Review Article

A Systematic Review on Skin Whitening Product

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ABSTRACT

Skin whitening is a term used for lightening the complexion of the skin through artificial means like creams, lotions, soaps and injections. Unfortunately, the appeal of these skin bleaching products is based on the obsession of people across the world with skin color. Melanins are produced by specialized cells, termed melanocytes, which are located primarily in the skin, hair bulbs, and eyes. The melanins can be of two basic types: eumelanin's, which are brown or black, and phaeomelanin's, which are red or yellow, in mammals typically there are mixtures of both types Increased production and accumulation of melanins characterize number of skin diseases, which include hyperpigmentation such as melanoma, post-inflammatory melanoderma, solar lentigo, etc. Several modalities of treatment for these problems are available including chemical agents or physical therapies. The aim of this review article is to show that some of the skin whitening creams, often sold illegally without a prescription may contain dangerous ingredients that could put people health at risk.

Keywords: Anatomy and function of skin, Skin whitening agents, Market Scenario, Future Development.

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INTRODUCTION

Skin Whitening products is a high trend in all over the world for skin beautifying and lightening. Skin whitening is defined as "the practice of using chemical substances or any other product with a depigmenting potential in an attempt to lighten the skin tone or improve skin complexion by lessening the concentration of melanin to obtain a reduction of the physiological skin pigmentation. Skin lightening products are used in medical treatments for a range of skin disorders, including hyperpigmentation.[1] However, a major market has been develop in its use for cosmetic and source for cosmetic could be natural, semi-synthetic and synthetic that affect the halal status of product.[2]Numerous chemical substances have already been proven as effective skin whiteners, and some even display beneficial side-effects (antioxidants, antiproliferative activity, protection of macromolecules such as collagen against UV radiation etc.), but others have recently raised safety concerns, leading to teir ban in some countries.

Anatomy and Physiology of Skin

Skin is the largest organ within the body and acts as a protective barrier. It is a connective tissue that consists of cells, fibres and extracellular matrix. The three main layers in it are:

- Epidermis
- Dermis
- Hypodermis

Functions of the Skin's Layers

Epidermis Responsible for Skin Coloring

Epidermis is the outermost layer of your skin, making it the protective barrier which prevents the entry of harmful bacteria, viruses and other foreign substances into the deeper layers.

Prevents water loss from the skin and is also responsible for its color due to the presence of melanocytes.

The different layers of epidermis are:

A. Stratum Basale

This is the lowest layer of epidermis and is composed of keratinocytes, melanocytes and tactile cells. Keratinocytes produced here constantly undergo cell division and are pushed to the upper layers of the epidermis. A keratinocyte is a cell composed of keratin, a fibrous protein that gives skin, hair and nails the hard texture. The cells in this layer are attached to the dermal layer of the skin via collagen fibres, referred to as the basement membrane.

B. Stratum Spinosum

This layer is composed of daughter keratinocytes and dendritic cells, which fight infections in the body. Stratum

spinosum is shiny in appearance due to protruding structures called desmosomes.

C. Stratum Granulosum

This layer is composed of 3-5 layers of Keratinocytes. It appears grainy due to the changes in keratinocytes that are being pushed to this layer

D. Stratum Lucidum

This layer has closely packed keratinocyte cells with seleiden, a clear protein rich in lipids. This is the thick skin that you find in your palms and feet and its transparency is due to seleiden.

E. Stratum Corneum

This layer consists of 15-30 layers of dead keratinized cells. They are shed every four weeks. The layer derives its name ffrom the process of keratinization or cornification that happens.

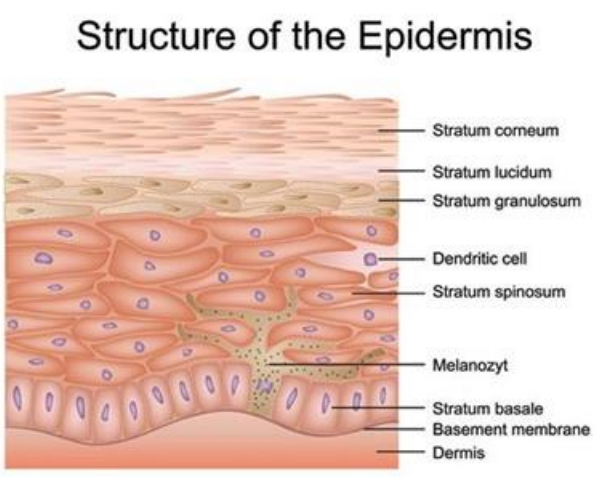


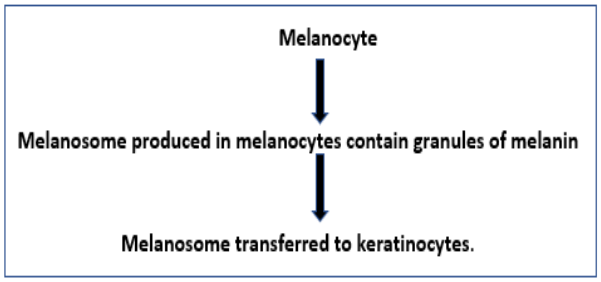
Figure 1: Structure of the Epidermis

The Biology of Skin Pigmentation and Disorders

- Pigmentation refers to skin colouring (some areas or patches of skin turns darker in colour) due to the deposition of the pigment melanin, which is produced by specialized cells called melanocytes.
- Carotenes and melanin plays an important role in imparting colour to the skin[3].

Colour of the skin

- Melanin is synthesized in the dendritic cells (melanocytes) which are present in the basal epidermal layer



- Production of melanin pigment is stimulated by UV radiation as well as melanocyte stimulating hormone secreted by anterior pituitary gland.

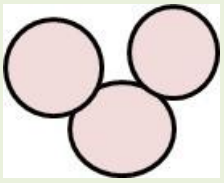
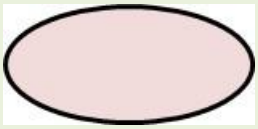
Variation in skin colour reflect primarily the differences in the amount and distribution of melanin pigment in the epidermis.

Chemistry of Melanin

Two types of melanin are synthesized in Melanosomes:

1. Eumelanin: Eumelanin is a dark brown-black insoluble polymer (derived from the polymerization of tyrosine oxidation products).
2. Pheomelanin: pheomelanin may be a light red-yellow sulphur- containing soluble polymer.

Table 1: Differentiation between types of melanosomes

White skin Melanosome	Black skin Melanosome
	
▪ Less mature	▪ Mature
▪ Smaller, round and are usually bound in groups.	▪ Single, ovoid and membrane-bound.

