



REVIEW ARTICLE

Potential of Natural Bioactive Compounds in Management of Melasma

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ARTICLE HISTORY

Received: 05 December 2023

Accepted: 14 February 2024

Available online

Version 1.0 : 11 March 2024



Additional information

Peer review: Publisher thanks Sectional Editor and the other anonymous reviewers for their contribution to the peer review of this work.

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Indexing: Plant Science Today, published by Horizon e-Publishing Group, is covered by Scopus, Web of Science, BIOSIS Previews, Clarivate Analytics, NAAS, UGC Care, etc See https://horizonepublishing.com/journals/index.php/PST/indexing_abstracting

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CITE THIS ARTICLE

Gupta J, Rani A, Kumar A, Kumar B. Potential of Natural Bioactive Compounds in Management of Melasma. Plant Science Today (Early Access). <https://doi.org/10.14719/pst.3164>

Abstract

Melasma is a form of inherited hyper-melanosis that appears as asymmetrical, brown-colored, uneven, reticulated macules on UVR-exposed skin, particularly on the facial area. The etiopathogenesis of melasma has been linked to several causes, including UV exposure, endocrine factors, genetic predisposition, anti-epileptic medications, and various cosmetics. The initial course of treatment for hyperpigmentation involves applying topical formulations of widely used substances like kojic acid, glycolic acid, and hydroquinone. Pharmaceuticals such as melatonin, tranexamic acid, and cysteamine hydrochloride are administered orally in this process. Chemical peels and laser therapy are examples of second-line therapies that are applied under the direction of trained experts. Unfortunately, these treatments have certain drawbacks and complications, including erythema, dryness, and skin peeling, and they take time to work, necessitating the use of herbal formulations for the management of hyperpigmentation. Bioactive compounds isolated from plants, such as arbutin, aloesin, flavonoids, hesperidin, licorice, ellagic acids, genistein, and quercetin, inhibit melanogenesis without melanocytotoxicity by different mechanisms. This review provides information on natural bioactive compounds used for the management of melasma.

Keywords

bioactive compounds; melasma; management; treatment

Introduction

Skin hyperpigmentation, a common dermatological condition, causes the skin's color to typically darken (1). This happens when melanin in specific skin regions is overproduced. Numerous internal and environmental variables, such as hormonal fluctuations, inflammation, injury, eczema, acne, certain drugs, ultraviolet radiation, etc.; can cause these changes in skin color (1,2). Several often-seen hyperpigmentation diseases include ephelides, lentigines, post-inflammatory hyperpigmentation, melasma, and numerous others (1-3).

Melasma originates from the Greek word "melas," which means black. (4-6). Melasma is characterized by evenly spaced, pale to dark brown patches on the face, and rarely on the forearms and neck (3, 7-12). Melasma is usually confused with chloasma, a kind of hyperpigmentation triggered by pregnancy or alterations to ovarian and uterine hormone levels (5, 9, 13). Even though melasma develops during pregnancy, it is referred to as "the

mask of pregnancy" and usually disappears soon after giving birth, necessitating no treatment. Yet, there are a variety of different factors that might cause melasma (9). Both sexes are affected, but women are more likely to experience it, especially when they are pregnant. Every race is affected, but people with intermediate skin phototypes who live in places with a lot of ultraviolet exposure are more susceptible (4, 13). Pregnancy, the use of oral contraceptives, endocrine malfunction or hormone therapy, genetic susceptibility, and exposure to UV light are some of the most significant contributing factors. (9).

There has been a great deal of interest in bioactive substances derived from natural sources in recent decades. There is a vast array of bioactive chemicals due to the wide range of plant biodiversity. The majority of bioactive chemicals are particular secondary metabolites possessing antibacterial, immunomodulatory, inflammatory, and antioxidant capabilities. It is crucial to examine the bioactive components of various types of terpenes, flavonoids, alkaloids, coumarins, stilbenes, etc. as well as some of their modes of action for the management of melasma. Some of them are focused in this study (14).

Materials and Methods

This review provides information on natural bioactive compounds used for the management of melasma. The literature search was done using keywords viz. bioactive compounds, treatment of melisma, and management of melisma using various search tools from Science Direct, PubMed, Elsevier, etc.

