MS.ID-IJPBS-2677
International Journal of Pharmacy and Biological Sciences-IJPBS™ (2022) 12 (2): 07-19
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Review Article | Pharmaceutical Sciences | OA Journal | MCI Approved | Index Copernicus

Skin Pigmentation Disorders and Treatment

Rohini N. Jadhav*, Diksha K. Nunse and Amol S. Deshmukh
Department of Pharmaceutics, SMBT college of pharmacy, Nandi Hills, Dhamangaon, Tal- Igatpuri, Dist- Nashik, Pin- 422403, Maharashtra, India.

Received: 12 Oct 2021 / Accepted: 6 Nov 2021/ Published online: 01 Jan 2022
***Corresponding Author Email:** jadhavrohini235@gmail.com

Abstract
Pigmentation means coloring. Skin pigmentation affect the colour of skin. The skin gets its color from a pigment called Melanin. When these cells become damaged or unhealthy, it affects melanin production. Along with hormones, genes are responsible for regulating the melanin production process. If body produces too much melanin, skin gets darker. If body produces insufficient melanin, skin gets lighter. Hyperpigmentation includes melasma, Age spots, post inflammatory Hyperpigmentation are more likely to affect areas of skin. Hypopigment molecule are one of the most common skin lesions encountered in clinical practice. Hypopigmentation or Hypomelanosis is occurs due to decreases melanin production. Present review consists of information about Treatment of skin pigmentation this include covering smaller patches with long lasting dyes, light sensitive medicines, UV light therapy, Corticosteroids creams, surgery, and removing the remaining pigment from the skin. Some natural ingredients play an important role in treatment of skin pigmentation disorders. Herbal cosmetics as anti-hyperpigmentary agents are very useful in cosmetic industries. There are various causes of skin pigmentation which includes chemotherapy drugs, pregnancy hormones, melasma, skin irritation or trauma. The treatment for skin pigmentation varies depending on the cause.

Keywords
Melanin, Hyperpigmentation, Hypopigmentation, Natural Ingredients.

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INTRODUCTION
In humans, pigmentation is one of the most varied traits. Melanin, a generic word for a complex set of biopolymers created by specialised cells known as melanocytes, is principally responsible for the colour of skin, hair, and eyes [1]. The synthesis and alteration of melanin by melanocytes is associated to the broad variance in constitutive skin pigmentation of different ethnic groups. Melanocytes are highly branching dendritic cells found in the basal epidermis that interact with approximately 35 keratinocytes in the epidermis' top layers-the'melanocytic unit [2]. The most noticeable aspect of human variability is variation in skin and hair colour, and several studies in evolution, genetics, and developmental biology have contributed to understanding the mechanism underlying human skin pigmentation, which is responsible for differences in skin colour across populations [3]. Melanocytes, a small population of cells that are produced from precursor cells termed melanoblasts during embryological development, specialize in the synthesis and dispersion of the pigmented biopolymer melanin [4]. Melasma, post-inflammatory hyperpigmentation (PIH), solar lentigines, ephelides (freckles), inherited dermal hyperpigmentation, and drug-induced hyperpigmentation are all examples of common skin pigmentation disorders [5]. Pigmentation diseases of the skin are very frequent in basic care. Although they are frequently benign and easily distinguished

based on appearance and location, a skin biopsy may be required to rule out melanoma and its precursors. Some illnesses cause the patient to have cosmetic or psychological problems, prompting evaluation and therapy. A correct diagnosis enables the clinician to provide appropriate skin therapy, reassurance, or referral [6]. Cutaneous pigmentation is a highly complicated human feature that ranges from white to pink to tan, dark brown, or black, with significant variance even within ethnic groups. Skin colour changes are seen in a wide range of illnesses, each with its own set of causes [7]. Solar radiation consists of 5-7 percent UV, 45 percent visible light (VIS), and 48-50 percent infrared (IR) radiation at the earth's surface. UVB and UVA-mediated effects on skin have been the subject of studies on the cutaneous impact of radiation [8].

SKIN

The skin is the body's biggest organ. It completely encircles the body. It protects you from things like heat, light, harm, and infection. There are three layers to the skin.

1. **Epidermis:** The epidermis is the thin outer layer of the skin it consists of 3 types of cells – Sqamous cells, Basal cells, Melanocytes.
2. **Dermis:** The dermis is the middle layer of skin. It contains blood vessel, Lymph, hair follicle, Sweat gland, collagen bundles, fibroblasts, Nerves, Sebaceous glands.
3. **Subcutaneous layer (hypodermis):** The subcutaneous layer is deepest layer of skin. It consists of network of collagen and fat cells.

Fig.1: Structure of Skin

FITZPATRIC SKIN TYPE

The Fitzpatrick scale is used to characterise and estimate skin response to ultraviolet radiation, and it goes from I to VI. Solar lentigines or ephelides in lighter skin [types I to III], melasma in darker skin [types IV to VI]) are more common in certain skin phenotypes. [6]

- **Skin type I:** Typical features are pale white skin. Tanning ability is always burn, does not tan.
- **Skin type II:** It includes fair skin which burn easily but tan poorly.
- **Skin type III:** It includes darker white skin which tan after initial burn.
- **Skin type IV:** It includes light brown skin which burn minimally and tan easily
- **Skin type V:** It includes brown skin which rarely burns but tans darkly
- **Skin type VI:** It includes dark brown or black skin which never burn but always tan darkly.