- Riley surveys the evidence that two types of oxidations are involved:

1. Oxygen addition to aminophenol (cresolase activity)

2. Dehydrogenation of diphenols (catecholase activity)

Genes involved in Melanogenesis

Melanogenesis may be a complex process which is regulated by many genes. In order to know the pathogenicity of pigmentation disorders and subsequent development of potential therapeutic options, there's an urge for proper identification and comprehension of the genes regulating the mechanism of melanogenesis. Below table represents the list of different genes involved in melanogenesis and those which are responsible for melanin synthesis and regulation[4].

Table 2: Illustration of gene and protein function

Gene	Protein	Function
MITF	Micropthalmia Associated Transcription Factor	Transcription factor which regulates function of pigmentary enzymes and survival of melanocytes
PAX3	Paired box gene 3	Proliferation, differentiation, survival of melanocyte
MC1R	Melanocortin1 receptor	Receptor of α-MSH hormone, upregulates melanogenesis
AC	Adenylate Cyclase	Increase cAMP level in melanocyte
PKA	Protein Kinase A	Phosphorylates transcription factors which activates MITF
β-Catenin	Beta catenin	Upregulates transcription of MITF
C-kit	Tyrosine kinase receptor	Melanocyte physiology, influencing melanogenesis, proliferation, migration, and survival of the pigment-producing cells.
RAS	Ras GTPase protein	Melanocyte cell growth, differentiation and survival by activating RAF protein
RAF	RAF kinase protein	Melanocyte cell growth, differentiation and survival by activating MEK protein
MEK	Mitogen-activated protein kinase kinase	Activating ERK protein
ERK	Extracellular signal-Regulated Kinase	Negatively regulates activity of MITF protein by phosphorylate and ubiquitation
TYR	Tyrosinase	Initiates melanin biosynthesis process
TYRP1	Tyrosinase Related Protein1	DHICA-oxidase function in melanogenesis and regulates activity of TYR.
TYRP2	Tyrosinase Related Protein2	Produce DHICA from Dopachrome which is a precursor product of melanin

Biochemical pathways for melanogenesis

Biochemical pathways for melanogenesis: - According to variations in the structure and occurrence of melanin, its biogenesis is not a single and universal process. The study on various organisms led several biosynthetic pathways in melanin synthesis (Solano, 2014). The general features in all the pathways involve an initial phase with the enzymatic-catalysed oxidation of phenolic precursors to quinones followed by a final phase consisting of the mostly unregulated polymerization of quinones. The most universal and well-known pathway of animal is named the Raper-Mason pathway which is described below[5].

Raper-mason pathway of Melanogenesis

The initiation process of melanogenesis begins by virtue of the key enzyme, Tyrosinase (TYR) which oxidizes L-tyrosine to Dopaquinone

(DQ) the resulting Dopaquinone (DQ) will function a substrate for the synthesis of Eumelanin and Pheomelanin[6]

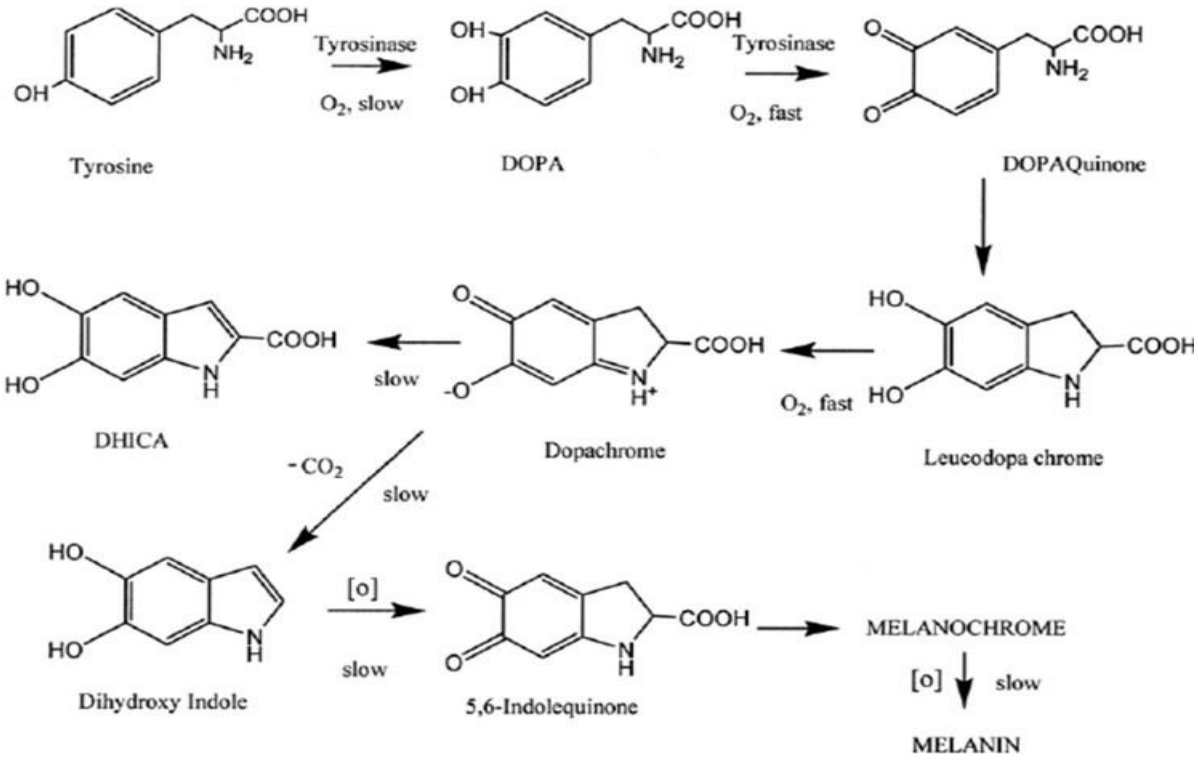


Figure 2: Raper-Mason Pathway of Melanogenesis.

