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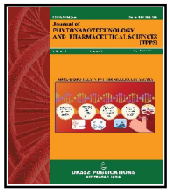

Review Article : Open Access

Medicinal plants for the management of Melasma: An overview

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Abstract

Melasma is a frequent acquired hyperpigmented skin disorder on the face due to melanogenesis and is characterized by nearly symmetrical pigmented macules on the face. Skin pigmentation problems are mostly because of disturbances in melanin synthesis. It mostly impacts darker-skinned women of reproductive age and has a significant influence on quality. Melasma does not pose a life-threatening hazard, but it has a significant influence on patients quality of life. Skin hyperpigmentation issue has been treated for millennia with natural substances. Emphasis has been placed on herbal products since they are thought to be biodegradable, mild and demonstrate minimal toxicity. This is because synthetic cosmetic chemicals can have possible adverse effects. The current review article discusses hyperpigmentation, its types, causes, and treatment options using medicinal herbs.

1. Introduction

Melasma is a frequent, persistent, and chronic condition of hyperpigmentation caused by melanocytes that deposit an excessive quantity of melanin in the epidermis and dermis. Melanin, which is created by the melanogenesis process, is a key pigment in skin hyperpigmentation. Melanosis is the term for an increase of melanin pigment in epithelial cells. Human skin, hair, and eye colour is because of two forms of melanin pigment called eumelanin (black or brown) and pheomelanin (yellow-reddish) (Banna *et al.,* 2018).

The most common areas for it to appear are above the lip (upper), on the chin, nose, and cheeks. Women are more likely than males to have it. Melasma commonly results from pregnancy. Multiple risk factors and biological/environmental triggers have been implicated in the etiopathogenesis of melasma, including sex, genetics, degree of exposure to solar radiation, pregnancy, use of oral contraceptives, hormonal therapies (*e.g.,* estrogen-progesterone treatments), and use of photosensitizing medications. Melasma tends to be patient are female. A person with dark skin is also more susceptible, particularly those with Fitzpatrick skin types of 4 to 6, although patients with all skin types and ethnicities can develop melasma (Grime *et al.,* 2005).

Reactive oxygen species (ROS), which are created by UV radiation in skin cells, activate intracellular signaling pathways, including mutagen-activated protein kinase. Higher p38 mitogen-activated protein kinase (MPAK) activity in a human keratinocyte exposed to UV-B radiation results in the release of pro-inflammatory cytokines such IL-1, cyclooxygenase (COX-2), and TNF-α (Afnan *et al.,* 2016). Tyrosinase and dopachrome tautomerase are two of the enzymes involved in the formation of melanin. Tyrosinase is a key enzyme in the synthesis of melanin, and its overactivity leads to hyperpigmentation (Mapunya *et al.,* 2012). Tyrosine is a component of tyrosinase, which upon hydroxylation transforms into L-3,4-DOPA, which then undergoes oxidation to produce DOPA-quinine, which is then further oxidised *via* a free radical coupling route to produce melanin (Wang *et al.,* 2006; Del Bino *et al.,* 2018). The process by which dopachrome is converted into 5,6-dihydroxyindole-2-carboxylic acid is catalysed by the enzyme dopachrome tautomerase (Choi *et al.,* 2004). Tyrosinase inhibitory properties may be found in a wide variety of therapeutic plants and phytochemicals. As a result, there is an increase in both industrial and clinical demand for tyrosinase inhibitors, which has led to the development of numerous *in vitro* test and screening methodologies for tyrosinase inhibition and other skin-whitening agents (Zolghadri *et al.,* 2019). Numerous plant species with flavonoids and polyphenols were discovered to exhibit tyrosinase inhibitory action (Grime *et al.,* 2005). Therefore, reviewing tyrosinase inhibitors derived from natural sources would be beneficial for treating melasma, and this review will serve as an updated comprehensive database that will aid in the creation of new, safe, and effective anti-tyrosinase agents for the treatment of melasma and other hyperpigmentation disorders.