MELANIN

The actions of melanocytes play a major role in skin colour [3]. A number of instrumental methods have been used to evaluate skin pigmentation as early as the 1920s and 1930s when it was recognized that 'the more melanin present, the lower the percentage of light reflected from the surface of the skin and the lower the brilliance [10]. Melanin pigmentation is important for shielding the skin from ultraviolet (UV) radiation's damaging effects. The regulation of pigmentation is influenced by a number of hereditary and environmental variables. Melanin diseases are characterised by abnormal skin pigmentation due to excessive or insufficient levels of melanin. While wrinkles and laxity are well-known signs of ageing skin, abnormal pigmentation is also a typical sympto [11]. Melanin pigment is synthesized in the epidermis by highly specialised cells called melanocytes, which are neural crest-derived cells that migrate as melanoblasts during embryogenesis [9]. Melanocytes are stem cells from the neural crest (NC) cells that line the dorsal surface of the neural fold. NC cells that migrate dorsolaterally as well as ventromedially give rise to melanoblasts-melanocyte precursors. Melanoblasts migrate from the dermis to the epidermis during embryonic development and then begin producing melanin. Melanin is a chemical molecule made up of 5,6-dihydroxyindole, which is produced from the amino acid tyrosine [12]. Epidermal melanocytes are found in a 1:10 ratio among basal keratinocytes and transfer their melanin to 40 suprabasal keratinocytes via their extended dendrites and cell/cell connections [13]. Melanocytes, pigment-producing cells of the follicular and interfollicular epidermis, produce the melanosome, which is a specialised lysosomal organelle. The melanosome produces biopolymers of the pigment melanin, which gives hair and skin, as well as other tissue, its colour. The endoplasmic reticulum structural proteins fuse with melanosome-specific regulatory glycoproteins released in coated vesicles from the Golgi apparatus in a bipartite mechanism

[14]. Melanocytes are made up of neural-crest progenitor cells called melanoblasts. The neural crest cells are a transient population of pluripotent cells that emerge from the most dorsal region of the neural tube (between the surface ectoderm and the neural plate) and are only present during embryonic development [7]. Melanocytes 'inject' pigment into ketarinocytes as melanosome bundles. There are two types of melanin pigments: dark brown to black eumelanin (which is photoprotective) and reddish brown phaeomelanin (which is not photoprotective) [15]. Melanin is produced in melanocytes by a biochemical pathway known as melanogenesis, which entails a sequence of enzymes and chemically catalysed reactions. Melanin is synthesised in melanocytes, which are found inside melanosomes. The melanogenic enzymes (tyrosine and associated proteins) that are introduced with the help of certain protein complexes regulate melanin synthesis [4]. On Fontana–Masson-stained skin slices, the total melanin concentration in the epidermis can be measured. Skin samples with varied constitutive pigmentation had their total melanin content measured. The melanin index (MI) was calculated as the area covered by melanin staining in the epidermis, including the stratum corneum, and the basal layer, where it is produced by melanocytes, in both the complete epidermis and the basal layer, where it is produced by melanocytes [9]. Melanin functions as a natural sunscreen and is especially effective in protecting DNA and proteins from the detrimental effects of shorter wavelengths of electromagnetic radiation (300 nm). Sunburn is the first reaction to UVR exposure, and it is characterised by erythema (redness), edoema, and sometimes discomfort and blisters. Severe sunburn can damage sweat glands, disrupting thermoregulation and increasing the risk of infection in injured skin cells [1]. Melanin synthesis in melanocytes, melanosome transfer to keratinocytes, and melanosome breakdown all play a role in skin pigmentation. Melanin production is limited to melanosomes, which contain tyrosinase, a critical regulator of melanogenesis, as well as tyrosine-related proteins (TRPs). Tyrosinase is involved in the conversion of dopaquinone to brownblackeumelanin and yellow red pheomelanin, which is common to both forms of melanin. Eumelanin protects against UV radiation by dispersing and absorbing it [11].

PIGMENTATION DISORDERS

Melasma, post-inflammatory hyperpigmentation (PIH), solar lentigines, ephelides (freckles), hereditary dermal hyperpigmentation, and drug-induced hyperpigmentation are all common skin pigmentation diseases. In general, hyperpigmentation is caused by an increase in melanin in the skin as a result of UV damage, inflammation, and skin injuries (such as acne scars), all of which can cause skin darkening. Hypermelanotic pigmentation disorders have an excess of melanin but a normal number of melanocytes, whereas hypermelanocytic pigmentation disorders have an excess of melanin but an increased number of melanocytes. These skin diseases are hypomelanotic/ameianotic and hypomelancytic/ amelanocytic, respectively, and are caused by a lack of melanin in the melanocytes [5].

Generalized Pigmentary disorders

Some population genetics researches have helped to explain the evolution of the human pigmentation system. However, the genetics of pigmentation is complicated: a number of genes responsible for the range of pigmentation phenotypes contributing to human skin pigment diversity seen both between and within human populations arise from a number of systemic conditions such as morphea, systemic sclerosis, paraneoplastic pigmentation, and acanthosisnigricans have been identified for decades using mouse coat colour mutations (and more recently zebrafish). Other pigments, such as those seen in haemochromatosis, renal insufficiency, and argyria (cutaneous silver diposition), can cause broad skin darkening. Hypothyroidism and pituitary failure with decreased melanocyte-stimulating hormone concentrations are two more systemic causes of an acquired widespread decline in skin colour. [15]

- **Localized Pigmentary disorders**

Patches of hyperpigmentation can develop for a variety of reasons, and they can be congenital or acquired. The colour of cutaneous melanin varies based on its depth in the skin and the extent of visible light scattering and reflection. Because the tyndall effect makes scattered light bluish, deeper pigment appears blue. Mongolian spots (which normally appear as a well-defined bluish area on the lower back) are a common dermatological finding in people with darker skin. They are made up of large sheets of dermal melanocytes. The patches are symmetrical and appear on the face (peri-ocular and peri-oral regions), fingers, dorsae of the hands, genitals, axillae, areolae, feet, knees, elbows, and neck, among other places where friction occurs. Follicular sparing is common, albeit hairs lose colour later in the disease's course. Vitiligo is linked to a positive family history (in 30-40% of instances) as well as autoimmune disorders include endocrine and connective tissue diseases, as well as alopecia areata [15].