Disorders of Pigmentations

- Freckles- The most common type of pigmentation. They develop after repeated exposure to sunlight particularly if you have fair complexion.[7]

Figure 3: Freckles disorder

- Melasma- Melasma or chloasma is pigmentation that is deeper in the skin dermis and common among people with darker skin tone.[8]

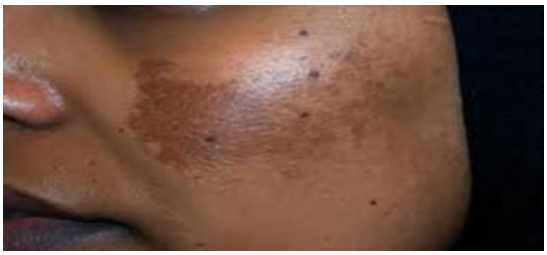


Figure 4: Melasma disorder

- Solar lentigines- Also referred as liver spots or sun spots. They may occur anywhere on the body and vary in colour from light brown to black.[9]

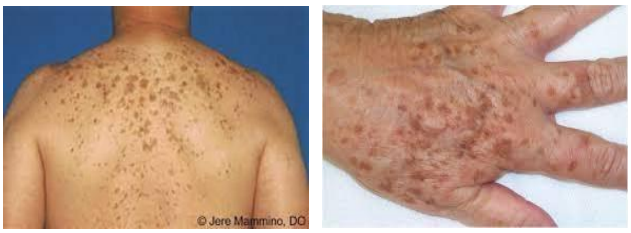


Figure 5: Solar lentigines

Post inflammatory pigmentation

This is often a response to injury of the skin and may be the results of acne, burns, and friction. It is even be thanks to cosmetic procedures for skin like chemical peels, laser treatments or combination therapy. This type of pigmentation leads to tan, brown or black colour to skin.

Figure 6: Post Inflammatory Pigmentation

Depigmentation

Depigmentation is the lightening of the skin or loss of pigmentation. Depigmentation of the skin are often caused by variety of local and systematic conditions.

Mechanisms: - The compound may-

1. Selectively destroy the melanocytes.
2. Inhibit the formation of Melanosomes and alter their structure.
3. Inhibit the biosynthesis of tyrosinase.
4. Inhibit the formation of melanin.
5. Interfere with the transfer of Melanosomes
6. Have a chemical effect on melanin or enhance the degradation of Melanosomes in keratinocytes.[10]

• Depigmentation can be achieved by using –

A. Active Ingredients
B. Anti-Oxidant
C. Vitamins
D. Sun protecting Factor Skin Whitening Agent

Cosmeceuticals for hyperpigmentation can be classified based on their mechanism of action

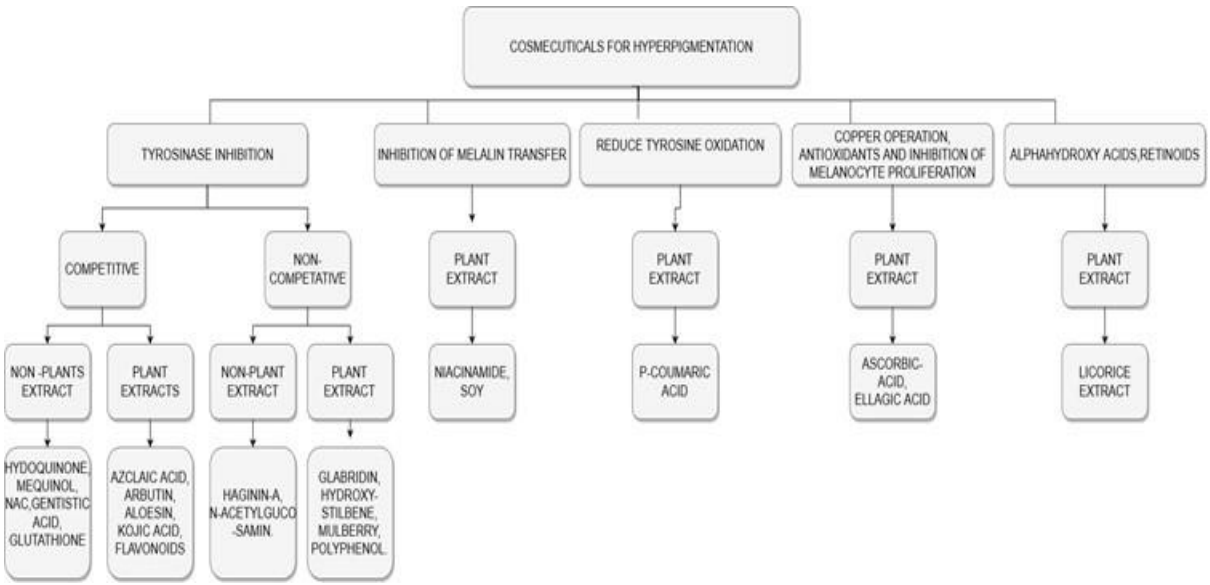


Figure 7: classification cosmeceuticals for hyperpigmentation

Skin Whitening Agents

Tyrosinase Inhibition

Tyrosinase is a copper enzyme, which catalyses both the hydroxylation of monophenols to o-diphenols and the oxidation of o-quinones to o-quinones. Most whitening agents act specifically to reduce the function of this enzyme by means of the following mechanisms (2): (i) interference with its transcription and/or glycosylation, (ii) inhibition by different modalities, (iii) reduction of by-products, and (iv) post-transcriptional control.

Hydroquinone

It is considered as one of the best inhibitors of the Melanogenesis, by decreasing the tyrosinase activity by 90% and hence is used in the treatment of melanosis and other hyper pigmentary disorders. This phenolic compound causes reversible inhibition of cellular metabolism by affecting both DNA and RNA synthesis.[11] It is also a very good depigmented when used at concentration levels of less than 2%. Hence products containing higher HQ concentrations than 2% is considered as a pharmaceutical product and is strictly to be used when prescribed by a medicinal practitioner.[12] HQ concentration above 5% is not advisable because of the side effects like skin irritation problems and sometimes may even cause permanent depigmentation with long term treatment.[13] HQ solution turns brown on exposure to air, hence use of stabilizer like sodium meta-bisulphite or sodium sulphite become compulsory with addition of vitamin C. High concentration not used due to various side effects, Hydroquinone is very reactive and potent melanocyte cytotoxic and mutagenic compound, therefore not authorized in cosmetics anymore. [14]

Mono benzyl ether Hydroquinone

(MBEH) MBEH causes depigmentation by eclectic melanocytic destruction through radical formation and competitive inhibition of tyrosinase enzyme system. However, unlike its parent compound HQ, MBEH almost causes irreversible pigmentation of skin and hence should be used only in treatment of severe vitiligo. [15]

Arbutin

Arbutin is one of the foremost widely prescribed skin-lightening and de-pigmenting agents worldwide. Arbutin, the b-D-glucopyranoside derivative of hydroquinone, may be a present plant derived compound found within the dried leaves of variety of various plant species including, bearberry (Arctostaphylos uva-ursi), and blueberry, cranberry, and pear trees. Arbutin, inhibits tyrosinase activity competitively but at non-cytotoxic concentrations during a dose dependent manner in cultured melanocytes.[16] It also inhibits melanosome maturation and is a smaller amount cytotoxic to melanocytes than hydroquinone. Although, higher concentrations could also be more efficacious, greater risk for paradoxical hyperpigmentation exists[17].