2. Classification

The most typical facial pattern is the central facial pattern, which includes the forehead, cheeks, upper lip, nose, and chin. The malar pattern includes the cheek and bones, while the mandibular pattern includes the ramus of the jaw. Similar to how melasma is categorized into four histologic kinds by the wood's light analysis.

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- The epidermal kind of melasma, which is the most prevalent form, exhibits heightened pigmentation in the Wood's light test. All epidermal layers exhibit a rise in melanin, which is its defining feature.
- The dermal type is shown by the many melanophages that are found throughout the dermis, and the Wood light inspection did not reveal any enhanced pigmentation.
- A mixed type is created by an increase in melanin in the epidermis and the presence of several melanophages in the skin. Only a few locations are pigmented, according to Wood's light assessment.
- Skin type VI persons with indeterminate types do not benefit from Wood's light assessment (Grime *et al.,* 2005; Glichrest *et al.,* 1977).

3. Symptoms include

- Symmetrical patches of dark, brown, or greyish skin
- Enlarged melanocytes (melanin cells)
- A rise in the number of melanin cells
- An abnormal buildup of elastic tissue; and
- An increase in the number of blood vessels in the face (Verdier Sevrain *et al.,* 2006).

4. Epidemiology

Patients with darker skin who have Fitzpatrick skin types IV to VI and reside in regions with high levels of ultraviolet radiation (UVR) are more likely to develop melasma. It affects Hispanic, Asian, and Afro-descendant people more frequently. The condition often manifests between the ages of 30 and 55, with uncommon cases of adolescence or the post-menopausal era being reported (Moin *et al.,* 2006).

5. Diagnosis

Melasma is easily diagnosed with a visual examination. The degree of the skin's pigmentation may then be clearly viewed by employing Wood's light. Blacklight is a particular kind of lamp. When compared to normal skin, it lights the skin and makes it easy for the technician to identify pigmentation and UV damage. A Wood light displays sun damage on the skin's surface as well as deeper damage that is still hidden and not visible to the naked eye. The Wood's lamp is a long-wavelength UV light source that generates light with a wavelength between 340 and 400 nm with a peak at 365 nm (Glichrest *et al.,* 1977).

6. Effect of hormone on melasma

Because melasma frequently develops during pregnancy, while using hormonal contraceptives, while receiving oestrogen therapy for prostate cancer, and while using conjugated oestrogen in postmenopausal women, hormones play a role in the pathogenesis of melasma. Melasma is more common in females than in males. Unwanted cutaneous side effects of oral contraceptives include melasma. Melasma is frequently thought of as a hormonally induced physiological alteration in the skin. Oestrogens are crucial in both physiological and pathological skin disorders, such as pigmentation. The many receptors for oestrogen and progesterone regulate their biological effects (Cestari *et al.,* 2009; Lee, 2015; Sheth and Pandya, 2011).

7. Causes

- **Anti-seizure medications:** Medications that keep seizures from happening can contribute to melasma. Clobazam is an illustration of an anticonvulsant.
- **Contraceptive (contraception):** Melasma has been seen in patients on oestrogen and progesterone-containing birth control tablets.
- **Estrogen/diethyl stilbestrol:** The hormone oestrogen exists in the synthetic (human) form of diethylstilbestrol. Prostate cancer is frequently treated with it. There is a correlation between elevated oestrogen levels and melasma again**.**
- **Genetics**: About 33-50% of melasma patients say that a family member also has the disease. Melasma is common in matched twins.
- **Hypothyroidism**: Your thyroid gland is underactive if you have hypothyroidism.
- **LED screens**: The LED lights in TVs, computers, smartphones, and tablets might contribute to melasma.
- **Pregnancy**: The cause of the "mask of pregnancy" in pregnant women is unknown. The third trimester of pregnancy is when higher amounts of oestrogen, progesterone, and melanocyte-stimulating hormones are believed to be responsible.
- **Hormones**: Some persons may be impacted by hormones like progesterone and oestrogen. When postmenopausal women are administered progesterone, melasma is occasionally discovered. Your melasma lesions most likely contain higher oestrogen receptor levels even if you are not pregnant.
- **Makeup (cosmetics):** Some cosmetics can result in a response known as a phototoxic reaction.
- **Phototoxic medications** (drugs that increase your sensitivity to sunlight): These include certain antibiotics, NSAIDs, diuretics, retinoids, hypoglycemic medications, antipsychotics, targeted medications, and some other medications.
- **Skin care items:** Products that often irritates skin can exacerbate melasma.
- **Soaps:** Melasma may be brought on by or made worse by some perfumed soaps.
- **Tanning beds**: The UV rays from tanning beds can often be even more harmful to skin than those from the sun (Sarkar *et al.,* 2012).