HYPERPIGMENTATION

Hyperpigmentation is a frequent dermatological condition that can have a significant influence on a patient's appearance and quality of life. Hyperpigmentation is a darkening of the skin's natural colour caused by an increase in melanin deposition (hypermelanosis) in the epidermis or dermis, an increase in nonmelanic chromophores (hyperchromia), or dermal deposition of endogenous or exogenous pigments. Hyperpigmentation is a common reason for seeking medical help, especially in persons with darker skin [16]. Hyperpigmentation is a frequent dermatological problem that affects people of all skin types. Pigmentation disorders are the third most frequent dermatologic disorder, and they can have serious psychological consequences. Melasma, solar lentigines, and postinflammatory hyperpigmentation are all common hyperpigmentation diseases that can be caused by a variety of skin ailments such as acne, eczema, contact dermatitis, or trauma. UV light-induced diseases and damage are often difficult to treat, and a number of medications are available, ranging from prescription to over the counter (OTC) to cosmeceuticals [17]. Skin hyperpigmentation is a condition in which regions of skin become darker than the rest of the body. Melanin overproduction in particular areas of the skin cause this. Melanin is formed during the process of melanogenesis and is a key pigment in skin hyperpigmentation. Melanosis refers to an increase in the pigment melanin in epithelial cells. Melanocytes are normal in quantity, but melanin is enhanced in hyper pigmented skin in epidermal melanosis, and melanin is present within the dermis between collagen bundles in dermal melanosis [18]. Although exposure to natural or artificial ultraviolet (UV) radiation is the most common cause of hyperpigmentation, hormonal variables have been linked to the pathophysiology of more severe forms of hyperpigmentation, such as melasma. This is due to the fact that these skin diseases are more common in women and have been linked to hormonal issues, oral contraceptives, and pregnancy [5]. Metabolic, autoimmune, and endocrinopathies are the three types of systemic disorders that cause hyperpigmentation [12].

An increase in melanin synthesis and, less typically, an increase in the number of active melanocytes cause hyperpigmentation diseases. UV irradiation from sun exposure is the most major risk factor in the development of all hypermelanotic diseases, however inflammation has an equal, if not greater, role in acne. Melanocytic activity can be sustained even in the absence of sunshine. Because UVA and UVB light stimulate melanocytic proliferation and enhanced melanosome transfer to keratinocytes, broad-spectrum sunblocks are an important part of any hyperpigmentation treatment plan [19]. An increase in melanin in the basal and suprabasal layers of the skin, along with a normal or enhanced number of melanocytes, causes hypermelanosis in the epidermis. Metals like iron have been shown to induce melanogenesis in people with hemochromatosis [16].

Hyperpigmentation is treated by first addressing the underlying problem, then lowering ongoing pigment production, and finally eliminating pigment from the epidermis; dermal pigment is resistant to treatment. Patients must be educated, and realistic treatment results must be established [15]. Skin lightening agents, the most common of which are phenolics, can be used as a single ingredient or as a mixture of actives in a formulation. In cosmetic formulations, herbal extracts containing numerous actives that operate synergistically to boost efficacy are used, with such actives proving to be very attractive options. Hydroquinone, vitamin C or scorbic acid, arbutin, and kojic acid and derivatives are all often utilised substances. In cosmetic compositions, mulberry, artocarpus, and orchid extracts are also employed [20]. Hyperpigmentation is routinely treated with cosmetics. Pigmentary diseases are the third most frequent dermatologic condition, and they can have serious psychological consequences. These conditions are notoriously difficult to cure, necessitating the use of skin lightening treatments such as cosmeceuticals. These drugs target hyperplastic melanocytes specifically and block crucial regulatory stages in melanin synthesis [21].

Fig. 2: Hyperpigmentation Disease

There are Three types of hyperpigmentation

1. Post-inflammatory hyperpigmentation

2. Melasma
3. Age spot

1. Post-inflammatory hyperpigmentation

It is acquired hypermelanosis that develops after a skin irritation or injury and can affect people of all skin types. Infections like dermatophytosis, allergic reactions like mosquito bites, psoriasis, hypersensitivity reactions to drugs, or harm from an allergen, or cosmetic operations can all cause it. Post-inflammatory hyperpigmentation (PIH) is most common in dark-skinned patients after acne. After inflammation, PIH is caused by an excess of melanin or an uneven dispersion of pigment. Melanocyte activity may increase, which may be triggered by inflammatory mediators and reactive oxygen species. Epidermal post-inflammatory hyperpigmentation is light to dark brown in hue, whereas dermal PIH is grey to black in colour [18]. PIH develops as a result of face acne vulgaris, which is common in Fitzpatrick skin types IV–VI and can have a significant impact on quality of life. For patients, PIH can be a cause of humiliation, self-consciousness, and frustration, and it frequently interferes with day-to-day activities. Other common treatments for PIH include glycolic acid peels, salicylic acid peels, topical tretinoin, topical prednisone, topical kojic acid, Q-switched laser, and combination therapy [5]. As a result of laser or light therapy, or after cryotherapy, postinflammatory hyperpigmentation appears as uneven, darkly pigmented skin near sites of past damage or inflammation. The best results are usually achieved with a combination of therapies. Treatment of the underlying ailment (e.g., acne, eczema) can aid healing, albeit weeks or months of treatment may be required, and hyperpigmentation removal is sluggish [6]. The darkening of skin that happens following an inflammatory eruption or cutaneous injury is known as pos tinflammatory hyperpigmentation (PIH). The melanocytes' response to the cutaneous insult induces an increase in melanin synthesis and/or redistribution, resulting in hyperpigmentation. Patients with darker skin are more likely to experience this colour change. Both the epidermis and the dermis can have postinflammatory alterations. There is increased melanin synthesis and/or transfer to keratinocytes in the epidermal form of hyperpigmentation. Melanin enters the dermis through a broken basement membrane in dermal PIH, where it is phagocytosed by dermal macrophages known as melanophages [22]. PIH is most commonly caused by cutaneous irritation or damage. Hypermelanosis is caused by acne vulgaris, one of the most frequent inflammatory skin conditions. All age groups are affected equally, and there is no gender difference; however, people with darker skin types are more prone to acquire PIH [19].