Melanin and Its Role in Melasma

Skin hyperpigmentation is caused by a process known as melanogenesis, which produces the pigment melanin. Melanosis refers to the overproduction of melanin pigment in epithelial cells (Fig. 1). The quantity and epidermal distribution of melanin in hyperpigmentation is a crucial biological characteristic. Melanin is a blend of biopolymers created by melanocytes found in the basal layer of the epidermis, not a single molecule (15, 16). Humans have distinctive skin, hair, and eye colors because melanocyte cells generate two distinct kinds of melanin pigments eumelanin (black or brown) and pheomelanin (yellow-reddish) (17). About 36 keratinocytes surround one melanocyte (11). Numerous studies show that people with darker complexions possess elevated amounts of eumelanin than those with lighter complexions (3, 15). In terms of biological behavior, pheomelanin differs from eumelanin in that it can generate the superoxide radical anion and activate oxygen. These features could be the reason for pheomelanin's high phototoxic potential, which could help those with lighter skin types acquire photoinduced malignancies (2, 15, 18). The enzymes tyrosinase and dopachrome tautomerase are both necessary for the production of melanin (15, 17, 19). Tyrosinase, an essential enzyme in the production of melanin, has the potential to overexcite and result in hyperpigmentation (15). Tyrosine is hydroxylated by the enzyme tyrosinase, which results in the formation of L-3,4-

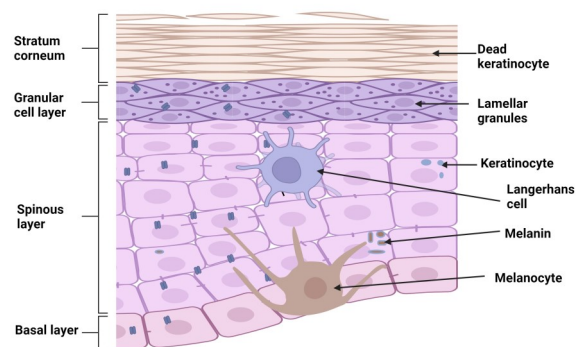


Fig. 1. Location of Melanin and Melanocytes

DOPA. The subsequent oxidation of DOPA-quinine results in L-3,4-DOPA, which is again subjected to oxidation to yield melanin by a free radical coupling mechanism. The enzyme dopachrome-tautomerase transforms dopachrome into 5,6-dihydroxyindole-2-carboxylic acid (DHICA). Numerous plants and chemical substances exhibit tyrosinase-inhibitory properties (3).

Clinical Classification of Melasma

Melasma only affects places that have been exposed to the sun. In addition to the face, the neck and forearm might also infrequently be affected. Its clinical manifestation is more pronounced during and immediately after exposure to the sun. The melasma patches' edges have an irregular, serrated, and symmetrical distribution. Possible spots for melasma are well depicted in (Fig. 2). Three melasma patterns have been identified based on clinical manifestations viz. centrofacial pattern, malar pattern, and mandibular pattern (7, 5, 11, 20, 21). Centrofacial pattern affects the nose, cheeks, forehead, chin, and upper lip (7, 11). About 65% of cases exhibit a centrofacial pattern. Malar pattern affects the nose and cheeks. About 20% of cases of melasma exhibit a malar pattern (11). Mandibular pattern affects the mandibular ramus (6, 16). About 15% of cases of melasma exhibit a mandibular pattern (11).

