

Feature: Skin Lightening
John Woodruff
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For various reasons skin lightening products are enjoying a rapid growth in sales. They may be used to treat large areas of skin such as the face and hands or more localised areas of hyperpigmentation that occur when an excess of melanin forms deposits in the skin, usually caused by sun damage, acne scars or other skin injuries. Solar lentigines, commonly called age or liver spots and found on the hands and face or other areas frequently exposed to the sun are a common form of hyperpigmentation. Melasma or chloasma spots are similar in appearance to age spots but are larger areas of darkened skin that appear most often as a result of hormonal changes. Pregnancy, for example, can trigger overproduction of melanin that causes areas of discolouration on the face and abdomen and birth control pills may also have a similar effect. Corticosteroids may also cause areas of pigmentation.

The best means of prevention is not to get pregnant, to avoid steroids and to stay out of the sun, or at least to wear protective clothing and sun products. As is often the case; cure is more difficult but there are various approaches, ranging from the use of botanical extracts to laser treatments.

At one time chemical bleaches were used but today the more responsible approach to chemical correction of areas of hyperpigmentation is to inhibit melanin synthesis. Melanin forms through a series of oxidative reactions involving the amino acid tyrosine in the presence of the enzyme tyrosinase. The first step is the most critical because the remainder of the reaction sequences can proceed spontaneously at physiological pH. Thus, tyrosinase converts tyrosine to dihydroxyphenylalanine (DOPA) and then to dopaquinone. Subsequently, dopaquinone is converted to dopachrome, through autooxidation, and finally to dihydroxyindole or dihydroxyindole-2-carboxylic acid (DHICA) to form eumelanin, a brown-black pigment. The later reaction occurs in the presence of dopachrome tautomerase and DHICA oxidase. In the presence of cysteine or glutathione, dopaquinone is converted to cysteinyl DOPA or glutathione DOPA to form the yellow-red pigment, pheomelanin. The colour of the skin and its intensity therefore depend on the rate of formation of the melanin, its degree of polymerisation, the speed of exfoliation and the thickness of the horny layer, which contains the most pigment.

Inhibiting melanin production does not result in a noticeable reduction in pigmentation for the first few weeks but because the skin naturally renews itself every 28 days or so pigmented cells are gradually sloughed off and keratinocytes with less melanin are eventually brought to the surface, giving the skin a lighter, more even toned complexion. Many treatments try and accelerate this process by exfoliation, using either abrasive scrubs or chemical peels, such as alpha-hydroxyacids. The problem using the latter is they leave the skin more sensitive to solar radiation so a high factor sunscreen is essential. In fact, whatever method is used to lighten skin the work of weeks can be undone by one high dose of sunlight.

For many years hydroquinone was the most common active ingredient for lightening skin and it is still often used to benchmark other actives. However hydroquinone is not allowed as a cosmetic ingredient in many areas of the world, including Europe, although it may be used at up to 2% in cosmetics and at 4% in prescription products in the USA. It is said that 4% is the optimum concentration; less than this is not very effective and higher levels can cause skin inflammation and subjective irritation for the user. In addition, application can cause increased sun sensitivity and can lead to sunburn and possible darkening of the skin. Its mode of action is unclear; suggestions are that it inhibits melanogenesis by inhibiting the production of tyrosinase but other sources suggest that it has a cytotoxic effect on the melanocytes.

Arbutin can be isolated from bearberry leaf or bearberry extracts and is often used as an alternative to hydroquinone. Arbutin is a glycoside of hydroquinone but it is not easily absorbed into the skin and has less whitening effect than hydroquinone. USP 40042984 claims a method whereby a two part composition, one part containing about 3% arbutin, the other part about 1000 units of glucosidase, is mixed together immediately before topical application. The glucosidase enzyme hydrolyses arbutin into hydroquinone that then inhibits

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melanogenesis. It is said that the slow conversion of arbutin provides a less irritant alternative to hydroquinone and it appears to be equally efficacious.

