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EFFECTS OF NATURAL COMPOUNDS AS TOPICAL MELANOLYTIC AGENTS AND THEIR MECHANISM FOR THE TREATMENT OF HYPERPIGMENTATION

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ABSTRACT

Skin lightening products are available in the market for aesthetic purposes, and also for the treatment of depigmentation disorders, such as melasma and post-inflammatory hyperpigmentation. They work with multiple stages of melanin synthesis in the skin such as tyrosinase inhibitors, which have been the main enzymes associated in melanogenesis. Melanin is a pigment that determines skin colour and other phenotypic characteristics which also helps to protect the skin from UV radiation. But its excess production and distribution leads to hyperpigmentation and its related disorders. Several treatment strategies have been used to treat abnormal melanin or hyperpigmentation, including chemical peeling, dermabrasion, laser, topical treatment, etc. But skin burn, dyspigmentation, acne, swelling, pain etc. are some of the after-effects found associated with these treatment options. Hence there is a need to develop natural depigmenting agents for the treatment of abnormal skin pigmentation or depigmentation without any side effects. In the present review, we have discussed some of these plants and their active ingredients which have been successfully used for the treatment of hyperpigmentation. It provides an overview of natural whitening agents for the treatment of diminished skin pigmentation by interfering with pigmentary processes.

KEYWORDS: Melanin, hyperpigmentation, Pigmentation, Whitening agents.

INTRODUCTION

Skin-lightening products are commercially promoted for cosmetic purposes. They are also used to treat pigmentary diseases including melasma and post-inflammatory hyperpigmentation. A large amount of melanin production in the skin is affected by widely used whitening chemicals which cause serious health problems. Recently, many topical depigmenting agents have been developed and widely used for the treatment of pigmentary diseases. Depigmenting formulations can be classified as either pharmacological agents or cosmetic agents. Many of them have been identified as competitive inhibitors of tyrosinase, a critical enzyme in the process of melanogenesis. Skin-lightening formulated cosmetics including arbutin, niacinamide, and vitamin C derivatives are the most popular in the cosmetics industry, but consumer satisfaction with their safety and skin-lightening performance is poor.[1,2,3,4]

A triple combination of hydroquinone HQ, tretinoin, and fluocinolone acetonide is also the most successful topical medication used for the treatment of depigmentation. Hence, as a topical depigmenting agent use of HQ has been found for the treatment of abnormal melanin which causes several adverse side effects such as skin irritation, redness, skin cancer, etc. The cosmetics industry has a higher need for melanogenesis inhibitors derived from plants that prevent hyperpigmentation without any toxicological effect.[5,6]

In the cosmetic industry, there are numerous chemically prepared skin whitening products, and many of them do more harm than benefit. The goal of this communication is to uncover the information on naturally occurring skin whitening products that may help reduce hyperpigmentation, as well as natural substances that can help lighten the skin without causing any toxicological side effects. Additionally, the review evaluates the effectiveness of natural skin-whitening agents based on their mechanism of action on melanogenesis and discusses them in terms of their chemical classification. A summary of the current research approach used to assess the bioactivity of compounds is also given. The objective of this review is to offer insightful advice for the creation of secure and efficient depigmenting agents for use in the cosmetics sector.

The present review is dedicated to the updated knowledge of melanocyte biology, including the scientific validation of plant extracts and their mechanisms used since time immemorial in AYUSH. As a result, natural compounds that inhibit tyrosinase may be useful for skin whitening.