8. Melasma treatment

A distinguishing feature of melasma is its difficulty in treatment. Whereas some types of hyperpigmentation can be treated with topical creams, melasma is not treated so easily due to the hormones that contribute to its cause in the first place. Even though most treatment options are the same as other forms of hyperpigmentation, the success rate is typically much lower. Because hormones are a personalized set of chemicals, each person's melasma responds differently to treatment, making it notoriously difficult to treat.

The majority of doctors advise a combination therapies, which may include powerful sunblock, vitamins, and skin-brightening medicines like hydroquinone. In some cases, the melasma can clear up quickly. In other cases, it might take a while longer. For some people, treatments must be repeated indefinitely, or the melasma returns. Just as each individual's hormones are different, each person's response to treatment is different, making it almost impossible to predict who will respond well and who will take more time and effort (Ball Arefiev and Hantash, 2012).

9. Topical treatment

Melasma is still mostly treated with topical therapies along with other hyperpigmentation problems. The most common anti-melanogenic drug, hydroquinone (HQ), works by competitively blocking tyrosinase, the rate-limiting enzyme in melanogenesis, to prevent the conversion of l-3,4-dihydroxyphenylalanine to melanin. Tyrosinase and other membrane lipids and proteins including, may be harmed by the oxidative products from HQ. Unfortunately, concerns over HQ's safety continue to be heated. Due to its possible side effects, including exogenous ochronosis and irreversible depigmentation, the European Committee forbade the use of HQ in cosmetics (Kwon *et al.,* 2016). Concerns were also raised about its possible carcinogenic risk due to the liver's production of its metabolites, called p-benzoquinones (Westerhof *et al.,* 2005). Additionally, vitiligo, one of the most difficult skin conditions to treat, has been found to be induced by rhododenol, a recently developed tyrosinase inhibitor (Nishigori *et al.,* 2015). These indicate that more dependable and efficient topical chemicals must be developed.

The above-mentioned pigmentary diseases will frequently reoccur since the environmental factors that influence melanogenesis in melasma still exist, despite the fact that topical therapy can reduce melanogenesis. Then, topical treatment must be paired with an anti-aging strategy, including topical tretinoin, laser or light therapy, or other antiageing methods. Four per cent HQ, 0.05 per cent tretinoin, and one per cent fluocinolone acetonide make up a triple combination cream (TCC) (Ball Arefiev *et al.,* 2012). The Food and Drug Administration (FDA) of the United States has only authorized TCC as a means of treating melasma (Gupta *et al.,* 2006; Rendon *et al.,* 2006). In addition to having an antiwrinkle action, tretinoin also has a hypopigmenting property (Kang *et al.,* 2009). Endothelin-1 and granulocyte-macrophage colony-stimulating factor, which are implicated in UV-induced melanogenesis, are secreted less when steroids are present (Lee *et al.,* 2001; Kim *et al.,* 2001).

