

**HYPERPIGMENTATION, CAUSE & TREATMENT CONSIDERATIONS: A REVIEW****Rahul Jaiswal\*, Dr. Amit Kishor Srivastava, Gulab Chandra, Dr. Rohit Mohan, Dr. Amresh Gupta and  
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DOI: <https://doi.org/10.17605/OSF.IO/UBR3C>

Article Received on 25/05/2021

Article Revised on 14/06/2021

Article Accepted on 04/07/2021

**ABSTRACT**

Disorders of facial hyperpigmentation, including melasma, solar lentigines and postinflammatory hyperpigmentation are most common cutaneous situations which can have an enormous impact on patients' quality of life and often prove hard to treat. Facial hyperpigmented problems are a familiar complaint in the adult population of all races. These disorders show a localized rise in pigmentation, which may be due to an increased number of melanocytes (e.g. solar lentigo) or to a rise in melanin pigment (e.g. melasma and PIH). Hyperpigmentation of skin is due to many factors. UV exposure, in inclusion to oxidative stress, raised inflammatory mediators stimulating melanogenesis. This review briefing addresses the causes of skin hyperpigmentation and extensively summarizes the status of many compounds like synthetic as well as an herbal extract currently used in skin-lightening cosmetics.

**KEYWORDS:** Hyperpigmentation, Postinflammatory Hyperpigmentation, Melasma, Melanogenesis, Treatment.**INTRODUCTION**

Hyperpigmented situation such as post-inflammatory hyperpigmentation (PIH), melasma and solar lentigines influence an extremely large portion of the adult population. These disorders show a localized rise in pigmentation, which may be due to a rising number of melanocytes (e.g. solar lentigo) or to a rise in melanin pigment (e.g. melasma and PIH). PIH has increased epidermal melanin and also the melanin accumulation in dermal macrophages. Skin pigmentation is the outcome of different biochemical and cellular processes, as well as regulation of melanogenesis by way of microphthalmia-associated transcription factor (MITF-M), melanocyte homeostasis and melanin creation by way of tyrosinase and other melanogenic enzymes and melanosome transfer.<sup>[1,2]</sup> Melanin keeps safe the skin from the damages caused by exposure to UV radiation. The interference in the normal homeostasis of melanin synthesis in an individual conduct to skin pigmentation disorders.<sup>[3]</sup>

The world is becoming a Global village where humans are completely engaged in their busy schedule's activity giving less priority to their health and especially in skin care. Event of skin disorders are circulated every year and the most common includes those disorders relating to skin pigmentation, modernization and changes in lifestyle and diet also raise the sensitivity to skin disorders.<sup>[4]</sup> The human skin colour is affected by both the distribution and quantity of melanocytes. Difference in type and basal epidermal melanin quantity is a major

factor that contributes to the inborn coloration of human skin.<sup>[5]</sup> Melanin is important to save the skin from the damages caused by exposure to UV radiation. The interference in the normal homeostasis of melanin synthesis in an individual conduct to skin pigmentation disorders, that's why a proper understanding of the skin pigmentation and the cure of such disorders which are important for its treatment and to initiate different strategies for its prevention and cure. The explore for novel lightening agents has led to the examination of natural plant extracts and many of the active chemical constituents of plants may be more potent inhibitors of melanin formation.<sup>[4,6]</sup>

In this review, our aim was to examine the mechanism of action, causes of hyperpigmentation and the supporting clinical studies of various option used depigmenting agents and therapy in cosmeceuticals.

UV radiation stimulates keratinocytes to secrete a small peptide hormone derived from proopiomelanocortin (POMC) and  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH) which binds to melanocortin 1 receptors (MC1R) expressed on the surface of melanocytes, as well as melanogenesis by way of multiple signaling pathways, developing from cAMP, protein kinase A (PKA), cAMP response element-binding protein (CREB), and microphthalmia-related transcription factor (MITF) activity. MITF is a lead transcription factor controlling the transcription of melanogenic enzymes, which are tyrosinase, tyrosinase-related protein-1 (TRP-1), and

tyrosinase-related protein-2 (TRP-2). As tyrosinase can be endogenously broken down by proteasomes, keep an ideal poise between tyrosinase synthesis and breakdown is mandatory for the management of skin, eye and hair pigmentation.