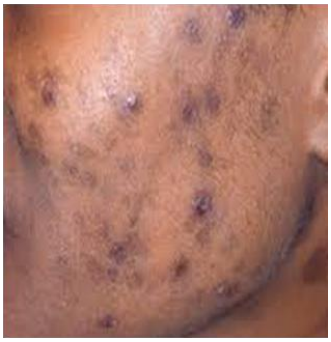

Fig. 3: Post inflammatory Hyperpigmentation

2. Melasma

The word melasma comes from the Greek word melas, which meaning "black." It's also known as the pregnant mask. The most common cause of face hyperpigmentation is melasma. This condition primarily affects women, with men accounting for only 10% of all causes [4]. Melasma is a type of hyperpigmentation that develops over time and is most typically observed on the face. It is a common hyperpigmentation problem that affects millions of people around the world [22]. Melasma is a hyperpigmentation disease that causes uneven light to dark brown patches on the forehead, cheeks, upper lip, and chin [23]. Melasma is a well-known and well-understood dermatological disorder that mostly affects women. It is characterised by symmetric, brownish-grey macules and patches on the face, as well as the neck, chest, and forearm. It is a chronic, relapsing hyperpigmentation. Melasma is also known as chloasma, or "pregnancy mask," because to the fact that it is frequently connected with pregnant women. Melasma is asymptomatic and has no apparent link to a systemic ailment, although it can be damaging to many patients' psychosocial well-being [24]. Although the cause of melasma is unknown, it is thought to be caused by sun exposure and a hereditary predisposition. Melasma manifests itself as irregular, light to dark brown, grey, blue, or black macules and plaques on the face, neck, and décolletage. Despite the fact that melasma is more common in women, men account for 10% of recorded cases [5]. Sunscreen is universally recommended to prevent melasma from deteriorating due to continued sun exposure. Pregnancy-induced melasma fades naturally after delivery, hence therapy should be postponed to allow for this [6]. Melasma is characterised based on its location as well as the extent of its involvement. Centrofacial, malar, and mandibular melasma are the three most prevalent forms of melasma, which

characterise the patterns of facial involvement. Melasma is classified further by the depth of involvement, which is commonly determined by using a Wood's lamp and is separated into four categories: epidermal, dermal, mixed, and undetermined [24]. Because melasma is common in pregnancy, hormonal contraception, oestrogen therapy in prostate cancer patients, and conjugate oestrogen use in women beyond menopause, hormones have a role in the aetiology of melasma. Melasma is more common in women than in men. Melasma is a cutaneous side effect of oral contraceptives that is unfavourable. Melasma is usually thought to be a hormonally induced physiological change in the skin. Oestrogens are involved in a variety of physiological and pathological skin disorders, including pigmentation. The biological effects of oestrogen and progesterone are controlled by their respective receptors [18]. Other variables that contribute to the aetiology of melasma, in addition to hereditary influences and chronic exposure to UV radiation, include hormone therapy, pregnancy, phototoxic pharmaceuticals, cosmetics, and even antiseizure medications [4]. In terms of therapeutic implications, topical depigmentants are still the most common treatment for melasma. Hydroquinone, the most popular anti-melanogic agent, blocks the conversion of 1-3,4-dihydroxyphenylalanine to melanin by competitive tyrosinase inhibition, although it has also been linked to exogenous ochronosis, irreversible depigmentation, and cancer risks [18].

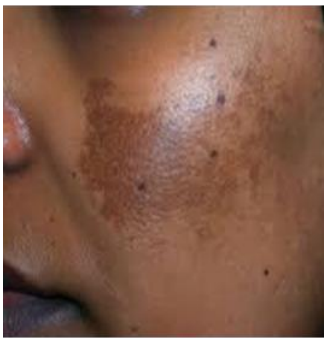

Fig. 4: Melasma

3. Age spot

Aged marks are brown blotches on the skin. Skin regions that are frequently exposed to sunlight, such as the face and the backs of the hands, grow largely on that part of the skin. The lipofuscin bodies of the basal cells cause age spots to be brown. Lipofuscin is a lysosome lipid and protein combination in which lipids attach to protein fragments via malondialdehyde. Age spots come in a variety of shapes, sizes, colours, and degrees of protrusion in the skin. Basal cells link to the basement membrane in the epidermis to form age spots on the skin. Basal cells are stem cells that are responsible for epidermal regeneration and repair in new epithelial cells. Reduced neighbourhood cell productivity in resolving environmental changes and increased damage fragility; and impaired local tissue repair performance are two impacts of an aged cell on a tissue. As a result, nearby cells in an aged cell are more vulnerable to damage and misrepair. An old cell leads nearby cells to age as a result of this process [18].