BIOSYNTHESIS OF MELANOGENESIS

Synthesis of melanin occurred in melanosomes by melanocytes during the process of melanogenesis, which is a complex process.[7] The production of melanin by the melanocytes defines the color of the skin. It is also playing a vital role to protect skin from UV radiation. Eumelanin and pheomelanin are the two kinds of melanin that are formed after oxidation and hydroxylation of tyrosine by the tyrosinase enzyme which is responsible for the first step of producing melanin. Three enzymes (Tyrosinase, tyrosinase-related supermolecular one (Tyrp-1), and tyrosinase-related protein (Tyrp-2)) are involved in the process of melanogenesis. It begins with the hydroxylation of an essential amino acid L-tyrosine or the direct hydroxylation of L-tyrosine to L-dihydroxyphenylalanine (L-DOPA). L-DOPA quinone is formed when dihydroxyphenylalanine is transformed into L-DOPA quinone (DQ). Tyrosinase is a critical rate-limiting accelerator in melanogenesis it catalyzes each of these steps.[5,8,10,11]

The downstream route of melanogenesis requires the addition of a building block from the treated group to DQ, culminating in DOPA chrome. Finally, eumelanin is formed when indole and quinones undergo chemical modifications. Pheomelanin production requires the presence of aminoalkanoic acid, which interacts with DQ to produce cysteinyl-DOPA, then regenerates into quinoline before polymerizing to form pheomelanin. Melanin is necessary for quinoline production, which subsequently polymerizes into pheomelanin. While melanin is important for skin protection, high production of melanin causes physiological problems.[11,12,13]

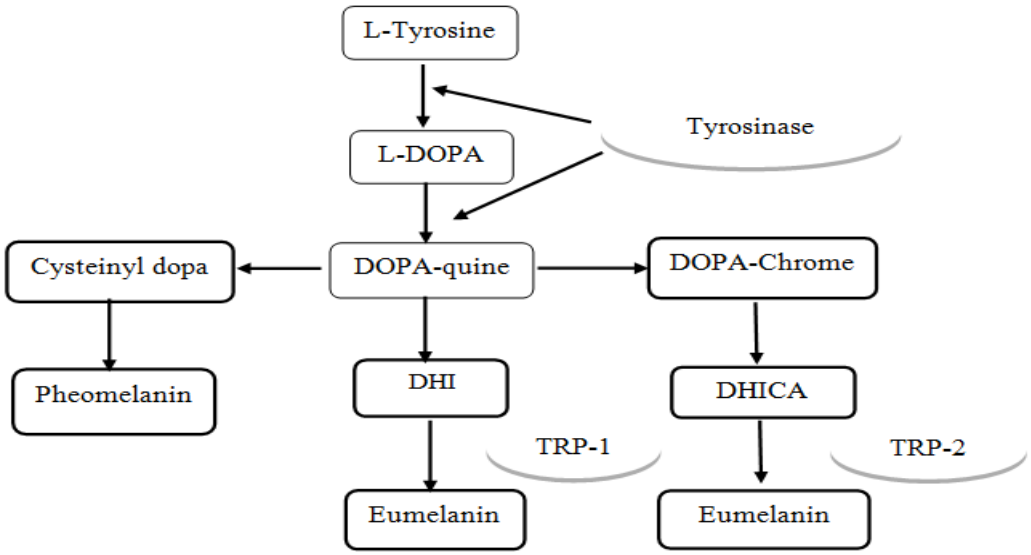

Fig 1: Formation of the two types of melanin and illustration of the purposes of the major enzymes complex.

SIGNALING PATHWAY OF MELANIN PRODUCTION

Melanogenesis is a multi-step process that leads to melanin synthesis. The production of melanin involves a number of signaling pathways, each of which is regulated at different levels. The melanocortin-1 receptor (MC1R), Wnt/-catenin, and tyrosine kinase receptor KIT/stem cell factor SCF) signaling pathways is involved in the regulation of melanogenesis, and they are all downstream stimulated by the master regulator, microphthalmia-associated transcription factor (MITF).[14] According to genetic, biochemical, and pharmacological evidence, MC1R signaling is a critical component of controlling melanogenesis.[15] MCIR is a class A G-protein coupled receptor that is activated by α-MSH and produces cAMP by activating adenylyl cyclase (AC)[12,16] discovered that α-MSH impacts pheomelanin and eumelanin levels through the MC1R.