Mitogen-activated protein kinases (MAPKs) are play important role in hyperpigmentation and its three subtypes: stress-activated protein kinases (SAPKs)/cJun NH2-terminal kinases (JNK), p38, and extracellular signal-regulated kinases (ERKs). JNK and p38 kinases are restorative by pro-inflammatory cytokines and environmental cause stresses like exposure to UV irradiation, hydrogen peroxide, and heat, resulting in DNA damage. Melanogenesis is regulated by MAPKs, by MITF being switched on by p38 phosphorylation. As opposed to, ERK switch on inhibits melanin synthesis with downregulating MITF expression. Consequently, the suppression of the ERK signaling pathway induces upregulation of tyrosinase activity and cell differentiation, stimulating melanogenesis. Additionally, the MAPK signaling pathway adjusts nuclear factor E2-related factor 2 (Nrf2), which is a major transcription factor managing the antioxidant reply to, save skin cells from oxidative stress, such as that occurring on the exposure of melanocytes to UV radiation.<sup>[7]</sup> And a synopsis of melanogenesis pathways are represented in Fig.1.

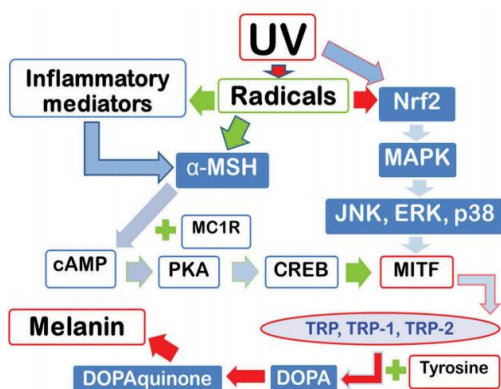


Figure 1: Process of melanogenesis.

**Causes of hyperpigmentation**

**Postinflammatory hyperpigmentation**

Postinflammatory hyperpigmentation (PIH) is an acquired hypermelanosis of the epidermis or dermis that happen with cutaneous inflammation or injury. While this pigmentary change can be detected in all skin types and it most often affects individuals with Fitzpatrick skin types (FST) IV–VI due to the raised reactivity of melanocytes within the skin.<sup>[8,9]</sup> Postinflammatory changes can found both in the dermis and epidermis, in the epidermal form of hyperpigmentation, there is grows transfer to keratinocytes and/or melanin production. In dermal PIH, an injured basement membrane permit melanin to enter the dermis, where it is phagocytosed by dermal macrophages, mention to as melanophages. Melanin within dermal melanophages may continue for

years.<sup>[10,11]</sup> As the skin in darker patients convalescent from an acute inflammatory disease, it may become hypopigmented (known as postinflammatory hypopigmentation) or hyperpigmented (PIH). Lightening or darkening of the skin is related to numerous primary disorders, including but not little to discoid lupus erythematosus, seborrheic dermatitis, tinea versicolor, sarcoidosis and atopic dermatitis.<sup>[12]</sup> Postinflammatory hyperpigmentation presented in (Fig. 2).



Figure 2: Postinflammatory hyperpigmentation (multiple, small, brown, coalescing macules on the beard area).

**Melasma**

Melasma (a term derived from the Greek word melas, meaning black) is an ordinary acquired hypermelanosis that occurs exclusively in sun-exposed areas, occasionally on the neck and forearms and mostly on the face. Melasma is more popular in women and men have been reported to represent 10% of cases. Melasma is more obvious during and after time of sun exposure. The exact cause of melasma remains elusive, but the two major factors implicated in its etiopathogenesis which are sunlight and genetic predisposition (Fig. 3). The quantity of hyperpigmented patches may range from one single lesion to multiple patches discovered usually symmetrically on occasionally the V-neck area and the face.<sup>[14,15]</sup>



Figure 3: Melasma of the forehead.