Kojic Acid

(5-hydoxy-4-pyran-4-one-2-methyl) Kojic acid, is another popular antibiotic skin whitening substance produced in an aerobic process by a spread of micro-organisms, usually derived from species like aspergillus and penicillium, may be a well-known skin lightening agent which inhibits tyrosinase activity thereby reducing melanin production. Copper ions are an important metal of the active tyrosinase site of melanin synthesis. It functions by chelating Copper at the site of tyrosinase enzyme.[18] It also acts as a radical scavenger However, it's reported to possess high sensitizing potential but is beneficial to patients who cannot tolerate HQ and may be combined with topical corticoid to scale back skin irritation. the main applications of KA and its derivatives in medicine are supported their biocompatibility, antimicrobial and antiviral, antitumor, antidiabetic, anticancer, anti-speck, anti-parasitic, and pesticidal and insecticidal properties. additionally , KA and its derivatives are used as antioxidant, anti-proliferative, anti-inflammatory, radio protective and skin-lightening agent in skin creams, lotions, soaps, and care products[19].

Azelaic acid

Azelaic acid (AZA) may be a present 9-carbon dicarboxylic acid compound isolated from cultures of Pityrosporum Ovale. It inhibits tyrosinase activity in vitro and should also interfere with DNA synthesis and mitochondria activity in hyperactive and abnormal melanocytes.[20] AZA has been wont to treat melasma and post-inflammatory hyperpigmentation and to arrest the progression of the lentigo maligna to melanoma. This specificity could also be attributed to its selective effects on abnormal melanocytes. AZA produced ultra-structural damage to normal melanocytes[21].

Aloesin

Aloes in, a natural hydroxymethylchromone derivative isolated from burn plant , acts by two different mechanisms of action on tyrosinase activity, e.g., aloesin inhibits the formation of DOPA quinone by competitive inhibition at the DOPA oxidation site, reduction of copper ions at the hydroxylase site, and consequently tyrosine hydroxylation by non-competitive inhibition as compared with other depigmenting agents, aloesin shows no cytotoxicity in cell-based assays, no skin irritation in preliminary human studies and any genotoxicity or mutagenicity within the Ames assay. Cultured cells utilized in tyrosinase activity assays show no morphologic abnormalities when treated with aloesin, and human melanocytes appear normal with multiple dendrites.[22]

Thus, aloesin may be a potent inhibitor of human tyrosinase. However, due to the hydrophilic nature of the compound and moderately high relative molecular mass , penetration of human skin was poor. Jones et al. demonstrated aloesin dissolved in ethanol penetrates the skin slowly with approximately 1.59% of a finite dose penetrating the heal a 32-hour period. At non-cytotoxic concentration aloesin probably acting as acompetitive inhibitor on DOPA oxidation and as a non-competitive on tyrosine hydroxylase activity. Aloesin treatment showed pigmentation suppression during a dose-dependent manner; thus, aloesin could be used as an agent that inhibits melanin formation induced by UV radiation. In vivo, aloesin and arbutin co-treatment inhibits UV-induced melanogenesis during a synergistic manner.

The mixture of aloesin and arbutin showed a big inhibition on tyrosinase activity of human melanocytes and reduced significantly melanin content, and had little influence on melanocytes viability[25].

Paper Mulberry Extract

Mulberry extract springs from the plant white mulberry L from the Moraceae family. The leaves of this plant have anti-hyperglycaemic activity. The derivatives of its root bark are found to possess skin lightening effect. This might flow from to inhibition of dopa oxidase activity of tyrosinase and superoxide scavenging activity. IC50 (concentration causing 50% inhibition of activity of tyrosinase) is extremely low (0.396%) as compared to five .5% for hydroquinone and 10.0% for kojic acid.[26] However, clinical trials regarding skin lightening effects are lacking. A skin test using 1% Broussonetia papyrifera extract revealed no significant skin irritation at 24 h and 28 h.[27]

Liquorice Extract

Liquorice extract is obtained from the basis of licorice Linnera. It's cultivated extensively in India. Liquorice extract improves hyperpigmentation by dispersing the melanin, inhibition of melanin biosynthesis and inhibition of cyclooxygenase activity thereby decreasing radical production. Glabridin, a polyphenolic flavonoid is that the main component of liquorice extract. Studies have shown that glabridin prevents Ultraviolet B (UVB) induced pigmentation and exerts anti-inflammatory effects by inhibiting superoxide and cyclooxygenase activity.[28] However, more studies are needed.

Ellagic Acid (Copper Chelation)

A polyphenol cosmopolitan in plants, is capable of preventing pigmentation caused by sunburn. Ellagic acid inhibits tyrosinase non-competitively during a dose-dependent manner, through its capacity to chelate copper, albeit other mechanisms, like a scavenger effect are suggested. Interestingly, in brownish guinea pigs, ellagic acid induced a reversible inhibition of melanin synthesis only in UV-activated melanocytes.[29]

Inhibition of Melanosome Transfer

The activation of protease-activated receptor-2 (PAR-2), a seven trans-membrane G-protein coupled receptor, which is expressed in keratinocytes and not in melanocytes, was found to activate keratinocyte phagocytosis, enhancing the melanosome transfer.[30] Inhibition of PAR-2 cleavage by serine PI, like RWJ-50353, completely avoids the UVB-induced pigmentation of epidermal analogues[31,32].

Niacinamide (Vitamin B3)

Furthermore, referred to as nicotinamide (3-pyridine-carboxamide) is that the physiologically active amide of niacin (vitamin B3). Niacin is involved within the synthesis of the enzymes Nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) required for cellular metabolism.

Study done on pigmented reconstructed epidermis (PREP) showed that niacinamide interferes with the interaction between keratinocytes and melanocytes, thereby inhibiting melanogenesis. It also modulates the protease-activated receptor (PAR-2) that's involved within the transfer of melanosomes from melanocytes to surrounding keratinocytes. Clinical trials using 2% niacinamide have shown that it significantly reduces the entire area of hyperpigmentation and increases skin lightness after 4 weeks of treatment. there's a plateau in treatment effect which might be thanks to balance between the up-regulation of melanogenesis within the hyperpigmented area and therefore the down-regulation by niacinamide. Alternatively, the plateau could reflect the fraction of the hyperpigmented area that's sensitive to niacinamide treatment. The study also showed that the daily use of niacinamide with sunscreen was effective in reducing hyperpigmentation and in increasing lightness of basal complexion compared with sunscreen alone.[33]

Niacinamide is that the main ingredient of the foremost popular cosmeceutical used for hyperpigmentation within the Indian market, that's fair and wonderful fairness cream where it's combined with sunscreen for extra benefits. In another sort of an equivalent product, niacinamide is employed alongside vitamin C.