Melanocortin receptor 1 (MC1R) signaling is the main receptor for the production of melanin. MC1R signaling is influenced by agonists such as alpha-melanocyte-stimulating hormone (α-MSH) and antagonists such as agouti signal proteins (ASP in mice, ASIP in humans) ([17]). When α-MSH hormone binds to melanocortin receptor 1 (MC1R) receptor on the melanocyte membrane, it activates adenylate cyclase (AC), which produces cAMP as an intracellular second message through a G-protein coupled receptor (GPCR). By activating the cAMP response element-binding protein, which is triggered by cAMP, PKA enhances the organic activities of MITF (CREB). Finally, by activating a melanogenesis-related enzyme, MITF efficiently initiates and promotes melanogenesis.

As a consequence, stimulation of the Wnt pathway increases MITF activity, which promotes melanogenesis. The extracellular signal-regulated kinase (ERK) pathway governs melanogenesis by degrading the MITF protein, in contrast to the α-MSH and Wnt signal pathways, which modulate MITF biological activities. According to prior results, ERK activation phosphorylates MITF at serine 73, which is followed by MITF ubiquitination and proteasome-mediated degradation. By lowering MITF

activity, activation of the ERK pathway lowers melanogenesis. Moreover, several studies have shown the importance of c-Kit in the ERK pathway.[18]