**Ephelides and lentigines**

Ephelides and lentigines are the most common manifestation of sun exposure in white patients and less seems in those with skin colour and ephelides, or freckles, are the outcome of grew photoinduced melanogenesis and transport of an grew number of fully melanized melanosomes from melanocytes to keratinocytes. Ephelides caused by sun-exposed areas of the body, mostly the face, upper trunk and dorsal hands. They may increase in distribution and number and

appear a tendency for confluence, but they can fade over time, and some ephelides may represent a subtype of solar lentigo.<sup>[16,17]</sup>

Lentigines are mostly in white subjects, but also occur in Asians. Solar lentigines are 3 to 2-cm well-circumscribed, oval, round or irregularly shaped patches or macules that differ in a range of colour from tan to dark brown. They are caused by sun-exposed areas, predominantly the dorsal aspects of the hands and forearms, back, upper chest and face.<sup>[18]</sup>

### Maturation dyschromia

Darkening of facial skin tone, even outside of large sun exposure, can be seen in mature dark skin. Maturation dyschromia, or a generally uneven tone, can be reported as diffuse hyperpigmentation that generally found on the lateral forehead and cheekbones (Fig. 4). One survey found that uneven skin tone was a main complaint in more than one-third of black women.<sup>[19]</sup> These changes in skin tone may occur from chronic sun exposure with many years.<sup>[20]</sup>



**Figure 4: Maturation dyschromia: hyperpigmented.**

### Periorbital hyperpigmentation

Periorbital hyperpigmentation (POH), also known as periorbital melanosis, periocular hyperpigmentation, dark circles, infraorbital darkening, infraorbital discoloration, or idiopathic cutaneous hyperchromia of the orbital zone, is most common situation encountered in dermatology practice.<sup>[21-24]</sup> Periorbital hyperpigmentation is an ill-defined entity that give out like bilateral round or semicircular homogenous dark brown or brown pigmented macules in the periocular region.<sup>[21,22]</sup> Sometimes it can affect an individual's confidence, emotion and change the quality of life (Fig.5). There is a lack of data about the incidence and generality of POH due to its lack of reasonable etiological explanation and transitory nature. According to Indian studies, it was getting going that POH was most popular in the age group of 16 to 25 years (i.e., 95 out of 200 patients [47.50%]). Among the 200 patients' reports, it was more popular in women (162 [81%]) than men and the majority of the affected women (91 45.50%).<sup>[25]</sup>



**Figure 5: Periorbital hyperpigmentation.**

### Riehl Melanosis

Riehl melanosis, or pigmented contact dermatitis, is distinguished by a brown-grey colour secondary to dermal melanin to gather. Its services sites of application of contactants, specifically cosmetics and cases are generally initiated with mild pruritus and erythema, followed by a diffuse-to-reticulated hyperpigmentation. Pigmentation differs, frequently dependent on to the causal agent. Mostly it can be brown or brown-grey, and can also have blue and red colour. The diagnosis of Riehl melanosis is aided with cosmetic series, closed patch testing to the standard series, patients' personal products and fragrance series. If reports are negative or equivocal, then the repeated open application test or provocative use test or can be administered in the diagnosis process of Riehl melanosis.<sup>[26]</sup>

### Exogenous Ochronosis

Ochronosis is the yellowish-brown discoloration seen on microscopic observation of tissue.<sup>[27]</sup> Even so, microscopically, tissues have a unique blue-gray discoloration and exist in one of two forms which are exogenous or endogenous.<sup>[28]</sup> Exogenous ochronosis (EO) does not present with the systemic manifestations of endogenous ochronosis (alkaptonuria) and is little to the cutaneous locating where the topical agent has been applied. EO mostly introduce as hyperpigmented macules or papules on photo exposed zone in patients with a past of long term application of skin-lightening products which are used for treatment of melasma. The asymptomatic hyperpigmentation mostly found over bony prominences, especially the face, extensor surfaces neck and back (Fig. 6).<sup>[29]</sup>