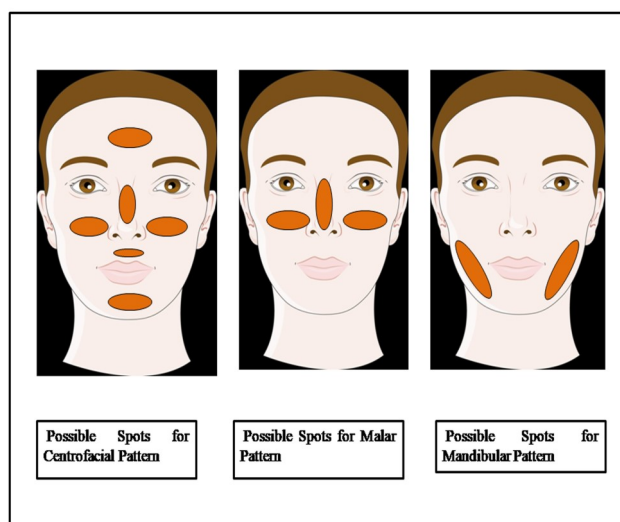


Fig. 2. Distinct Patterns of Melasma

Pretreatment Evaluation of Melasma

Pretreatment evaluation is categorized into four categories i.e. epidermal type, dermal type, mixed type, and intermediate type. Epidermal type is indicated by light brown hyperpigmented patches, the color difference between them and normal skin is emphasized by Wood's light. Patients of this group with melasma were discovered to be the majority. Dermal type indicates that the hyperpigmentation doesn't stand out due to any color contrast and instead appears ashen or bluish-gray, under Wood's light. In this instance, depigmenting chemicals cannot remove the pigment since it must be transported by macrophages. Mixed type indicates that Wood's light improves the color contrast in some regions of the hyperpigmentation, which is often dark brown, but not in others. Intermediate type indicates that patients with dark skin tones (skin types V–VI) frequently have lesions that are difficult to classify using Wood's light (5, 7, 18, 22-24).

Pathogenesis of Melasma

Melasma's pathophysiology is not entirely known (6, 9, 18). The etiopathogenesis of the disease has been linked to several causes, including endocrine factors, genetic predisposition, UVR exposure, and other factors (**Fig. 3**) (5, 7, 25). The endocrine factors involve the usage of contraceptives, the utilization of oestrogen in postmenopausal women, and the use of diethylbestrol to treat prostate cancer; both organic and synthetic oestrogen and progesterone have been linked in the etiology of melasma (5, 7, 26). Patients who suffered from melasma exhibited anomalies, including noticeably lower concentrations of serum estradiol and noticeably greater concentrations of luteinizing hormone, which suggested mild ovarian malfunction. In addition to having an unusual hormonal profile, male melasma patients also have low serum testosterone levels and excessive levels of

circulating luteinizing hormone. Additionally, it has been discovered that there is a substantial correlation between thyroid autoimmunity and melasma in women, particularly in those whose health deteriorated after using oral contraceptives or during pregnancy. Although the exact mechanism by which oestrogens cause melasma is unclear, it has been suggested that melanocytes have oestrogen receptors that make them more susceptible to the condition (5, 7). Genetic and racial factors (genetic predisposition) are also considered important causes as melasma is much more familiar in persons of Asian and Latino ancestry than in people of other races (26,7). The role of sunlight (UVR) is vital. Reactive oxygen species produced by UV radiation are known to cause oxidative damage. The biological impacts of UVR are strongly influenced by oxidative stress. UVR exposure causes oxidative damage to the skin and its constituent parts. Melasma almost always becomes worse after unregulated sun exposure, although it gets better when you avoid the sun or in the winter. Moreover, melanocytic activity is increased by UV exposure (4, 7, 19). Other factors include Antiepileptic medications, specific cosmetic chemicals (oxidized linoleic acid, salicylate, citral, preservatives), and sun exposure alone may all have an impact on the etiology of melasma (7).

Preventive Measures for Melasma

Patients should be counseled to avoid exposure to the sun, especially during times of high radiation. When exposure to the sun cannot be avoided, they should wear a wide-brimmed hat, cover-up, and broad-spectrum sunscreen (11, 27). In these circumstances, it is advised to use sunscreens with an SPF of at least 30 and formulations that contain physical photoprotective agents. Patients should be urged to refrain from using scented cosmetics or skincare products on their faces. Alternative treatments should be considered in cases where hormonal contraceptives or hormone replacement therapy is the cause of melasma (11).

Therapeutic Approaches to Treat Melasma

Numerous treatment modalities, such as topical whitening creams (hydroquinone [HQ], azelaic acid, retinoids, vitamin C, kojic acid, and arbutin), chemical peels, mesotherapy, and energy-based tools (laser, light, micro-needling, radiofrequency [RF], microdermabrasion, iontophoresis, and sonophoresis), have been tried till date with disappointing outcomes. Some of them are discussed in **Table 1** (28,29,30-35). Monotherapy using chemical peels and topical whitening creams frequently necessitates a lengthy course of therapy and results in a high rate of recurrence after stopping the regimen (34-36). Energy-based device application causes erythema, edema, post-inflammatory hyperpigmentation (PIH), guttate hypopigmentation, and rebound of pigmentation. These side effects come with many treatment options and significant expenses (37). For an effective response rate when treating melasma, an alternate approach is necessary due to the disease's multifaceted pathophysiology (35-38).