Fig. 5: Age Spot

Causes of hyperpigmentation

Many causes contribute to hyperpigmentation. Addison's illness, Cushing's syndrome, Acromegaly, Hyperthyroidism, Acanthosisnigricans, Diabetes are examples of exogenous and endogenous factors. Kwashiorkor, Vitamin B12 insufficiency, Folic acid shortage, Niacin deficiency, Tryptophan deficiency, Vitamin A inadequacy are all nutritional factors. Melasma is an unfavourable side effect of hormonal contraception [18].

NSAIDs, or nonsteroidal anti-inflammatory medicines, can cause hyperpigmented lesions, which usually appear as a fixed drug rash. The pathophysiological processes are unknown, although it is speculated that NSAIDs may function as a hapten, attaching to a protein attached to melanocytes and causing a cytotoxic reaction directed at the hapten-bound melanocytes. Paracetamol, salicylates, oxicam derivatives, and ibuprofen are the medicines most frequently linked to this side effect. [16]

Melasma, solar lentigines, and postinflammatory hyperpigmentation are all common hyperpigmentation diseases that can be caused by a variety of skin ailments such as acne, eczema, contact dermatitis, or trauma. UV light-induced diseases and damage are notoriously difficult to treat, despite the availability of a wide range of medicines ranging from prescription to over the counter to cosmeceuticals. [17]

Hyperpigmentation can be caused by a variety of anticancer drugs. Cyclophosphamide, ifosfamide, and thiotepa, for example, are alkylating agents that have been identified as causes. After the fourth week

of treatment, cyclophosphamide can induce hyperpigmented patches on the palms, soles, nails, teeth, and, in rare cases, the gums [16]. These patches can form on the palms, soles, nails, teeth, and, in rare cases, the gums.

Skin damage, hormonal fluctuations, ageing, sunburn, liver, gall bladder, kidney, and gastrointestinal tract disease

Natural ingredients used in hyperpigmentation treatment

1. **Aleosin:** Aleosin is a glycoprotein with a somewhat high molecular weight that comes from the Aloe vera plant. Aloe vera has been used in cosmetics for millennia, and plant extracts, particularly aleosin, have been shown to block the oxidation of l-3,4,-dihydroxyphenylalanine (l-DOPA) by mushroom and human tyrosinase. Aleosin is unique in that it inhibits both mammalian and fungal tyrosinase through a dual mechanism. In a dose-dependent manner, aleosin therapy was reported to reduce hyperpigmentation following UV radiation[17]. Aloesin and arbutin were applied four times daily during 15 days, individually and in combination. The aloesin therapy group showed dose-dependent inhibition, according to the authors. The synergy between arbutin and aloesin was also demonstrated in this trial, as cotreatment resulted in better pigmentation suppression than either chemical alone. [7]
2. ***Emblica officinalis:*** The nutritional value of E. officinalis is well known. Flavonolglycosides, carbohydrates, mucic acids, amino acids, sesquiterpenoids, alkaloids, flavone glycosidses, phenolic glycosides, phenolic acids, and tannins are among the compounds found. When compared to other fruit juices, E. officinalis fruit juice has the highest level of vitamin C and vitamin E. The extract inhibited tyrosinase by reducing microphthalmiaassociated transcription factor (MITF) and Trp-1 gene expression, but it also induced Trp-2 gene expression at low concentrations. The IC50 of EPE is higher than that of MPE; emblica fruit has an IC50 of 4346.95 166.23 g/mL. The antioxidant and anti-melnogenesis effects of ethanolic extract are stronger [18].
3. **Green tea**: Green tea's antioxidant and anti-inflammatory qualities have long been explored. Green tea extracts contain a variety of polyphenolic antioxidants, the most active of which is epigallo-catechin-3-gallate (ECGC). Green tea has proven therapeutic efficacy in treating melasma, according to the abstract of a single RCT. In the trial, 60 women with melasma were given either a 2% analogue of green tea extract (ECGC) in a hydrophilic cream or a placebo, and their progress was monitored using dermatological and photographic techniques. Lesions resolved in 60% of the treatment group versus 3% of the placebo group, indicating a clinically meaningful difference. However, because it has not yet been published in a peer-reviewed journal, this research is limited**.** Furthermore, more research is needed to confirm green tea extracts' therapeutic efficacy on pigmentary illnesses. Green tea extracts may have preventive characteristics in addition to curing melasma, such as suppressing UV-induced erythema, reducing the number of sunburn cells, and protecting DNA from UV radiation in human trials. [25]
4. **Vitexnegundo**: Local cosmetic practitioners use a poultice of this plant to diagnose hyperpigmentation as melasma or ephelides. Negundin has a functional lactone at the C-2 position and has a strong IC50 of 10.06 mM against the tyrosinase enzyme. Vitexnegundo is a skin whitening product that also acts as a tyrosinase inhibitor and prevents the formation of post-inflammatory pigmentation. There are several chemical ingredients in Vitexnegundo, one of which being negundin A [18].
5. **Turmeric:** Turmeric (Curcuma longa) is a popular Ayurvedic spice and herbal supplement. Curcumin, a hydrophobic polyphenol with a yellow colour, is the active ingredient in turmeric. Curcumin has been found in 39 studies to have anti-inflammatory and anti-carcinogenic effects. Curcumin may induce death in human melanoma cells via the mitochondrial route and activation of caspases, according to a recent in vitro study. The application of topical turmeric extract reduced the appearance of face hyperpigmentation, fine lines, and wrinkles, according to the abstract of a twin research RCT [25].
6. **Glabridin**: Glabridin, an anti-inflammatory component of licorice extract extracted from Glycyrrhizaglabra, works by inhibiting superoxide anion generation and cyclooxygenase activity[1]. Yokota et colleagues used cultivated B-16 murine melanoma cells and guinea pig skin in an in vitro investigation to explore the inhibitory effects of glabridin on melanogenesis and inflammation. The study used a colorimeter to measure depigmentation,

followed by a histochemical investigation of the quantity of melanocytes. Glabridin suppresses tyrosinase activity but has little effect on DNA synthesis, according to the authors [10]. Before appraising glabridin's clinical effects, more research is needed to investigate its lightening effects on humans [17].

