people age, such as loss of elasticity and wrinkling, and including preparations termed sunscreens and sunblocks, consisting of products topically applied to the skin for the purpose of protecting the skin from damage induced by exposure to sunlight, that contain melatonin.

2. Cosmetic formulations as defined in claim 1, that contain a combination of melatonin and a protein that binds to and stabilizes melatonin for the period that it is in storage in a container prior to application to the skin as well as for the period that it is exposed to the elements while on the skin.

3. Cosmetic formulations as defined in claim 1, that contain a combination of melatonin and a protein that binds to and stabilizes melatonin, and thus restricts diffusion of melatonin through the skin, so that the application to the skin of the formulations containing the melatonin does not induce an elevation of the concentration of melatonin in the serum to supra-physiological levels, which might have adverse physiological effects.

4. Cosmetic formulations as defined in claim 1, that contain a combination of melatonin, a protein that binds melatonin, and an ingredient that will promote the release of melatonin from that binding protein so that the melatonin can penetrate into the skin during the time the cosmetic formulation is applied to the skin.

5. Cosmetic formulations as defined in claim 1, that include melatonin as an additive, to prevent the oxidative damage to the skin.

6. Cosmetic formulations as defined in claim 1, that include melatonin as an additive in to inhibit the damage associated with photoaging.

7. Cosmetic formulations as defined in claim 1, that include melatonin as an additive to inhibit sunlight induced oxidative damage to the skin.

8. Cosmetic formulations as defined in claim 1, that include melatonin as an additive to inhibit sunlight induced oxidative damage to DNA in cells of the dermis and epidermis of the skin.

9. Cosmetic formulations as defined in claim 1, that include melatonin to inhibit ultraviolet irradiation-induced skin damage.

10. Cosmetic formulations as defined in claim 1, that include melatonin and albumin as additives to prevent the oxidative damage induced by sunlight.
11. Cosmetic formulations as defined in claim 1, that include melatonin and albumin as additives to inhibit the damage associated with photoaging.

12. Cosmetic formulations as defined in claim 1, that include melatonin and albumin as additives to inhibit sunlight induced oxidative damage to the skin.

13. Cosmetic formulations as defined in claim 1, that include melatonin and albumin as additives to inhibit sunlight induced oxidative damage to DNA in cells of the dermis and epidermis of the skin.

14. Cosmetic formulations as defined in claim 1, that include melatonin and albumin as additives to inhibit ultraviolet irradiation-induced skin damage.

15. Cosmetic formulations as defined in claim 1, that include melatonin and α-1-acid glycoprotein as additives to prevent the oxidative damage induced by sunlight.

16. Cosmetic formulations as defined in claim 1, that include melatonin and α-1-acid glycoprotein as additives to inhibit the damage associated with photoaging.

17. Cosmetic formulations as defined in claim 1, that includes melatonin and α-1-acid glycoprotein as additives to inhibit sunlight induced oxidative damage to the skin.

18. Cosmetic formulations as defined in claim 1, that include melatonin and α-1-acid glycoprotein as additives to inhibit sunlight induced oxidative damage to DNA in cells of the dermis and epidermis of the skin.

19. Cosmetic formulations as defined in claim 1, that include melatonin and α-1-acid glycoprotein to inhibit ultraviolet irradiation-induced skin damage.

20. Cosmetic formulations as defined in claim 1, that contain a combination of melatonin and a protein that binds to and stabilizes melatonin while it is in storage, and an ingredient that will promote the release of melatonin from that binding protein when it is applied to the skin in order to regulate the rate of penetration of melatonin into the skin during the time the formulation is applied to the skin.

21. Cosmetic formulations as defined in claim 1, that contain a combination of melatonin and a protein that binds to and stabilizes melatonin, and an ingredient that will promote the release of melatonin from that binding protein in order to regulate the rate of penetration of melatonin into the skin during the time the formulation is applied to the skin, so that the application to the skin of the formulations containing the melatonin does not induce an elevation of the concentration of melatonin in the serum to supra-physiological levels, which might have adverse physiological effects, but does promote the absorption of melatonin into the skin at levels that the antioxidative properties of melatonin will be effective.