**Figure 6: Exogenous Ochronosis: hyperpigmented grey macules over the malar distribution.**

### Hori naevi

Hori naevi, or acquired bilateral naevus of Ota-like macules, are a usual dermal melanocytic hyperpigmentation in Asians, primarily Japanese and



women in age of 20 to 70 years old. They are distinguished by blue-grey to grey brown macules primarily in the zygomatic area and less usual on the forehead, upper eyelids, temples and root and alae of the nose (Fig. 7).<sup>[30]</sup> In the eye and oral mucosa have not any effect of hori naevi. Sometimes hori naevi may be misdiagnosed and results seem like a character of melasma, lentiginos or ephelides.<sup>[31,32]</sup>



**Figure 7: Hori naevi: small discrete greyish-brown macules over the malar eminence.**

#### Erythema Dyschromicum Perstans

Erythema dyschromicum perstans (EDP) is a disease of pigmentation that is distinguished by patches or gray or blue-brown macules in individuals simultaneously Fitzpatrick skin types III-V.<sup>[33]</sup> The lesions are mostly dispensed symmetrically on both sun- and non-sun-exposed areas including the trunk (69.1%), neck, limbs and face (Fig.8). The EDP is a chronic progressive disease which can introduce similarly to some other pigmentation disorders like lichen planus pigmentosus (LPP), and thereby reports in troubles to establish a diagnosis and therapy.<sup>[34]</sup>

The exact etiology of the EDP is unknown and harm to melanocytes and basal cell keratinocytes that is detected with EDP is postulated to be due to an unusual immune response to antigens with a predominance of CD8+ T lymphocytes in the dermis and HLA-DR+, intercellular adhesion molecule 1+ keratinocytes in the epidermis.<sup>[35]</sup>



**Figure 8: Erythema dyschromicum perstans: circular, grey-brown patches on the neck.**

#### Dermatosis Papulosa Nigra And Seborrhoeic Keratoses

Dermatosis papulosa nigra (DPN) is a usual manifestation diagnosed initially in African-American, Afro-Caribbean and sub-Saharan African black patients, but it is also seen in other races and the disorders and pathogenesis is unknown. DPN tends to have an earlier

age of onset than that of seborrhoeic keratoses, but or else is alike and think about a variant of seborrhoeic keratosis. DPN introduce as 1- to 5-mm pigmented papules that are spread bilaterally across the malar eminences, forehead and, on the neck, less often, back and chest (Fig. 9). Commonly the lesions are asymptomatic but can sometime pruritic or irritated. The distinctive diagnosis includes acrochordons, seborrhoeic keratoses, melanocytic naevi, lentiginos, verrucae and other adnexal tumours. Treatment is mostly performed for cosmetic purposes and should be exercised with great care and modalities include curettage, snip excision, electrodesiccation, laser destruction and light cryotherapy.<sup>[36,37]</sup>



**Figure 9: Dermatosis Papulosa Nigra.**

#### Lichen Planus Pigmentosus

Lichen planus pigmentosus (LPP) is contemplate to be some variant of lichen planus (LP) by mostly all authors considering their alike immunopathogenesis and irregular coexistence in some patients. It is distinguished by chronic acquired dark brown to gray macular pigmentation with an unclear pathogenesis. It is not influenced by only sun-exposed areas of the neck and face, but also sun-protected flexural skin like as axillae and inguinal areas. It is most common in middle-aged patients who have dark skin and is few in Caucasians and LPP causes emotional depression by its aesthetic look and chronic nature (Fig.10). It may also be related to others disorders are endocrinopathies, hepatitis C virus induced liver disease and autoimmune diseases as well as other variants of the LP.<sup>[38-40]</sup> In India, LPP is caused by topical application and use of mustard oil containing a photosensitizer (allyl-thiocyanate), amla oil, henna, hair dye, cold cream, and environmental pollution.<sup>[39,40]</sup>