Symrise offers arbutin in a cyclodextrin complex as Arbutin 50% Cyclosystem Complex, which confers slow release properties and independent tests show it to have a significant skin whitening effect without associated irritation. Alpha-Arbutin, Pentapharm, is a water-soluble alpha-glucoside obtained by biosynthesis with skin lightening properties combined with safety in use. It is said to be ten times more effective than beta-arbutin obtained from bearberries.

There are many natural materials and their derivatives with claims to lighten skin including mulberry, lemon, orange, liquorice, cucumber, cinnamon and rosemary and many patents describe different ways of enhancing their efficacy. USP 40028712 proposes the use of leukocyte extract at levels up to about 20%. The applicants claim that when used in approximately the same proportions as the natural active ingredients there is significant improvement in results and a longer lasting effect. The same patent mentions many other materials that are generally thought to improve skin lightening products including chelating compounds to chemically bind copper between pH 3.0 and 7.0, thus isolating the tyrosinase which contains copper in its structure. Free radicals are thought to encourage hyperpigmentation and the patent cites various free radical scavengers including vitamin E, vitamin A, tea tree oil, BHA, BHT, cysteine, erythroic acid and ferulic acid that are said to inhibit further damage from this cause.

An interesting means of lightening areas of skin is to decrease the ratio of dark eumelanin to the paler pheomelanin. USP 50226827 describes a means of doing this using methyl sulphonyl methane (MSM), a naturally occurring sulphur compound which may be safely administered topically or orally. The patent claims topical preparations that contain between 1 and 20% by weight MSM and oral preparations containing approximately 200 mg to 5,000 mg MSM per dose. MSM causes dopaquinone to be diverted towards the production of pheomelanin, rather than eumelanin, by increasing intracellular sulphur levels. Under a high intracellular sulphur concentration, melanogenesis automatically leads to an increased synthesis of sulphhydryl-DOPA conjugates, resulting in the synthesis of the lighter coloured pheomelanin instead of the darker eumelanin.

Treating areas of hyperpigmentation may classify as a pharmaceutical treatment and various patents describe new compounds that most probably are not available for inclusion in cosmetic products. USP 30199558 describes the use of m-benzohydroxamic acid and its derivatives and p-benzohydroxamic acid and its derivatives to inhibit the enzymatic activity of melanocyte tyrosinase. Small molecular weight complexes of manganese possess superoxide dismutase activity and are useful for enhancing or restoring the resistance of an animal to oxidative or inflammatory damage.

The enzyme superoxide dismutase is an important defence against oxidative damage in the body. There are two types in humans; the Cu-Zn superoxide dismutase (SOD1), which is found mainly in the cytosol of the cell, and the Mn-superoxide dismutase (SOD2), which is found in the mitochondria. USP 600018851 claims topical application of suitable products containing a manganese-peptide complex, preferably in the presence of retinol, provide a method for treating hyperpigmentation of skin, either prophylactically to prevent hyperpigmentation, or therapeutically to ameliorate an existing condition characterised by hyperpigmentation.

The efficacy of any active for treating conditions within the stratum corneum is dependent on its ability to penetrate the outer layers. Thus delivery vehicles are important and skin penetration enhancers may be used. USP 60002874 describes various compounds used for this purpose and states the need for materials that are effective in increasing the rate at which a material permeates the skin but do not result in skin damage, irritation or sensitisation and which can be used to effect dermal delivery of high molecular weight materials such as peptides, proteins, and nucleic acids. The applicants claim to have discovered that bases, such as hydroxide-releasing agents, and organic bases, such as amines and other nitrogenous bases, are highly effective penetration

enhancers and are particularly effective in enhancing penetration into regions of skin hyperpigmentation. There are problems of compatibility between the bases proposed, that have a high alkaline pH and the majority of skin lightening compounds in current use that are either acidic or are more stable or efficacious under acidic conditions and this aspect is referred to at length in the patent.

Magnesium ascorbyl phosphate (MAP) is often cited as a skin lightening compound and many patents include it as a secondary active ingredient. A private communication described the results of in-vivo tests of a cream containing 10% MAP when applied to the pigmented area of 34 patients' faces twice a day for three months. Measurement by a colour difference meter showed that the pigmentation for 26 patients was lightened due to topical application of MAP cream. MAP cream was also applied to non-pigmented areas of 27 patients and was effective in lightening 11 out of 27 areas of healthy skin. These results suggest that MAP was absorbed by topical application and stayed in the skin, inhibiting tyrosinase activity of melanocytes, and demonstrate that topical application of MAP can be effective in lightening human skin pigmentations.