RWJ-50353

RWJ-50353, a serine PI that reduced melanosome uptake in culture, is shown to possess a dose-dependent depigmenting activity in vivo with no irritation or other side effects. Treatment with increasing concentrations of RWJ-50353 didn't affect tyrosinase mRNA levels. Interestingly, this treatment

led to decreased levels of TRP-1 and increased levels of TRP-2 mRNAs. The down regulation of TRP-1 by RWJ-50353should cause reduced tyrosinase activity and reduced pigment production.

RWJ-50353 inhibits melanosome transfer from melanocytes to keratinocytes by its inhibitory effect on the keratinocyte PAR-2 signaling pathway. RWJ-50353-treatedkeratinocytes are unable to actively take or receive melanosomes from the presenting dendrites. microscopy studies illustrated an accumulation of immature melanosomes inside melanocytes and abnormal dendrite dynamics in RWJ-50353-treatedepidermal equivalents.

In vivo RWJ-50353 (up to 10mM, twice-daily treatment to swine skin) couldn't completely inhibit melanogenesis or pigment transfer, and therefore the transferred melanosomes are of poor quality. Treatment of dark-skinned Yucatan swine for eight weeks withRWJ-50353 induced visible skin lightening. Histological analysis of treated sites at eight weeks shown only minimally stained melanin granules dispersed within the basal layer of epidermis.

Soya (glycine soja)

The main components of soy are phospholipids (45-60%), and essential fatty oils (30-35%). It also contains active ingredients like isoflavones, vitamin E and serine PI s-soybean trypsin inhibitor (STI) and Bowman-Birk protease inhibitor (BBI). The protease inhibitors inhibit PAR-2 activation, thereby inhibiting melanosome transfer[34]. The fatty acids in soy inhibit trypsin which may be a known activator of PAR-2. Furthermore, the isoflavones inhibit the DOPA oxidase activity thus inhibiting melanogenesis[35]. Soy has proven to be both efficacious and safe. Several skin care products containing soy are available to enhance hyperpigmentation. Skin lightening benefit are often seen after 12 weeks of twice daily application. The de-pigmenting effect of soymilk is reversible and daily topical treatments for 7 months end in no adverse effects[36].

Skin Turnover Acceleration

The capacity of several compounds to disperse melanin pigment and/or accelerate epidermal turnover may result in skin lightening. Chemical substances used as exfoliates, such AHAs, free fatty acids, and retinoic acid, stimulate cell renewal facilitating the removal of melanised keratinocyte, resulting in melanin granules loss.[37] Topical application has been shown to scale back the visibility aged spots without reducing their size or number, and may be useful within the treatment of melasma.[38] Unsaturated carboxylic acid , like monounsaturated fatty acid, linolic acid, or omega-3 fatty acid , suppress pigmentation, in vitro, whereas saturated fatty acids, like hexadecanoic acid , increase the speed of melanogenesis[39,40].

Alpha Hydroxy Acids

The benefits of AHAs have long been recognized. Sour milk [contains carboxylic acid (LA)] and sugarcane juice [contains glycollic acid (GA)] were applied to the face. In low concentrations, AHAs decreased corneocyte cohesion, resulting in sloughing of dead cells and stimulation of latest cell growth within the basal layer. In higher concentrations, they cause epidermolysis. AHAs are reported to be effective in treating pigmentary lesions like melasma, solar lentigines, and post-inflammatory hyperpigmentation. The mechanism of this effect could be thanks to epidermal remodelling and accelerated desquamation, which might end in quick pigment dispersion. GA and LA might work on pigmentary lesions not only by accelerating the turnover of the epidermis but also by directly inhibiting melanin formation by inhibiting tyrosinase in melanocytes. GA or LA (at doses of 300 or 500mg/ml) inhibited melanin formation in similar dose-dependent manner, without affecting cell growth. The bioavailability of AHAs increases because the pH decreases (desirable pH 2.8–4.8), and that they are the sole peels that are time-dependent and may be neutralized easily[41].

Linoleic Acid (Vitamin F)

Linoleic acid in vivo showed the best lightening effect in UVB-induced pigmentation, without toxic effects on melanocytes. Several protease inhibitors caused the buildup of an approximately 60 kDa tyrosinase doublet promoted the interpretation of the enzyme to melanosomes[42]. The evidence suggests that tyrosinase in selectively targeted by fatty acids, which seem to act on the degradation of the enzyme during the physiologic proteasome-dependent mechanism.[43] linolic acid accelerates the method whereas hexadecenoic acid works in an antagonistic manner mimicking protease inhibitors.

Traditional Chinese Medicine

Traditional Chinese herbs are a really popular mode for the treatment of hyperpigmentation disorders. 2 hundred nineteen sorts of herbs are screened; among them 19 kinds are shown to inhibit tyrosinase in vitro. The inhibitory effects of tyrosinase activity of Atractylodes macrocephaly, domestic silkworm moth , Ligusticum sinense, Bletilla striata , Typhonium gigantism, Astragalus complanatus, Serissa erissoides, and Diospyros kakiwere either superior or almost like that of arbutin[44].

Cinnamic Acid

Cinnamic acid, a present aromatic carboxylic acid of low toxicity, features a long history of human exposure. The cinnamic acid induces cytostasis and a reversal of malignant properties of human tumor cells in vitro. The cinnamic acid was found to induce cell differentiation as evidenced by morphological changes and increased

melanin production in melanoma cells. Cinnamic acid doesn't influence the fungal growth but decreases the yield of the pigment from the mycelium.[45,46]

Sophorcarpidine

Tyrosinase activity are often greatly inhibited by cinnamic acid, aloin, and sophorcarpidine, of which sophorcarpidine functions as an uncompetitive inhibitor, compared to aloin and cinnamic acid, which are mixed-type inhibitors. Tan et al.

demonstrated that Skin Lightening Agents 213. Sophorcarpidine, aloin, and cinnamic acid can't only bind to the enzyme, but also to the enzyme-substrate complex also, resulting in the inactivation of tyrosinase.