10. Utilities of herbal extracts in Melasma

One of the phenomena seen in herbal extracts that helps increase potency and is frequently employed in cosmetic formulations is synergism. The most often utilized compounds are hydroquinone, vitamin C, also known as arbutin, and the derivatives of kojic acid. Alternatives made from blueberries, gooseberries, and grapes are also used in cosmetic formulation in addition to this herbal combination. One of the best tropical therapies for hyperpigmentation is hydroquinone. Its usage in persons with dark skin has been linked to side effects include skin irritation, ochronosis, and contact dermatitis. Corticosteroids can have local or systemic negative effects, even when used for a long time. The most recent additions to the list of melasma therapy alternatives are topical polyherbal medicines because they slow down and redirect melanin formation (Rathee *et al.,* 2021).

10.1 *Vaccinium cyanococcus*

The Ericaceae plant, *Vaccinium cyanococcus*, also known as the blueberry, inhibits the production of melanin, promotes skin elasticity, keeping skin moist, and delaying the ageing process, reducing and eliminating melanin and chloasma. Anthocyanoside, tannins, hydroxyl benzoic acids, and flavonol glycosides are among the chemicals that are present (Wing kwan Chu *et al.,* 2011).

10.2 *Emblica officinalis*

Compared to other fruit juices, *Emblica officinalis* (Gooseberry) fruit juice has the greatest concentration of vitamins C and E. Tyrosinase may be inhibited by the extract through MITF and Trp-1 gene expression inhibition; nevertheless, treatment with low concentrations of the extract may promote Trp-2 gene expression. Higher antioxidant and anti-melanogenesis properties are present in ethanol extract. Sesquiterpenoids, alkaloids, flavone glycosides, phenolic glycosides, phenolic acids, carbohydrates, mucic acids, amino acids, tannins, and a variety of other compounds are all present (Variya *et al.,* 2016).

10.3 *Glycyrrhiza glabra*

The liquorice plant, *Glycyrrhiza glabra* is a perennial plant belonging to the Leguminosae family. Liquorice extract lessens hyperpigmentation by reducing the production of free radicals by spreading the melanin, limiting melanin manufacture, and regulating cyclooxygenase activity. Tyrosinase inhibitory and anti-inflammatory effects have been found in glabridin, an oil-soluble liquorice extract derivative. One of the many organic substances that brightens skin when applied topically is liquorice extract. By spreading the melanin, preventing melanin manufacture, and suppressing cyclooxygenase activity, liquorice extract reduces hyperpigmentation by lowering the formation of free radicals (Yokota *et al.,* 1998).

10.4 *Vitis vinifera*

Climbing shrubs known as *Vitis vinifera*, or grapes, are endemic to many regions of the world, particularly the tropical, subtropical, and some temperate zones. Antioxidant proanthocyanidin is obtained from grape seeds. Proanthocyanidin treats melasma by preventing the tyrosinase enzyme (Salma Akbar Bagwan, *et al.,* 2022).

10.5 *Butea monosperma*

Butea monosperma also known as flame of the forest commonly belongs to Fabaceae family. Innate in flame of the forest, also known as Palash, is the emollient or smoothing vitamin E, which also possesses antioxidant and free radical-scavenging qualities. Steroids and flavonoids make up the ingredients (Anuradha Sehrawat and Vijay Kumar, 2012).

10.6 *Nelumbo nucifera*

Nelumbo nucifera (Lotus) leaves belonging to the family Nelumbonaceae, regenerates new skin cells with regulated melanin and eliminates dead skin cells to remove hyperpigmentation efficiently. It used as a skin whitening and antiwrinkle agents. Lotus contains a powerful antioxidant flavonoid luteolin-7-glucoside that protects the skin from damage caused by free radicals (Su-Yeon Kim and Gap-Soon Moon, 2015; Westerhof and Kooyers, 2005).

10.7 *Citrullus lanatus*

Citrullus lanatus (watermelon seed) seed belonging to the Cucurbitaceae family, contains vitamin A and other minerals that help to improve hyperpigmentation and overall skin appearance. Watermelon seed also act as a moisturizer. It contains various chemicals including phenols, saponins, tannins, flavonoids, and alkaloids (Maria Sorokina, *et al.,* 2021).