**Figure 10: Lichen planus pigmentosus: (a) on the face and (b) neck.**

### Acanthosis nigricans

Acanthosis nigricans (AN) is a cutaneous disorder of many aetiologies, distinguished by symmetric, dark, coarse, thickened, velvety appearing plaques commonly distributed on the neck, axillae, inframammary and groin zone antecubital and popliteal fossae and histopathology reveals papillomatosis and hyperkeratosis of the skin.<sup>[41]</sup>

The pathophysiology of AN is a multifactorial stimulation of proliferation of dermal fibroblasts and epidermal keratinocytes. Insulin-like Growth factor (IGF) and Insulin are proposed as promoters of this proliferation. Additional proposed mediators include fibroblast growth factor receptor (FGFR) and tyrosine kinase receptors like epidermal growth factor receptor (EGFR). These receptors are situated on keratinocytes and stimulate growth.<sup>[42]</sup>

### Actinic lichen planus

Actinic lichen planus is few and far between clinical variant of lichen planus, which mainly affects exposed areas. Actinic lichen planus classified in four clinical subtypes which are the annular, classic plaque-type, dyschromic, and pigmented forms. The main form is the annular type, which made up erythematous brownish plaques with an annular configuration and tends to be along by hyperpigmentation.<sup>[43]</sup> ALP typically found in young adults and/or children in all genders. The lesions mostly included of red-brown plaques with an annular configuration, but melasma-like hyperpigmented patches also found.<sup>[44]</sup> Lesions are as usual photodistributed

involving areas of the face, forehead, and neck and dorsal surfaces of the upper extremities. Lesions typically appear throughout the summer months and may better on one's own in the winter.<sup>[45,46]</sup>

### Treatment of Hyperpigmentation

Treating aesthetically unpleasant skin problems using synthetic and naturally derived chemical constituents, including herbal extracts is obtaining the interest amongst consumers due to their perception of safety. Skin-lightening agents, of which phenolics are the commonly used, can be incorporated into a formulation as either a single compound or a combination of actives. The use of herbal extracts containing several actives acting synergistically to upgrade the efficacy is also encountered in cosmetic formulations, with such actives proving highly advisable candidates.<sup>[47-49]</sup>

Topical treatments the way old and new of hyperpigmentation because melasma is a disorder of pigmentation, topical treatments are mainly aimed at disrupting the enzymatic processes of pigment production within the melanocytes. Tyrosinase is the rate-limiting enzyme in the mechanism of melanin production, changing L-tyrosinase to L-3,4-dihydroxyphenylalanine (L-DOPA), and is the major target for many of the agents that have been developed for melasma.<sup>[50]</sup> Many skins-lightening agents which have multiple effects leading to a decrease in melanization. The major compound and its mechanism of action are shown in Table 1.

**Table 1: Compounds under investigation to reduce cutaneous hyperpigmentation.**<sup>[51]</sup>

Mechanism of Action	Compound
Tyrosinase inhibition	Hydroquinone Mequinol Azelaic acid Arbutin and deoxyarbutin Licorice extract Rucinol Resveratrol 4-hydroxy-anisole 2,5-dimethyl-4-hydroxy-3(2H)-furanone N-acetyl glucosamine
Stimulation of keratinocyte turnover	Retinoids
Reduction in melanosome transfer	Retinoids, soybean trypsin inhibitor
Interaction with copper	Kojic acid Ascorbic acid
Inhibition of melanosome maturation	Arbutin and deoxyarbutin
Inhibition of protease activated receptor 2	Soybean trypsin inhibitor
Inhibition of plasmin	Tranexamic acid
Reduction of alpha melanocyte-stimulating hormone-induced melanin production	Beta-carotene

### Utilities of compounds in skin hyperpigmentation

Cosmeceuticals are cosmetic products that focus to deliver physiologically pertinent benefits without the incorporation of prescription drugs.<sup>[52]</sup> Cosmeceuticals are applicable in the problem of hyperpigmentation,

including melasma, to goal hyperactive melanocytes and impede fundamental steps in melanogenesis. Cosmeceuticals have about increased interest with the public and dermatological community, although their effectiveness and modes of actions are not always fully

understood. We discuss 10 of the most commonly used cosmeceuticals for melasma and hyperpigmentation disorders.<sup>[53]</sup>