Botanical/Plant Extract

Due to the potential side-effects of existing therapies, there's a rising trend towards development of natural derived extracts for hyperpigmentation. Various plant extracts are being studied for his or her role in melasma. Hwang et al. conducted an in vitro study with 101 plant extracts and evaluated their effect on melanin synthesis in B16 melanoma cells[47]. They found that Broussonetica kazwoki, B. Papyrifera, Cornus officinalis, Rhus javanica and Japanese red pine inhibited tyrosinase and Dihydroxyphenylalanine (DOPA) oxidation during a dose dependent manner due to the shortage of side-effects, various plant extracts are getting used in various cosmeceuticals creams.

Grape seed extract

Grape seed extract contains proanthocyanidin, which may be a powerful antioxidant. Although, there are not any studies on the topical use of grape seed extract, but oral intake for six months has been found beneficial in patients with melasma during a study conducted by Yamakoshi, et al[48].

Orchid extract

Tadokoro et al. conducted a study in 48 female patients to guage the efficacy of a cosmetic formulation containing orchid extract and compared it to three vitamin C derivative[49]. The authors found that orchid extract has efficacy almost like vitaminC in melasma and lentigines.

Aloe vera extract

Study conducted in animals found that the leaf extract of A. Vera and its active ingredient aloin induced powerful, dose-dependent, physiologically significant melanin aggregating effects resulting in skin lightening via adrenergic receptor stimulation[50]. Burn plant extract is an ingredient of varied market preparations.

Pycnogenol

Pycnogenol obtained from the bark of French maritime pine Pinus pinaster is evolving for its use in hyperpigmentation. Its main constituents are procyanidins, polyphenolic monomers, phenolic or cinnamic acids. It's antioxidant and anti-inflammatory properties and hence scavenges free radicals. Pine extract has been utilized in various market preparations. Oral pynogenol has been found to scale back melasma severity although, studies on topical use are lacking.[51]

Marine algae extract

Cha, et al. evaluated the effect of 43 marine algae extracts on melanin synthesis and located that few extracts evidenced potent tyrosinase inhibitory activity almost like that of positive control, kojic acid without causing any side effects.[52]Hence, these extracts are often used as an ingredient in skin lightening cosmeceuticals.

Cinnamic acid

It may be a phenyl propanoid derivative occurring in plants that inhibits tyrosinase activity as demonstrated in studies conducted on human and guinea pig melanocytes. Study conducted by Tan et al. found that cinnamic acid (2 mmol/L; 0.5 mmol/L) showed greater inhibition of tyrosinase activity compared to hydroquinone (0.5 mmol/L).[53]

Flavonoids

Flavonoids are present polyphenolic compounds with anti-inflammatory, antioxidant, antiviral and anti-carcinogenic properties. Various plant derived flavonoids still under investigation include catechin conjugated with acid (from tea leaves), ellagic acid (from tea, eucalyptus, strawberry, etc.) and aloesin (from aloe tree).

Green tea extracts

Green tea extracts contain polyphenolic compounds that act on various biochemical pathways hence causing anti-inflammatory, anti-oxidant and anti-carcinogenic effects.[54] Epigallocatechin-3-gallate is that the main active ingredient contained in tea. Study conducted by No, et al. has shown that tea extracts cause in vitro inhibition of mushroom tyrosinase, which can be liable for the de-pigmenting effect. However, more in vivo studies are needed to substantiate this action.

Coffeeberry

Coffeeberry extract is understood to possess anti-oxidant properties. However, its de-pigmenting action is yet to be proven. Study conducted by McDaniel et al. in 30 patients with photo-damage showed improvement in hyperpigmentation following 6 weeks of Coffeeberry extract application[55].

Umbelliferon

Umbelliferon (UMB) or 7-hydroxycoumarin, a widespread natural product of the coumarin family, may be a phenolic compound of plant origin, that many biological activities are reported. It occurs in many plants from the Apiaceae (Umbelliferae) family like carrot, coriander. UMB absorbs ultraviolet strongly at several wavelengths (300, 305, 325 nm) and is employed in sunscreens. It's also used as an antioxidant with minimal toxicity. It also has anti-inflammatory activity because it decreases lipid peroxidation. Thus, UMB may be a phytochemical with sun-blocking, antioxidant and anti-inflammatory properties.

Boswellia

Boswellia (BAs) are pentacyclic triterpenes, with strong anti-inflammatory activity, extracted from the gum resins of the tropical tree salai that grows in India and Africa. Until recently, work on Boswellia focussed on the immunomodulatory properties of the resin. In numerous clinical trials and in vitro and in vivo studies Boswellia acids are found to exert significant anti-inflammatory and pro-apoptotic activity[56]. The mechanism of action in hyperpigmentation isn't clear although, it's utilized in many cosmetic products.

N-Acetyl Glucosamine

N-Acetyl Glucosamine (NAG) reduces the quantity of melanin in melanocytes, thereby improving hyperpigmentation and skin tone. It inhibits the conversion of pro-tyrosinase to tyrosinase and also affects the genes involved in hyperpigmentation. During a study conducted by Bessett, 2% NAG was found to scale back facial hyperpigmentation after 8 weeks of application. Its combination with niacinamide has been found to possess greater de-pigmenting effect in various clinical studies[57]. It's a component of varied over-the-counter products used for hyperpigmentation.[58]

Mequinol

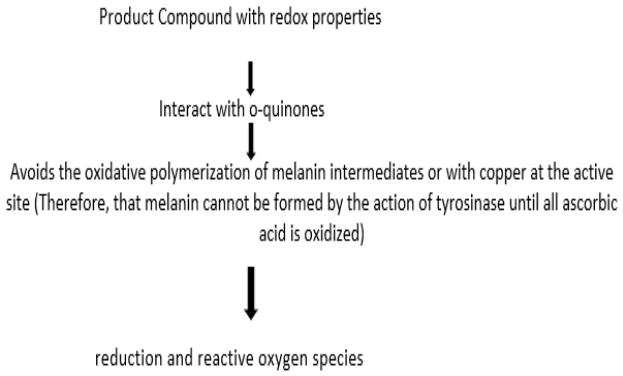
4-hydroxyanisole, hydroquinone monomethyl ether, may be a derivative of hydroquinone. Its mechanism of action is unclear. It acts as a substrate for tyrosinase, thereby inhibiting the formation of melanin precursors[59].
In a randomized parallel group study involving 216 subjects, mequinol 2%/tretinoin 0.01% solution was found to be highly effective and well tolerated treatment for solar lentigines and related hyperpigmented lesions on the forearms and of comparable efficacy for lesions on the face.[60]

It is marketed in USA at a degree of twenty-two together with 0.01% tretinoin. The mixture can cause erythema, burning, pruritus, desquamation, skin irritation, halo hypopigmentation. Combination with sunscreens reduces the incidence of adverse effects.[61]