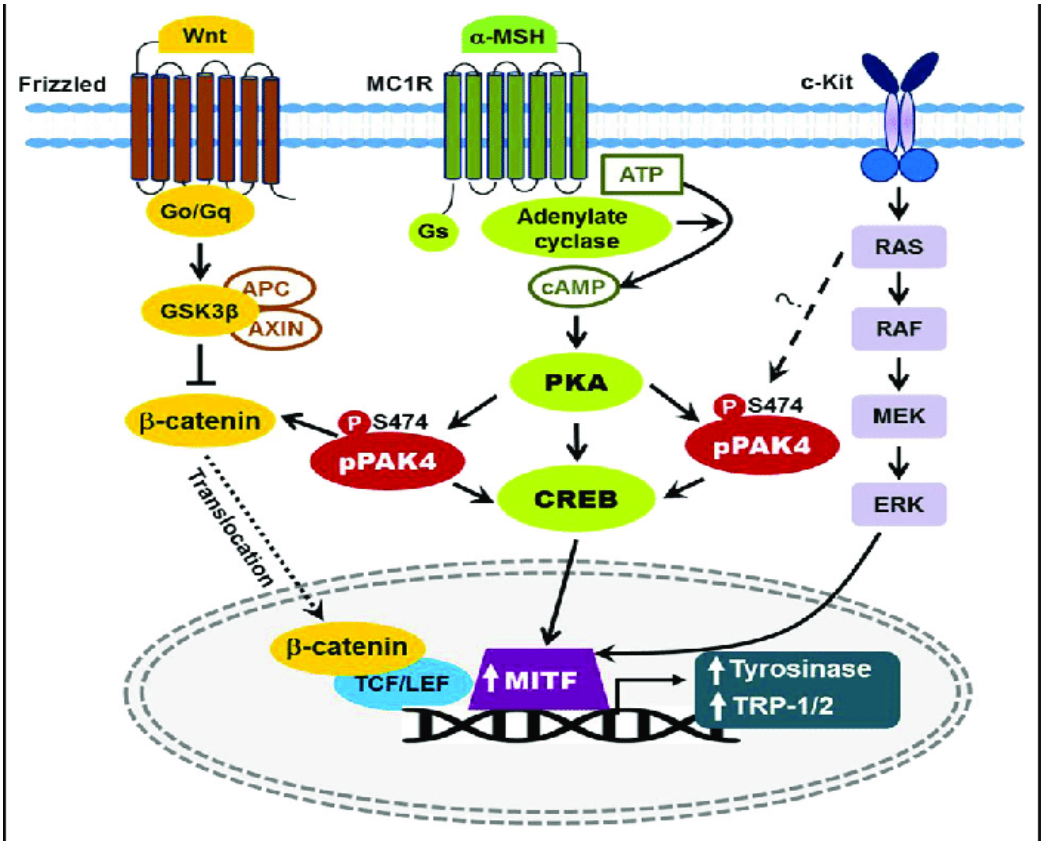

Fig 1: Melanin synthesis in melanocytes is regulated by a number of molecular mechanisms. The MITF transcription factor, which is controlled by a variety of critical signaling pathways, including α-MSH/MC1F (green), KIT/SCF (blue), and Wnt/frizzled, regulates genes encoding particular melanogenic enzymes, such as TYP, TRP1 and TRP2 (red). The cAMP/PKA, RAS/MEK/ERK, and -catenin pathways all play a role in signal transduction. cAMP, (cyclic AMP), MEK, MAPK/ERK kinase; Wnt, wingless related integration site; GSK 3, glycogen synthase kinase-3; AXIN, axis inhibitor; APC, adenomatous polyposis coli; SCF, stem cell factor; MC1R, melanocyte-specific melanocortin-1 receptor; α-MSH, melanocyte-stimulating hormone.[5]

HYPERPIGMENTARY DISEASES

The synthesis and distribution of melanin depend on the specialized cells called melanocytes through the process of melanogenesis. It involves various steps from the development of an embryo, synthesis of melanin, and transfer of melanosomes to neighboring keratinocytes.[19] The significance of these steps and their mechanisms is evident in pigmentation defects in the form of hyperpigmentation and hypopigmentation. When the skin exposes to UV radiation or other endo or exogenous allergen causes the formation of inflammatory mediators, erythema, and excess production of melanin which ultimately results in a pigmentation disorder called hyperpigmentation.[20] Post-inflammatory hyperpigmentation, maturational dyschromia, melasma, solar lentigines, ephelides, and lichen planus pigmentosus are the various diseases of hyperpigmentation. Melasma is the common disorder of hyperpigmentation affecting thousands of individuals worldwide and about 90% are females. Melasma is also known as 'the mask of pregnancy because the condition is often associated with pregnant women. Hyperpigmentation refers to the darkening of the skin in patches. The size and symmetry of the hyperpigmented patches or macules are different in different forms of hyperpigmentation diseases. Skin hyperpigmentation started from the sun-exposed areas of the body including the face, neck, trunk, forehead, etc.[21]

AVAILABLE TREATMENT MODALITIES FOR HYPERPIGMENTATION

Treatment for hyperpigmentation seems to be challenging as there is no completely satisfactory treatment available and also the existing depigmentation agents have different efficacy. Generally, the target of treatment includes reduction of pigment either topically or physically, photoprotection, and elimination of provoking factors.[21,22] Treatments for hyperpigmentation include the use of sunscreen, chemical peel, cosmetic camouflage, dermabrasion, topical treatment, treatment with laser, etc. In chemical peeling, a chemical solution is applied to the skin which makes it exfoliate and ultimately peel off. Cosmetic camouflage is the application of makeup including

cream, and powder to conceal colour. Dermabrasion is the process of removal of upper skin, non-chemically with abrasive tools. Laser of shorter or longer wavelengths can also be used to treat pigmented skin. Topical treatment includes the application of different chemical agents such as kojic acid, hydroquinone, arbutin, etc. which can be used either alone or in combination.

EFFECTS OF A PLANT INGREDIENTS ON HYPERPIGMENTATION

Natural extracts are widely employed in cosmetic compositions because of the synergistic effect they have on each other. Arbutin, kojic acid and its derivatives, hydroquinone, vitamin C, and arbutin are some of the most often utilized agents. In addition to mulberry, Artocarpus, and orchid extracts, cosmetics also use them. In terms of tropical hyperpigmentation treatments, hydroquinone is regarded as the best. Dark-skinned individuals have reported skin irritation, exogenous ochronosis, and contact dermatitis as side effects of this product. Using corticosteroids over an extended period of time might have adverse local or systemic consequences. In order to find new depigmenting agents, researchers looked into natural plant extracts and discovered a slew of useful substances (Table: 1).[21]

Table 1: Some naturally occurring tyrosinase inhibitors and their mechanism.