#### Arbutin

Arbutin is the naturally occurring  $\beta$ -D-glucopyranoside derivative of hydroquinone that is obtained from the bearberry plant, and deoxyArbutin is a dehydroxylated derivative of arbutin. Arbutin is hydrolyzed in the skin to hydroquinone and develop skin lightening by inhibition of tyrosinase.<sup>[54]</sup> A cream containing 2.51% arbutin was used twice a day for 8 weeks and lightening and skin tone homogenization was observed in 66% of patients.<sup>[55]</sup>

#### Hydroquinone

Hydroquinone (1,4-dihydroxybenzene) is the excellent compound for the treatment of facial hyperpigmentation. Hydroquinone inhibit the tyrosinase thus reducing the formation and melanization of melanosomes.<sup>[56,57]</sup> Being an oxidizing agent, hydroquinone altered from white to brown at which time its necessary to be discarded as it is ineffective.<sup>[58]</sup> In a simple trial, 4% hydroquinone and broad-spectrum sunscreen was shown to be effective in the treatment of melasma, with 89.5% of patients showing good to excellent responses.<sup>[59]</sup>

#### Azelaic Acid

Azelaic acid is a 9-carbon dicarboxylic acid obtained from *Pityrosporum ovale*, which is cytotoxic and antiproliferative to melanocytes. Its efficacy as a weak, reversible, competitive inhibitor of tyrosinase. Second possible mode of action includes reduced free radical formation. It has been useful in the melasma and PIH disorders. In the patient of melasma, 20% azelaic acid was found to be as effective as 4% and superior to 2% hydroquinone without side-effects.<sup>[60]</sup>

#### Liquorice extracts

Liquorice (*Glycyrrhiza glabra* L) is a perennial plant belonging to Fabaceae family, which have sweet-tasting root. The extracts of liquorice roots save the skin against injuries caused by oxidative stress. Many bioactive natural products are present in liquorice extracts.<sup>[61,62]</sup> Liquorice extract has anti-inflammatory characteristic and carry glabridin, which inhibits tyrosinase in *in vitro*.<sup>[63]</sup> In a split-face trial, a 20% liquiritin cream was found to be efficacious at 4 weeks in epidermal melasma disorder.<sup>[59]</sup>

#### Retinol

Vitamin A and its derivatives (retinoids) are widely used as topical formulations anti-aging. Retinoids make an effort their effects on pigmentation through a number of mechanisms which include: inhibition of matrix metalloproteinase activation, decreased melanosome transfer, inhibition of oxidative stress and through the rebuilding of the extracellular matrix.<sup>[64]</sup> Retinoids are inhibited tyrosinase related proteins 1 and 2 and inhibit tyrosinase transcription, interrupt melanin synthesis.<sup>[65]</sup>

Available retinoids (retinoic acid, tretinoin, adapalene, tazarotene) used in the treatment of melasma and PIH.<sup>[66]</sup>

#### Kojic acid

Kojic acid (KA) (5-hydroxy-2-hydroxymethyl-4-pyrone) is a natural organic acid and fungal byproduct of *Acetobacter*, *Aspergillus*, and *Penicillium*. The action of KA to inhibit tyrosinase genesis with antioxidant effects and exhibits anti-aging properties and also KA can inhibit NF- $\kappa$ B in keratinocytes, whose activation might be connected to melanogenesis.<sup>[67]</sup> Side-effects connected with hydroquinone have made KA an advisable alternative and KA to be used at concentrations of 1.0% topically.<sup>[68]</sup>

#### Soy

Soybean trypsin inhibitor and reversibly inhibits the protease-activated receptor-2 pathway that is required for melanosome transfer.<sup>[69]</sup> Inhibition of this pathway brings about a dose-dependent loss of pigmentation by as early as 4 weeks with highest tested dose.<sup>[70]</sup>