7. **Arbutin:** Hydroquinone-O-d-glucopyranoside, also known as arbutin, is structurally linked to hydroquinone. Bearberry leaves, fresh fruit of California buckeye, Aesculuscalifornica (Spach) Nutt, and in smaller amounts, cranberry and blueberry leaves are all sources of the component. At noncytotoxic doses, the naturally occurring glucopyranoside inhibits the activity of melanosomaltyrosinase and 5,6-dihydroxyindole-2-carboxylic acid polymerase. Arbutin's activity is driven by structural similarity with the substrate tyrosine, which results in competitive inhibition of tyrosinase's catalytic function [17].
8. **Santalum album**: Antiseptic, antispasmodic, carminative, diuretic, emollient, hypotensive, memory enhancer, sedative, and other properties. Sandalwood oil provides anti-inflammatory, antiphlogistic, and skin antiwrinkling effects, as well as protecting, smoothing, moisturising, and hydrating capabilities. The oil possesses DPPH radical scavenging action and inhibits the oxidative enzyme 5-lipoxygenase. Sandalwood oil is primarily composed of alpha-santalol. It is a powerful tyrosinase inhibitor when compared to kojic acid and arbutin. [18].
9. **Mulberry:** Morusalba, or dried mulberry leaves, are used to make mulberry extract. Mulberry leaves are used to feed silkworms in various East Asian countries, and they've also been employed in traditional Chinese and Thai medicine to treat and prevent diabetes. Mulberroside F, the active component of mulberries, suppresses tyrosinase activity, melanin generation in melanocytes, and melanin transfer in vitro, and may also act as a reactive oxygen species (ROS) scavenger. To present, only one randomised controlled trial (RCT) has looked into the use of mulberry in pigmentary disorders [25]. Tyrosinase activity has been demonstrated to be inhibited by dried mulberry (Morusalba) leaves (85 percent ethanol extract). Its leaves have also yielded various phenolic flavonoids, such as gallic acid and quercetin, as well as fatty acids, such as linoleic acid and palmitic acid. [26]
10. **Hesperidin**: Hesperidin is a bioflavonoid found in the peel and membrane of citrus fruits. Hesperidin's capacity to decrease melanin formation without causing cytotoxicity has been demonstrated in studies. Hesperidin's notable effects include protection against UVA-induced fibroblast damage and the prevention of collagen oxidative degradation. Hesperidin can be utilised as a potential skin lightening agent because it improves general skin tone and has anti-yellowing properties [4].
11. **Caricapapaya**: It contains papain, chymopapain A and B, all of which are antioxidants. Calcium, sugar, fibre, vitamin C, thiamine, riboflavin, niacin, amino acids, carotene, and malic acids are all found in it. Proteins and lipids are also included. Carica fruit extract has been discovered to have an antioxidant activity of 87 percent. Two major categories of phenolic chemicals were found in papaya fruit. These phenolic compounds are the most important natural antioxidant groups [18].

Drugs causing hyperpigmentation [15]

- Anti-malerial drugs – chloroquine, hydroxychloroquine, quinine/quinidine
- Tetracyclines – minocycline
- Phenothiazines–chlorpromazine
- Phenytoin and hydantoin derivatives
- Oestrogens
- Zidovudine
- Chemotherapeutic agents
- Hydroxyurea
- Clofazimine

Cosmetic procedures for hyperpigmentation [27]

- Laser therapy: Light amplification by stimulated emission of radiation (laser) is source of high intensity monochromaticcoherent light. The introduction of laser therapy transfigured the treatment options for many skin disorders, especially hyperpigmentation.
- Chemical Peels: Chemical peels are a prevalent option for several hyperpigmentation disorders. Chemical peels work by causing desquamation and removal the superficial topmost layer of the stratum corneum.
- Intense pulsed light: Intense pulsed light has shown promising improvements in the treatment of hyperpigmentation. It involves the use of a xenon-chloride lamp that emits light with a wide spectrum.

Topical creams for hyperpigmentation [27]

For the treatment or management of site-specific skin hyperpigmentation, topical medications are

commonly employed. Since the 1960s, hydroquinone has been used topically to treat hyperpigmentation. It works by blocking tyrosinase, which prevents melanin formation. The available products have a strength of up to 4%. Glycolic acid is a sugarcane-derived white crystalline alpha hydroxy acid. Glycolic acid has a concentration-dependent action. Because of its numerous processes, including tyrosinase inhibition, kojic acid is often used for hyperpigmentation disorders. Vitamin A or retinol, as well as its structural and functional derivatives, make up retinoids.

HYPOPIGMENTATION

Mutations altering the complicated route of melanocyte growth and function may cause human congenital pigmentation abnormalities such as hypomelanosis. Melanoblast migration (piebaldism, WS, and Tietz syndrome), melanin synthesis (oculocutaneous albinism), and melanosome creation and transfer to keratinocytes are all affected by these mutations [7]. Skin hypopigmentation is linked to oxidative stress induced by mitochondrial redox imbalance or antioxidant enzyme deficiency. Symptoms are frequently accompanied by skin and hair problems, including hypopigmentation. Kearns-Sayre syndrome, a mitochondrial multisystem illness marked by ophthalmoplegia and pigmentary retinopathy, is caused by the loss of mitochondrial DNA [11]. Melatonin has been linked to the development of vitiligo. There's also a link between vitiligo and low testosterone levels caused by secondary hypogonadism. Vitiligo patients, in particular, are prone to major psychological issues such as sadness and anxiety. When vitiligo patients were compared to healthy controls, the levels of dehydroepiandrosteronesulfate, an antioxidant, were lower, but the ratios of cortisol to dehydroepiandrosteronesulfate were higher. The findings point to a function for dehydroepiandrosteronesulfate in the development of vitiligo and give solid evidence for the link between vitiligo and stress hormones. The two types of systemic illness that cause hypopigmentation are diffuse systemic and localised systemic [12].