10.8 *Acalypha indica*

Acalypha indica (Kuppaimeni) belongs to Euphorbiaceae, is a very well-known medical plant that is frequently used to treat conditions and diseases of the skin. Kuppaimeni is rich in alkaloids, flavonoids, phenolic compounds, saponins, and steroids. It has effective anti-bacterial and anti-inflammatory properties (Sudhakar Chekuri, *et al.,* 2020).

10.9 *Senna auriculata*

Senna auriculata (Senna/avaram) belongs to Fabaceae. It is good for external application and helps to treat many skin disorders. It lessens uneven skin tone, cures black spots, and enhances complexion. They contain a lot of antioxidants, and the flower's extract is full of cardiac glycosides, flavonoids, steroids, terpenoids, saponins, and other compounds. Senna flowers are used to cure rashes, dry skin, irritation, and red areas on the skin. It also regulates the pigmentation of blackheads on the face (Vijayakumar Rajendran *et al.,* 2017).

11. Phytocompounds

11.1 Arbutin

Arbutin is a glycoside, a glycosylated hydroquinone that is isolated from a variety of medicinal plants, mostly from the family Ericaceae, including the bearberry plant (*A. uvaursi*) of the genus Arctostaphylos. Tyrosinase is inhibited when applied topically, which stops the production of melanin. Arbutin may also be degraded by the natural skin microflora, however, hydroquinone has more powerful free-radical scavenging action and tyrosinase inhibition than arbutin. Arbutin's effects are dose-dependent and less harmful than those of hydroquinone (Bang *et al.,* 2008).

11.2 Flavonoids

Flavonoids are widely utilised in cosmetics because they are multi-functional ingredients with antioxidant and calming properties. The biggest class of plant-derived active compounds, more than 5000 flavonoids have been isolated and identified. Due to their antiradical qualities, flavonoids are most well-known for their skin-related effects. Resonance-stabilized anion radicals are created when high reduction potential phenol groups are present. Flavonoids are important because they can suppress the tyrosinase enzyme, which in turn regulates the synthesis of melanin, according to recent studies (El-Nashar *et al.,* 2021). Many flavonoid compounds originating from plants exhibit hypopigmentary effects, and it is yet unknown how these chemicals function. These include aloesin (from the aloe tree), ellagic acid (from green tea, strawberry, and eucalyptus), and catechin conjugated with gallic acid (from green tea leaves) (Choi and Shin, 2016).

12. Tyrosinase inhibitors naturally present in plants

A crucial enzyme to target while creating novel chemical ligands to inhibit melanogenesis is tyrosinase. Topical drugs affect several phases of melanogenesis; the most frequent form of action is suppression of the tyrosinase enzyme. Listed some medicinal plants and phytochemicals with tyrosinase inhibitory effects in Table 1. Gupta

Table 1: Tyrosinase inhibitory plants for the management of Melasma

Name of the plant	Phytocompounds	Pharmacological effect
Vitex negundo	Negundin	Used as a tyrosinase inhibitor, a skin lightening agent, and to prevent the production of post-inflammatory pigments (Azhar-Ul-Haq *et al.,* 2006)
Aloe vera	Aloe resin E, barbaloin, aloesin, aglycone of aloenin, 2-O-feruloyl aloesin, and 2-O-feruloyl aloesin	Exhibits potent tyrosinase inhibitory action (Gupta and Masakapalli, 2013)
Morus alba	Oxyresveratrol and mulberroside-A	Antioxidant and tyrosinase-inhibiting properties (Lee *et al.,* 2002)
Panax ginseng	Ginsenosides. P-coumaric acid	Inhibit L-tyrosine oxidation. Additionally, leaves offer characteristics that help retain moisture, preserve skin, and whiten skin (Lee *et al.,* 2008)
Ginkgo biloba	Quercetin and kaempferol	Gingko has tyrosinase, antioxidant, anti-inflammatory, and anti-vasculature effects (Wang *et al.,* 2008)
Azadirachta indica	Azadirachtin, isoeldenin, nimbin, nimbinene, 6-desacetyllnimbinene, and nimbandiol	Exhibits antioxidant and antibacterial capabilities in addition to inhibiting the tyrosinase enzyme (Chiocchio *et al.,* 2018)
Santalum album	Alpha-santalol	Sandalwood oil provides antioxidant, preserving, smoothing, moisturising, hydrating, and skin anti-wrinkling effects in addition to inhibiting the oxidative enzyme 5-lipoxygenase (Bhowmik *et al.,* 2011)
Muntingia calabura	Fisetin, pinostrobin, and rhamnetin	Plant extracts have a melanogenesis inhibiting effect (Ragasa *et al.,* 2015)
Blumea balsamifera	Flavonoids	Possess anti-tyrosinase activity and antioxidant (Thach *et al.,* 2017)