Topical agent	Source	Depigmenting Mechanism	References
Tyrosine inhibitors			
Octaphlorethol A OPA)	*Ishige foliacea*	OPA downregulated tyrosinase activity	[23]
Linoleic acid	Spent coffee grounds	Downregulation of cAMP/PKA, PI3K/AKT and MAPK signaling pathway	[5,23]
Hinokitiol	cupressaceous plants	Downregulatory role in melanogenic signaling through AKT/mTOR signaling.	[24]
Kojic acid,	Acetobacter, Aspergillus, and Penicillium	Chelating agent	[25]
Hydroquinone	Cranberries, blueberries, wheat and pears, Derivative of benzene	Alternative substrate	[2,5]
Arbutin	Pear, cranberry, blueberry, bearberry shrub	Tyr, DHICA polymerase	[1]
Cinnamic acid	*Cinnamomum cassia*	Reversible inhibitor of tyrosinase	[12]
Shogaol	Ginger	Activates ERK pathway, leading to reduced expression of MITF	[26]
Cardamomin	*Alpinia katsumadai*	Inhibits the GSK-3β pathway	[27]
Azelaic acid	Pityrosporum ovale	Competitive inhibitor of tyrosinase	[28]
Prunus armeniaca	3,4-Dihydroxy benzoic acid, quercetin	Antioxidant activity	[22]
Berberine	Berberis aristate	Tyrosinase inhibitor	[22]
Glabridin, glycyrrhizin	*Glycyrrhiza glabra*	Free radical scavenger	[22]
Gallic acid	Gallnut, lacquer tree, tea	Inhibition of PI3K/AKT, MEK/ERK and Wnt/β-Catenin signaling to downregulate MITF	[29]
Hesperidin	Citrus fruits	Inhibit melanin synthesis, Activation of ERK ½ and downregulation of MITF	[5]
Circumin	*Curcuma aromatica salisb.*	Inhibition of tyrosinase expression	[30]
Soybean extracts	Soybean	Inhibition of tyrosinase expression and activity	[31]
Isoorientin	*Gentiana veitchiorum* Hemsl. Flowers	*Gentiana veitchiorum* Hemsl. Flowers	[27]
Eugenol	*Ocimum sanctum*	Tyrosinase activity, Inhibition of pigment translocation	[32]
Sesamol	Sesame	Regulation of melanin- related signal transduction	[33]
Quercetin	*Sophora japonica*	Competitive inhibition	[34]
Resveratrol	Grape, *polygonum cuspidatum*	Alternative substrate	[35,36]
Ganodermanondiol	*Ganoderma lucidum*	Inhibition of tyrosinase expression	[25, 37]

- **Arbutin**

Arbutin is a naturally occurring hydroquinone beta-D-glucopyranoside derivative, which is derived from the bearberry plant. It is commonly used in the production of cosmetics agents and is known to exhibit depigmenting activity at nontoxic concentrations. A non-cytotoxic quantity of tyrosinase and the polymerase of DHICA prevents the enzyme from being synthesized and expressed. Arbutin is an excellent topical therapy for hyperactive melanocyte-induced cutaneous hyperpigmentation. It has been shown that arbutin stops the action of 5,6-dihydroxyindole-2-carboxylic acid polymerase and slows down the action of tyrosinase without changing the expression of its mRNA.[38]