Patents are a useful source of information; as well as a warning to avoid patented combinations they also reveal many interesting ideas that can be used. However when it comes to the formulation stages there is a need to find suitable ingredients that are commercially available. For skin lightening compositions the material suppliers offer a wide range of possible actives, many of which are supported by efficacy studies.

Multi-functional materials are always of interest and few offer as many cost-effective benefits as sodium lactate and lactic acid. They are used to adjust and buffer the pH of topical compositions; they are part of the skin's natural moisturising factor and have moisturising properties when used for topical application. They have an inhibitory effect on microbial growth, partially by a reduction in pH, but it is also suggested that the lactate ion interferes with the energy cycle of the micro-organism. They can be used at higher concentrations as exfoliating agents and are considerably less irritating than glycolic acid and its salts. It is also suggested that sodium lactate be used as skin lightening agent in combination with ascorbic acid.

Another multi-functional ingredient is octadecenedioic acid, which is synthesised from oleic acid by bio-fermentation and sold under the trade name Arlatone Dioic DCA by Uniqema. Its prime action is to level skin tone by enhancing overall skin radiance and it appears to have a particular lightening effect on hyperpigmented areas. It also has mild deodorant properties and is a mild anti-acne agent. With similar multi-functional properties, potassium azeloyl diglycinate is the INCI name of a material formed by the condensation of azelaic acid and glycine and marketed by Sinerga as Azeloglicina. The results of efficacy studies show it to have significant moisturising properties, to enhance skin elasticity and to regulate sebum production. It also improves skin brightness and reduces pigmentation. Arlatone Dioc is oil-soluble whereas Azeloglicina is water-soluble so selection may depend on the choice of product for application.

Silab suggests the use of two ingredients that appear to work in synergy. Clariskin II is from wheatgerm and works by orientating melanin production towards pheomelanin, the lighter form of melanin, and it also has an antioxidant effect against photo-induced free radicals. Dermalight is an extract of Nasturtium (Indian cress) and inhibits tyrosinase activity, thus reducing melanin production. Surfachem offers Glabridin, an alcoholic extract of Glycyrrhiza glabra or liquorice that is said to inhibit the activity of tyrosinase and to have anti-inflammatory and anti-oxidant properties. In comparison tests it significantly outperformed kojic acid as an inhibitor of TRP-2 and is said to be non-irritating and non-sensitising.

A copper-glycine complex from Nikkol is claimed to induce the production of metallothioneine, a cysteine-rich peptide that the body produces under stress that has antioxidant properties and which binds to cadmium, zinc and copper to detoxify their harmful effects. The complex supplied by Nikkol is said to reduce intracellular oxidative stress and to inhibit tyrosinase activity.

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Stem cell research is one of the most active areas of medical advance but it is not limited to the use of human cells. CIC-2 from Biotechmarine is a stem cell culture from *Crithmum maritimum* that, when topically applied, is said to have a lightening effect on brown spots, to renew skin radiance and improve its tone, to stimulate cell renewal and to have an overall anti-aging effect on the skin. CIC-2 inhibits the transformation of phenylalanine into tyrosine and also protects against UV-induced free radical damage.

There are many natural materials with skin lightening properties: ClariTea, Solabia, is a vegetal active ingredient, containing polyphenols and proanthocyanidic oligomers obtained by the hydroglycolic extraction of *Camellia sinensis* (White tea) leaves. Its preparation is limited to minimal procedures aimed at preserving its phytochemical properties and is specially designed to protect the skin against external aggression, to restore its radiance and enhance the complexion. The very comprehensive brochure from Solabia includes folk lore and legends about the complexion enhancing properties of white tea as well as test protocols describing its activity and the results of melanin inhibition tests.