Fig. 6: Hypopigmentation Disease

Diffuse systemic [12]

- **Oculocutaneous albinism:** Oculocutaneous albinism (OCA) is the most common kind of diffuse hypopigmentation. Oculocutaneous albinism (OCA) is a category of inherited melanin biosynthesis disorders defined by a widespread loss in hair, skin, and eye colour.
- **Phenylketonuria:** PKU is caused by a lack of the enzyme phenylalanine hydroxylase (PAH) in the liver. PKU patients have high levels of L-phenylalanine in their blood, which causes mental impairment and skin and hair hypopigmentation.
- **Hermansky syndrome**: Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disease with genetic variability; nine subtypes have been identified. Oculocutaneous albinism, a platelet storage pool shortage with resulting bleeding diathesis, and lysosomal buildup of ceroidlipofuscin are all symptoms of HPS.
- **Homocystinuria:** Homocysteinuria is a transsulfuration condition caused by a lack of cystathionine beta-synthase (CBS), which results in high homocysteine and methionine in the blood and decreased cysteine. Homocysteine inhibits tyrosinase, a key pigment enzyme, causing pigment synthesis to stop.

Localized systemic [12]

- **Sarcoidosis** : Sarcoidosis is a multisystemic inflammatory illness that is characterised by noncaesiating graulomas. In sarcoidosis, the growth and buildup of granulomas is the primary abnormality.
- **Scleroderma**: Scleroderma is a type of rheumatic autoimmune illness. Vitiligo-like leukoderma is the clinical picture. This looks like idiopathic vitiligo that has started to repigment as a result of treatment, with

normal-pigmenting perifollicular macules visible within areas of depigmentation**.** .

- **Waardenburg syndrome:** Waardenburg syndrome is an uncommon condition that causes deafness and pigmentary abnormalities in the skin, hair, and eyes. This is a kind of neurocristopathy in which two neural crest–derived components, one of which is melanocytes, migrate or survive abnormally during embryonic development.

- **There are some types of hypopigmentation**

1. **Piebaldism**: Piebaldism is a rare autosomal dominant condition characterised by depigmented patches or scars on the mid-forehead, chest, belly, and extremities in the absence of melanocytes. Hyperpigmented macules may be seen in these regions. Cutaneous depigmentation ranges from merely a white forelock with modest ventral depigmentation, to practically a complete body and **in** hair depigmentation [7].

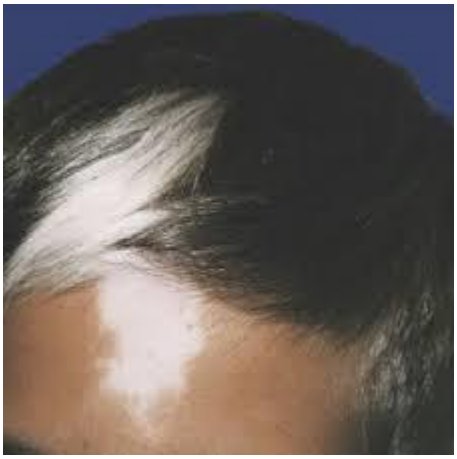

Fig. 7: Piebaldism

2. **Vitiligo:** Vitiligo is a pigment-losing skin disorder caused by an immunological response. The specific cause is unknown. It affects all skin types and is commonly thought of as a cosmetic condition, but it can cause severe psychological discomfort, particularly in black individuals, prompting treatment demands. The quality of life is frequently harmed [6]. Vitiligo, which affects about 1% of the population, is the most common cause of localised hypopigmentation. It is acquired and frequently initially observed in areas with a lot of sunlight. Hypopigmentation or total depigmentation are common symptoms (acromia). The removal of all skin pigment [15]**.** Vitiligo patients should use sun protection. Broad-spectrum sunscreens, sun-protective gear (hats, shirts, pants), and some cosmetics can help protect the skin. Skin pigment discrepancy can be reduced with concealers (e.g., Dermablend, Covermark), topical dyes, and sunless self-tanning products (ideal for skin types II and III) [6].

Fig. 8: Vitiligo

3. **Tietzsyndrom:** Tietz syndrome is a rare autosomal dominant condition with the pigmentary symptoms of OCA (generalised depigmentation, blue eyes without nystagmus) and the congenital deafness of WS. Mutations in the area of the MITF gene that codes for the DNA binding domain cause it. Tietz syndrome is caused by a mutation in the same gene that causes WS2 [7]. Patients with Tietz syndrome have congenital, completely penetrant deafness and do not have heterochromiairides or patchy depigmentation.
4. **Postinflammatory Hypopigmentation**: Pigment loss can occur as a result of inflammatory skin disorders. Pigment production and transport may be affected by tinea versicolor, atopic dermatitis, pityriasisalba, psoriasis, and guttateparapsoriasis. Hypopigmentation may improve over time if the underlying problem is treated. Local pigment reduction can also be achieved by dermabrasion, chemical peels, cryotherapy, and intralesional corticosteroids, and these risks should be explained with patients prior to treatment [6].