- **Flavonoids**

Antioxidant and calming properties make flavonoids popular ingredients in cosmetics. Plants with active qualities have more than 5000 flavonoids to choose from, making them the biggest collection of compounds. Flavonoid is well recognized for their antiradical actions on the skin. Radiant anion radicals are formed in the presence of phenol groups with a high reduction potential. Flavonoids' ability to scavenge free radicals depends on their structure and physicochemical qualities. Antioxidant-fighting flavonoids present in green tea, red wine grapes, and Mediterranean pine bark have been shown to be particularly efficient in protecting the skin from free radicals. Vitamin C is essential for collagen production. Vitamin C depletion in the skin is mostly due to the action of free radicals in the epidermis.[39]

- **Kojic acid**

Many species of Aspergillus and Penicillium produce kojic acid (5-hydroxy-2-hydroxymethyl-4H-pyran-4-one), an antibiotic. Its ability to chelate and stop the activation of nuclear factor-kappa B (NF-B) in keratinocytes has both been linked to its hyperpigmenting effect.[40]

- **Aloesin**

Aloesin is a compound isolated from *Aloe vera* plant. According to research, aloesin inhibits the tyrosine hydroxylase and DOPA (3,4-dihydroxyphenylalanine) oxidase activities of tyrosinase from normal human melanocyte cell lysates in a dose-dependent manner.[36] When aloesin was applied topically to a human volar forearm that had received 210 mJ of UV radiation four times per day for 15 days, pigmentation was suppressed in a dose-dependent manner.[11] Aloesin and arbutin were found to work together to reduce the synthesis of melanin through a combination of noncompetitive and competitive tyrosinase inhibitions.[41]

- **Niacinamide**

Niacinamide is a biologically active form of niacin (vitamin B3) that is present in a variety of root vegetables and yeasts. It is also a crucial precursor of the nucleoside analogues NADH and NADPH (nicotinamide adenine dinucleotide phosphate). The variety of cosmetic advantages, including barrier enhancement seen with topical niacinamide usage, may be due to the great number of cellular enzymatic processes in which these cofactors engage.[42] In studies using cocultures of human keratinocytes and melanocytes, niacinamide has been found to prevent the transfer of melanosomes from melanocytes to keratinocytes. In clinical investigations, niacinamide administered topically showed a reversible reduction in hyperpigmented lesions and an increase in skin lightness compared to vehicle alone. In a different clinical study[43], it was also shown that topical niacinamide reduces collagen oxidation products and improves the yellowing or sallowness that comes with age.

- **Hesperidin**

Citrus fruit membranes and peel contain large amounts of the bioflavonoid hesperidin. Hesperidin has a strong inhibitory effect on melanin formation without cytotoxicity, according to studies by Zhu and colleagues. In this study, dose-dependent tyrosinase activity of hesperidin showed melanoma B16 cells and primary human melanocytes.[44] Hesperidin was also discovered to guard against collagen oxidative degradation and UVA-induced fibroblast damage.[45] As a result, hesperidin may help lighten skin by improving general skin tone and having anti-yellowing properties.[46]

- **Mulberry**

Tyrosinase activity has been demonstrated to be inhibited by dried mulberry (*Morus alba*) leaves (85% ethanol extract). In addition, various phenolic flavonoids from its leaves, including gallic acid and quercetin, as well as fatty acids like linoleic acid and palmitic acid, have been extracted. The active ingredient, mulberroside F (moracin M-6, 30-di-O-beta-D-glucopyranoside), inhibited the tyrosinase enzyme's activity as well as the production of melanin in melano-a cells. According to Lee et al.[47] and Katsube et al.[48], this substance also demonstrated superoxide scavenging activity, which is important for the prevention of auto-oxidation. This suggests that *Morus alba* could be used as a way to whiten the skin in cosmetics.

CONCLUSION

In conclusion, even while pharmacological depigmenting treatments for hyperpigmentation, such as HQ cream, tretinoin cream, and TCC, have been found to be beneficial, negative side effects are frequently experienced. The majority of these adverse reactions were minor and brief, but a high incidence of unpleasant effects may lower patient compliance and satisfaction. Thus, there is an urgent need for topical treatments that are efficacious but have fewer side effects.

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