Magnolia officinalis	Magnoloside	Exhibits depigmenting activity and antityrosinase activity (Ding *et al.,* 2011)
Pueraria thunbergiana	Geneistein, daidzein, formononetin, apigenin	Exhibits skin whitening agent and antityrosinase activity (Han *et al.,* 2014)
Curcuma longa	Curcumin, demethylcurcumin, and bisdemethyl curcumin	Have tyrosinase inhibitory or de pigmentary activity (Du *et al.,* 2011)
Camellia sinensis	Epigallocatechin-3-gallate, gallic acid	Show higher tyrosinase inhibitory activity (Kim *et al.,* 2015)
Crocus sativus	Isorhamnetin	Used as a skin-lightening agent and to cure skin hyperpigmentation (Li and Wu, 2002)
Hemidesmus indicus	Hemidesminine, lupeal, and vanillin	Antioxidant and tyrosinase inhibitory activity (Kundu and Mitra, 2014)
Euphorbia supina	Nodakenin, protocatechuic acid, and 3-O-glucoside	Antioxidant and tyrosinase inhibitory activity (Song *et al.,* 2014)
Acacia catechu	Protocatechuic acid, taxifolin, epicatechin	Tyrosinase inhibitory activity (Anurukvorakun *et al.,* 2019)
Carica papaya	Papain, chymopapain A and B, vitamin C, thiamine, riboflavin, niacin and carotene,	Antioxidant (Rodrigo and Perera, 2018)
Arnica montana	3β,16β-dihydroxy-21a-hydroperoxy-20[30]-tariaxasten	Inhibit melanin synthesis (Aeda *et al.,* 2007)
Artemisia dracunculus	piperidylamide with undeca-2E,4E-dien-8,10-dynoic acid	Inhibit melanin synthesis (Yamada *et al.,* 2011)
Thymelaea hirsuta	Genkwadaphnin and gnidicin	Inhibit melanin synthesis (Kawano *et al.,* 2007)
Betula pendula	Chrysoeriol, isoquercitrin, catechin, p-coumaric acid, chlorogenic acid, catechin, and quercetin-3-O-glucuronide	Antioxidant and tyrosinase inhibitory activity (Germanò *et al.,* 2012)
Caesalpinia sappan	Homoisoflavanone, sappanone A	Inhibit melanin synthesis (Chang *et al.,* 2012)
Calcarpa longissima	Carnosol and carnosic acid	Inhibit melanin synthesis (Yamahara *et al.,* 2016)

13. Conclusion

Melasma causes sufferers mental and psychological stress. Many people get several therapy, ranging from invasive medical procedures to cosmetic procedures, which are either useless or worsen their condition. Some people spend more money for years as therapy costs. It is frequently characterized as a troubling issue that lowers the patient's quality of life. Plant-derived active ingredients are becoming more and more popular for enhancing skin. It is obvious that natural sources and extracts serve as a storehouse of substances that may be used topically to enhance skin's general look and hyperpigmentation. Through their antioxidant effectiveness and ability to shield macromolecules like collagen from UV rays, these substances may potentially provide further potential for protective cosmeceutical application. In the near future, effective anti-tyrosinase drugs with improved efficiency and safety were developed as a result of the current review.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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