Fig. 9: Post inflammatory Hypopigmentation

5. **Tinea versicolor**: Malassezia spp. causes tinea versicolor (pityriasisversicolor), a superficial fungal skin infection. On the neck, chest, back, belly, and proximal extremities, it commonly appears as hypopigmented or pink plaques with fine scale. It can be hyperpigmented on occasion. The diagnosis is frequently clinical, with microscopy utilising a potassium hydroxide preparation for confirmation. Topical selenium sulphide, zinc pyrithione, and antifungals are common therapies [6]. Tineaversicolor causes the skin to seem lighter, darker, or redder than the surrounding skin.

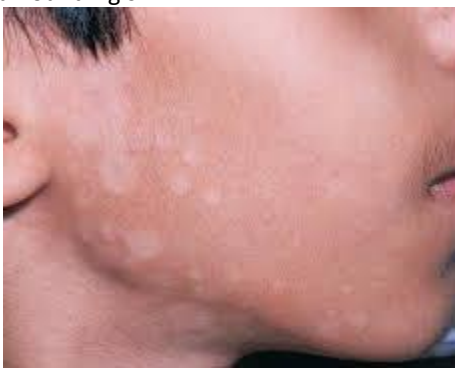

Fig. 10: Tinea Versicolor

6. **Waardenburg syndrome**: Waardenburg syndrome is a piebaldism and sensorineural deafness-related autosomal dominant genetic condition. Due to the inability of melanoblasts to migrate or survive, deafness is linked to the absence of neural-crest-derived melanocytes from the striavascularis of the cochlea [7].

Fig. 11 : Waardenburgsyndrom

7. **Albinism**: Albinism is a condition in which melanocyte differentiation is disrupted. As a result, it is caused by a hereditary malfunction of pigment cells rather than a developmental loss of pigment cells, resulting in full or partial loss of cutaneous pigmentation. Tyrosinase and other essential pigment enzymes (including P gene, TRP1 and MATP) are absent or severely dysfunctional in OCA types 1–4, resulting in melanocytes that are intact but unable to produce pigment[7].

There are some types of albinism:

- Ocular albinism
- Oculocutaneous albinism
- Griscelli syndrome
- Chediak-Higashi syndrome
- Hermansky-Pudlak syndrome.

Fig. 12: Albinism

8. **Pityriasis Alba:** Pityriasisalba is a disorder that is typically associated with atopic dermatitis that manifests itself in children and young adults as hypopigmented, uneven patches on the face, head, neck, and forearms. Skin types III through VI are the most affected. Occasionally, a fine scale with itching appears. Excessive unprotected sun exposure could be a contributing factor. [6]

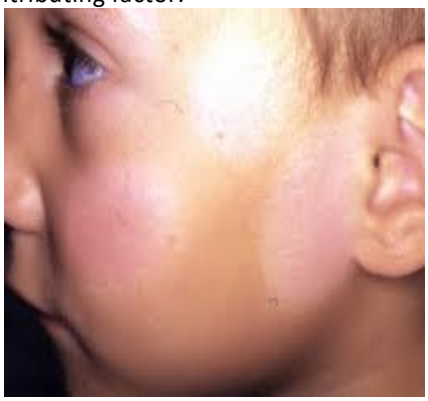

Fig. 13: Pityriasis Alba

9. **Lichen sclerosus** : Lichen sclerosus generates white areas that grow, bleed, and scar over time. The anal and vaginal areas are affected by these patches. They can appear on the breasts, arms, and upper body, among other places.

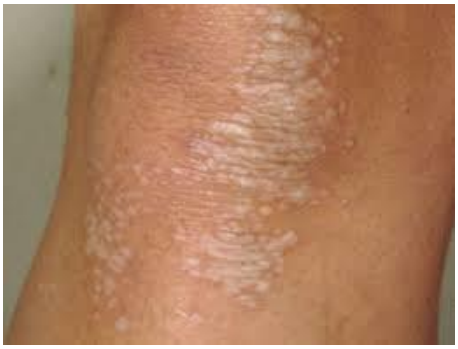

Fig. 14: Lichen Sclerosus

Causes of hypopigmentation

- Scars and burns
- Infection of the skin
- Atopic dermatitis
- Contact dermatitis
- Psoriasis
- Healed blisters

Drugs causing hypopigmentation [15]

- Arsenic
- Tranexamic acid
- Glutathione

Treatment of hypopigmentation

In general, the treatment of hypopigmentation involves treating the primary condition (e.g eczema, pityriasisvericolor, morphea), sun protection and expectant measures. Protection from the sun is vital to prevent sunburn and UV dimage in the depigmented areas that lack protective melanin pigment. In albinism, this should be strict and lifelong in order to prevent the generation of skin cancer.[15] Phototherapy – as oral psoralen with sunlight, psoralen-UVA or UVB alone - is often effective to induce partial repigmentation. Short courses of oral corticosteroids are occasionally tried. Grafts harvested from blisters or using split-skin or punch grafts and techniques involving autologous cultured melanocytes or melanocytes – keratinocyte cell suspensions have in some case produced successful repigmentation [15].

For vitiligo treatment involves High-potency topical corticosteroids, topical calcineurin inhibitors, narrowband ultraviolet B, systemic corticosteroids [6].

CONCLUSION

Hyperpigmentation and Hypopigmentation are common skin conditions; however, they can be emotionally devastating for patients. There are a variety of therapeutic choices for providing well-organized and low-risk treatment. When a patient suspects that he or she has a skin pigmentation condition, they should visit a doctor or an expert. Experts believe it is critical to provide support to people with skin conditions. Natural substances are thought to be safer and healthier when used to treat skin pigmentation issues.

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