#### Ascorbic acid

Ascorbic acid, also known as vitamin C which have antioxidant properties and decrease melanogenesis by interacting with copper at the active site of tyrosinase and by decreasing dopaquinone by blocking dihydrochinindol-2-carboxyl acid oxidation.<sup>[51,71]</sup> In a normal trial, patients of melasma shown a greater subjective better effect to one side of the face treated with 4% hydroquinone cream (93%) than the other side of the face treated with 5% ascorbic acid cream (62.5%).<sup>78</sup> <sup>[72]</sup> Improvement of melasma was found effective with 25% L-ascorbic acid formulation with a penetration enhancer quality.<sup>[73]</sup>

#### Niacinamide

Niacinamide is a biologically active form of niacin (vitamin B3) and is obtained from yeast and root vegetables.<sup>[74]</sup> Many benefits in terms of excellent barrier role, decreased sebum generation and pleasant look of photo-aged skin, including hyperpigmentation, redness and wrinkles have been defined by topical application of niacinamide.<sup>[75-77]</sup> It is a prime component of many over-the-counter lightening creams.<sup>[75]</sup>

#### Aleosin

Aleosin is a moderately high molecular weight glycoprotein found in the Aloe vera plant.<sup>[78]</sup> Aleosin is containing its dual mechanism of inhibiting both mammalian and fungal tyrosinase. Aleosin treatment inhibit hyperpigmentation after UV radiation in a dose-dependent manner.<sup>[79]</sup> Combination of aleosin and arbutin showed an additive effect.<sup>[78]</sup>

#### Ellagic acid

Ellagic acid (EA) is a polyphenol phytochemical that can be obtained from certain plants in nature and in some nutrients such as green tea, walnuts, strawberry, geranium, grapes and cherries.<sup>[80]</sup> EA efficacy to inhibit

skin pigmentation resulting from UV irradiation. EA suppresses melanogenesis by inhibiting tyrosinase activity and this is due to chelation of the copper atoms in the tyrosinase molecules.<sup>[81,82]</sup>

### N-Acetylglucosamine

N-Acetylglucosamine (NAG) is a carbohydrate and monomeric unit of chitin, the chief component of the cell walls of fungi and the exoskeletons of arthropods such as crustaceans and insects. It is inhibiting the conversion of protyrosinase to tyrosinase and NAG has been found to reduce melanin synthesis and downregulate the expression of various pigmentation, and its related genes.<sup>[83]</sup> According to clinical studies have applied either NAG alone or in combination with niacinamide. In an 8-week, double-blind, placebo-controlled, split-face clinical trial, 2% NAG decreased the look of facial hyperpigmentation.<sup>[84]</sup>

### Lignin peroxidase

Lignin peroxidase is a novel process of skin lightening and effect of targeting, enzymatically oxidizing and degradation melanin in the skin. The application of lignin peroxidase cream provided a significantly more rapid and observable skin-lightening effect than 2% hydroquinone or placebo. Overall, lignin peroxidase is well tolerated with minimal to no side-effects.<sup>[85]</sup>

### CONCLUSIONS

Treatment of hyperpigmentation disorders, including melasma is generally challenging, need protracted treatments with different agents. This review has been explained by collecting all the aspects regarding hyperpigmentation disorder, a process of melanogenesis and its treatment. Great proceed has been made in comprehensive the cellular and biochemical mode of action in pigment biology and the processes underlying skin pigmentation. This has led to the evolution of several skin lightening agents to decrease skin hyperpigmentation. Among natural compounds for skin depigmentation, soy and niacinamide are the ones with the maximum in vivo scientific evidence substantiating this clinical effect. It is the main point to note though that since melanin is a key natural skin protectant (absorbing and scattering UV to save skin cells from DNA damage), the object of depigmenting therapies is mainly to even skin tone and bleach only hyperpigmented areas, without influencing the intrinsic skin colour. Many methods of treatment are obtainable depending on the condition, and a thorough understanding of the underlying etiologies of facial hyperpigmentation is necessary for choosing the best treatment possible. On the basis of future research, we will be able to understand hyperpigmentation disorder.

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