N-acetyl-4-S-cysteaminylphenol

NCAP may be a phenolic agent that inhibits tyrosinase activity by acting as an alternate substrate. It's more stable and causes less irritation than hydroquinone. Clinical response is clear after 2-4 weeks. Various studies using 4% NCAP have found marked improvement in patients with melasma.[62]

Antioxidants



Depigmentation Effect

Ascorbic Acid (Vitamin C)

Vitamin C (AsA) interferes with the various steps of melanization, by interacting with copper ions at the tyrosinase site and reducing dopaquinone and DHICA oxidation. Melanin are often changed from coal black to light tan by the reduction of oxidizedmelanin.[63] AsA is an efficient reducer, which, at high concentrations, can momentarily retard the melanin-biosynthesis pathway, but never eliminate it. On the contrary, the resultant accumulation of diphenol produces an indirect activation on this pathway when the reductant is totally depleted.[64] However, AsA is very instable, being quickly oxidized and decomposed in solution and, due to its prevalent hydrophilic nature, features a low degree of penetration into the skin. Vitamin C iontophoresis could also be an efficient treatment modality for melisma.[65]

Sixteen women with idiopathic melasma were instructed to use, at night, 5%ascorbic acid cream on one side of the face and 4% HQ cream on the opposite side, for16 weeks. The development was observed on the HQ side with 93% good and excellent results, compared with 62.5% on the vitamin C side. Side effects were present in 68.7%with HQ versus 6.2% with vitamin C.[66]

The numbers of DOPA-positive melanocytes of guinea pigs treated with VC, VE, and cystine were significantly decreased compared with those in VC group. In B16melanoma cells, simultaneous treatment of VC, VE, and N-acetyl-cysteine was the foremost effective to decrease the melanin contents and to inhibit tyrosinase activity.
A multi-clinical, double-blind procedure on therapeutic effect of combination preparation of vitamins E and C

was undertaken as compared with single preparation of vitamin E and vitamin C within the treatment of chloasma or pigmented dermatitis (PCD). Objective data revealed significantly better results with combination treatment in chloasma than vitamin C alone and, in PCD, than vitamin E or C alone. the entire serum lipoperoxide level and its ratio to total serum lipids attended decline within the combination group and decreased significantly in vitamin E group. The sebum lipoperoxide level decreased significantly only within the combination group.[67,68]

Magnesium-L-Ascorbyl-2-Phosphate (VC-PMG)

AsA is quickly oxidized and decomposed in solution and thus isn't generally useful as a depigmenting agent. To resolve that problem, Magnesium-L-ascorbyl-2-phosphate (VC-PMG) was synthesized. VC-PMG is stable in water, especially in neutralor alkaline solution containing boric acid or its salt. VC-PMG is hydrolysed by phosphatases of liver or skin to AsA and thus exhibits vitamin C-reducing activity.[69] VC-PMG significantly suppressed melanin formation on purified tyrosinase or cultured cells and inhibited melanin formation without cell growth suppression on cultured human melanoma cells. Inhibition of melanogenesis was stronger when the activity of melanogenic enzymes was relatively high.

VC-PMG is absorbed percutaneously, stays within the skin, and inhibits tyrosinase activity of melanocytes. The addition of 1% to three 1, 1-methyleneglycol-bis increases the absorption of VC-PMG. in place experiments demonstrated that 10% VC-PMG cream was absorbed into the epidermis which 1.6% remained 48 hours after application. When the10% VC-PMG cream was topically applied to the patients, the lightening effect was significant in 19 of 34 patients with chloasma or senile freckles and in three of 25 patients with normal skin.[70]

Thioctic Acid (Alpha-Lipoic Acid)A disulfide derivative of octanoic acid, it exhibits several biologic effects, which include the quenching of ROS, metal chelation, interaction, and therefore the regeneration of other antioxidants, redox regulation of protein thiol groups, and effects on organic phenomenon andapoptosis.[71] Thioctic acid has been reported to stop UV-induced photo-oxidative damage, mainly through the down-modulation of NF-kappa B activation and to inhibit tyrosinase activity probably by chelating the copper ions.[72]

Dihydrolipoic acid, lipoid acid, and resveratrol reduced microphthalmia-associated transcription factor and tyrosinase promoter activities. Dark skinned Yucatan swine treated with these agents showed visible skin lightening, which was confirmed histological, whereas ultraviolet B-induced tanning of sunshine skinned swine was inhibited using these agents.[73]

Alpha-Tocopherol (Vitamin E)

Alpha-Tocopherol (alpha-Toc) and its derivatives inhibit tyrosinase in vitro and melanogenesis in epidermal melanocytes. The antioxidant properties of alpha-Toc, which interferes with lipid peroxidation of melanocyte membranes and increases the intracellular glutathione content, could explain its depigmenting effect. Alpha-Toc features a simpler and long-lasting antioxidant response. Topical application of alpha-Toc and AsA, in vivo, decreases the tanning response inhibiting the UV-induced melanogenesis and proliferation of melanocytes. an alternate compound is alpha-To-copherol ferulate (alpha-Toc-F), a derivative of alpha-Toc linked by an ester bond to ferulic acid, an antioxidant, which provides stabilization to alpha-Toc, almost like AsA. Alpha-Toc inhibited melanogenesis in cultured normal human melanocytes, although it didn't influence melanin synthesis in enzyme solution prepared as cell homogenates. additionally , alpha-Toc stimulated intracellular glutathione (GSH) synthesis.[74]

Thirty m/ml of alpha-TF dissolved in 150mg/ml of lecithin inhibited melanization significantly without inhibiting cell growth. No significant effect on DOPA chrometautomerase (DT) activity was observed.

- Vitamins as skin-lightening agents. Vitamins are known to enhance skin tone and texture, and that they have found remarkable acceptance among consumers. Most of the leading brands of skin-lightening agents that are available commercially utilize vitamins or their derivatives as ingredients.[75]

Vitamin A:-Vitamin A has been used for a few decades for the removal of spots in Kligman's Treatment. It's used alongside hydroquinone and topical steroids for the treatment of melasma.

Tretinoin acts as a skin-lightening agent by inducing exfoliation. Further, it accelerates the loss of epidermal melanin by increasing the employee turnover and by promoting the proliferation of keratinocytes. However, users of tretinoin suffer from side effects like burning and increased photosensitization. Retinyl palmitate, a derivative of retinoic acid, is employed in skin-lightening cosmetic preparations.[76,77]

Vitamin B

Among the classes of vitamins that comprise B-complex vitamin, two are identified to possess skin-lightening activity.