Topical use of alpha-linolenic acid lightens skin tones and it is the major omega-3 fatty acid found in *Vaccinium vitis-idaea* seed oil, from crops harvested in Arctic regions. It is available as Red Alfa, Aromatech, and incorporating this material into skin formulations offers an efficient way of providing skin with omega-3 fatty acids. RED ALFA is also rich in antioxidants and plant sterols and is claimed to provide a number of beneficial effects on skin, including reducing skin sensitivity and inflammation, to enhance tissue regeneration and to reduce skin pigmentation. Other oils from Aromatech that originate in Arctic regions and are rich in alpha-linoleic acid include *Oxycoccus palustris* (Cranberry) seed oil, *Vaccinium myrtillus* (Bilberry) seed oil, *Rubus idaeus* (Raspberry) seed oil and *Fragaria ananassa* (Strawberry) seed oil.

Gigawhite, Alpaflor, is a multi-component mixture of botanical extracts promoted for skin whitening, Melfade, Pentapharm, is a combination of bearberry extract and magnesium ascorbyl phosphate,; Merck offers RonaCare MAP, described as biotechnology-derived magnesium ascorbyl phosphate and Lipotec has IDB-Light, a 10% solution of Idebenone proven to inhibit melanin synthesis. Whitesphere, Soliance, is an aqueous dispersion of multilayered microspheres containing ascorbic magnesium phosphate.

From Greentech there is Clerilys, a natural skin lightener based on mulberry; Rayolys, a skin brightener obtained from peach, apple and raspberries and Flower Acids, described as a cell renewal stimulator, a new generation of AHAs without irritant side effects from *Hibiscus Sabdariffa*. Isocell Citrus, Lucas Meyer, is a skin lightening agent based on citrus extract microencapsulated in phospholipids.

Crodarom offers White Truffle extract as a luxury skin care ingredient said to lighten skin and to improve the complexion. Sederma provides Lumiskin, a solution of diacetyl boldine in caprylic/capric triglyceride that is said to regulate the calcium availability for melanin synthesis; tyrosinase activity is reduced by about 50% and the quantity of melanin produced is reduced by 70%.

Active Concepts suggest the use of Lemon Peel Extract, which is actually the result of macerating the whole fruit and incubating it with *Lactobacillus lacti* and then potential allergens such as citral and geraniol are removed and it is said to have both anti-tyrosinase and anti-oxidant activity. Atrium suggests Tyrostat and Grant Industries offers Gransil PS5-AA20, a silicone-coated ascorbic acid.

Ascorbic acid is a powerful antioxidant but difficult to formulate into stable products. Ways to improve its shelf life include providing it in liposome form or in microspheres and as various derivatives such as magnesium ascorbyl palmitate. AA2G, Hayashibara, is an ascorbic acid derivative with glucose attached to the C2 hydroxyl group of ascorbic acid and it is stable against heat, light and oxidation. In the skin, AA2G is broken down into ascorbic acid and glucose by the enzyme glucosidase and it then has the normal biological activity of ascorbic acid, including the inhibition of melanin synthesis.

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Extrapone Nutgrass (Motha) Root GW, Symrise, shows a melanin inhibition of 40% at a concentration of 0.5% and is a natural anti-irritant. It is used in Ayurvedic medicine for improving skin radiance, in wound-healing and as an anti-bacterial. The brown-blackish rhizomes are slightly fragrant and in Asia the essential oil is used as a perfume and insect repellent. Also from Symrise is Phytoderia Whitening, obtained by fermentation of liquorice with *Aspergillus* ferment and its activity is due to inhibition of tyrosinase.

Gatuline Whitening, Gattefossé, is a mixture of kojic acid, lactic acid, and a liquorice extract combined with a penetration enhancer, ethoxydiglycol. The kojic acid acts on the melanocytes to inhibit tyrosinase activity, lactic acid enhances cell renewal and the penetration enhancer improves penetration into the epidermis creating a reservoir at the dermal-epidermal junction. Finally, the presence of liquorice extract has soothing properties due to the presence of glycyrrhetic acid. As with the majority of materials mentioned in this feature this ingredient is well supported by test results detailing both its efficacy and its safety.

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