Vitamin B5 (panthenoic acid): A derivative of vitamin B5, calcium pantetheine sulfonate has been observed to interfere with the glycosylation of tyrosinase, thereby resulting in depigmenting effects. Retinoids and retinoid combination therapy:-Retinoids, that are derivatives of vitamin A, are wont to treat various pigmentation disorders like melasma and post-

inflammatory hyperpigmentation. It causes inhibition of tyrosinase and epidermal melanin dispersion.

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Retinoids and retinoid combination therapy

Retinoids, that are derivatives of vitamin A, are used to treat various pigmentation disorders like melasma and post-inflammatory hyperpigmentation. It causes inhibition of tyrosinase and epidermal melanin dispersion. Retinoids may also interfere with pigment transfer to keratinocytes and accelerate pigment loss by causing the epidermis to be shed more quickly. Retinoids use over prolonged period causes increased stratum corneum compaction and decreased melanin content.

Griffiths, *et al*. used tretinoin in 38 patients with melasma over a 40-week period and observed 68% improvement.[3]However, side-effects in the form of erythema and desquamation were seen in 88% patients.[78]

Studies have demonstrated good improvement in melasma with triple combinataions of corticosteroids, hydroquinone and retinoic acid. Retinoids reduce the atrophy of the corticosteroid and facilitate epidermal penetration and delivery of hydroquinone. However, irritant reaction causes paradoxical hyperpigmentation. Retinoids are not used in the commercial preparations used for hyperpigmentation.

Role of sun-protection

Broad spectrum sunscreens are the cornerstone of hyperpigmentation therapy. Avobenzone absorbs light in the UVA range. However, it is unstable. The stability of avobenzone is increased by combining with oxybenzone. Many cosmeceuticals have physical sunscreens like titanium dioxide, zinc oxide in the same formulation for added benefits

Market Scenario

Skin lightening products include products such as whiteners, fading creams, skin brighteners, and bleaching creams. Skin lightening products reduces melanin from the skin. Consumers use skin lightening products to recover from several skin problems which include age spots, discoloration, acne scars, and freckles. Skin Lightening Products Market is expected to grow at Significant CAGR from 2019 to 2023 as per MRFR Analysis.

The sales of the skin lightening products are anticipated to be driven by various factors. Growing importance for clear and fair complexion among consumers globally is expected to be one of the significant factors fuelling the demand for skin lightening products during the forecast period. Moreover, skin lightening products offer various benefits such as anti-aging, moisturizing, cleansing, UV protection, and antioxidants.

Segmentation

The global skin lightening products market has been segmented based on product type, category, end-user, distribution channel and region.

Based on product type, market has been classified into creams & lotions, cleansers & toners, face masks, scrubs, and others.

Based on category, market has been classified into conventional, and organic.

Based on end user, market has been classified into men, and women

Based on distribution channel, market has been classified into as store-based, and non-store based. Store-based distribution channel has been further segmented into supermarkets & hypermarkets, specialty stores, and others.

The global market has been analyzed for four key regions—North America, Europe, Asia-Pacific, and the rest of the world. The North American skin lightening products market has further been segmented into the US, Canada, and Mexico.

The European market has been classified as the UK, Germany, France, Italy, Spain, and the Rest of Europe.

Asia-Pacific has been divided into China, India, Japan, Australia and New Zealand, and the rest of Asia-Pacific. The skin lightening products market in the rest of the world has been segmented into South America, the Middle East, and Africa.

Global Skin Lightening Products Market, by Product Type

- Creams & Lotions
- Cleansers & Toners
- Face masks
- Scrubs

Global Skin Lightening Products Market, by Category

- Conventional
- Organic

Global Skin Lightening Products Market, by End Use

- Men
- Women

Key Players in the Global Skin Lightening Products Market

- L'Oreal S.A.(France)
- Beiersdorf AG (Germany)

- Unilever PLC (UK)
- Procter & Gamble Company (US)
- Shiseido Company (Japan)
- Estée Lauder Companies Inc.(US)
- Avon Products Inc.(UK)
- Kao Corporation (Japan)
- Lotus Herbals (India)

Cosmeceuticals for hyperpigmentation in leading brands in India

FAIR AND LOVELY MULTIVITAMIN FAIRNESS CREAM	NIACINAMIDE ASCORBYL PHOSPHATE TOCOPHERYL ACETATE ALLANTOIN TITANIUM DIOXIDE	82
HIMALAYA FAIRNESS CREAM	ALOE VERA CITRUS RETICULATA EXTRACT	65
PONDS FAIRNESS CREAM	NIACINAMIDE TOCOPHEROL ACETATE ALLANTOIN TITANIUM DIOXIDE	140
EMAMI FAIRNESS CREAM	LIQUORICE DISTILLATE NIACINAMIDE GRAPE SEED OIL WHEAT GERM OIL METHOXYCINNAMATE TITANIUM DIOXIDE ZINC OXIDE	45

Treatment of skin damaged by skin whiteners

The hyperpigmentation caused by skin whitening agents is not 'curable' and will persist for a lifetime. Using a sunscreen on a daily basis will assist in reducing the damage caused by sun exposure. Emollients are useful for dry and cracking skin and in cases of severe itching; a mild hydrocortisone cream may be used for a short period. Always consult a dermatologist for medical attention when treating skin damaged by long term use of skin bleaches.

Future development

Skin care products are now days most widely used. Mainly herbal cosmetics are generally used as they does not have side effect to the skin. In coming next years it will be expected that there are a lot of chances for the future development of herbal cosmetics. Various herbal and synthetic products are to be used for improving various skin related diseases related to skin darken, acne, wrinkle, sun burn etc. New development will give a better opportunity in the treatment of skin related diseases.

Side effects

Dermatitis with severe drying, cracking of the skin and itching

- Melasma and hyperpigmentation of the skin
- Mercury poisoning
- Fetal toxicity in pregnant women
- Cushing's syndrome
- Liver failure
- Skin cancer

Recommendations

The use of skin whitening agents must be controlled.

- In Sudan, the skin whitening agents sold in unlicensed places and might be affected by the high temperature; therefore the regulatory authority must increase the efforts to protect the people from the side effects of these agents.

- Different methods must be used to increase the awareness of the people about the use and danger of the whitening agents.
- Research should be conducted to study the effect of temperature on the stability and use of the whitening agents

CONCLUSION

The area of skin-lightening agents in an expanding field, with new ingredients being added to the repertoire with every new discovery. Although tyrosinase inhibition is still the most sought after mechanism skin lightening, newer pathways are being identified. It has been noted that ingredients that interfere with the path-ways affecting melanin synthesis and transfer show promise as depigmenting agents. Persistent research into skin lightening has also led to new mechanisms being discovered in recent years.

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