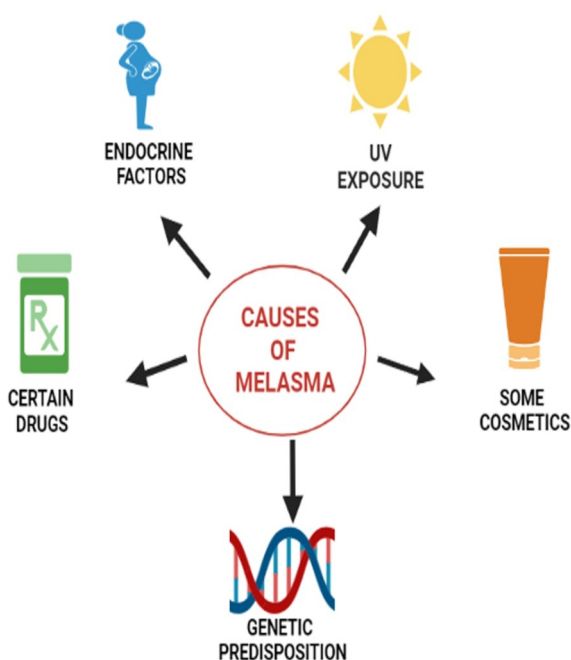


Fig. 3. Causes of Melasma

Table 1. Side Effect Associated with Local and General Treatment of Melasma

S.NO	TREATMENT	DRUG/THERAPY	SIDE EFFECTS	REFERENCES
1.	Local Treatment	Hydroquinone	risk of ochronosis, nail discoloration, allergic contact dermatitis, and depigmentation.	(39)
		Retinoic acid	erythema and desquamation	(40-41)
		Corticosteroid	skin atrophy and telangiectasia	(42-45)
		Tranexamic acid	gastrointestinal side effects, thrombotic disease, intracranial bleeding, traumatic events, and color blindness	(46-49)
		Kojic acid	Redness, burning sensation, erythema and contact dermatitis	(50-51)
		Chemical peels	Bacterial and viral infections, atrophy, telangiectasia, milia and pore enlargement	(4)
2.	General treatment	Laser therapy	Hypopigmentation, hyperpigmentation, hypertrophic scarring, and atrophy	(52-53)
		Vitamin c and E	stomach pain, diarrhoea, or even calculus may form	(54-55)

Natural Bioactive compounds used in the Treatment of Melasma:

Despite an abundance of allopathic medications, plant-based treatments are widely used and trusted because they pose fewer safety risks and are more environmentally friendly. A significant portion of the global healthcare system relies on medicinal plants, which are recognized to enhance the quality of life. Ayurveda, Unani, Siddha, Chinese, and other indigenous medical systems are practiced in India and Southeast Asia, whilst the rest of the world treats herbal items as complementary and alternative therapies (44). For patients with darker skin, several drugs and procedures can safely and effectively address their skin hyperpigmentation. As a result, natural

bioactive compounds are superior options for treating skin hyperpigmentation(13). Some natural bioactive compounds along with their mode of action for treating skin hyperpigmentation are shown in **Table 2**. The antityrosinase, antioxidant, and skin-whitening activities of herbs are some of their potential modes of action for treating skin hyperpigmentation. A large no. of herbs available with these activities i.e. *Vitis vinifera* L., *Pinus pinaster* Aiton, *Ginkgo biloba* L., *Aloe ferox* Mill., *Coffea Arabica* L., *Glycyrrhiza glabra* L., *Vitex negundo* L., *Morus alba* L., *Curcuma longa* L., *Panax ginseng* C.A, Mey, *Azadirachta indica* A.Juss, *Fragaria × ananassa* Duchesne, *Muntingia calabura* L., etc. to treat melasma.

Table 2: Overview of Natural Bioactive Compounds Associated with Melasma and Their Activities

Sl. NO.	Herb	Biological name and its family	Active constituent	Mechanism of action	Part (s) used	References
1.	Grape seed extract	<i>Vitis vinifera</i> L. (Vitaceae)	Proanthocyanidin	antioxidant, anti-tyrosinase activity	Seed and leaf	[3,57-59]
2.	Pycnogenol	<i>Pinus pinaster</i> Aiton (Pinaceae)	Procyanidin	anti-inflammatory and antioxidant	Bark	[4, 60]
3.	Ginkgo	<i>Ginkgo biloba</i> L. (Gingkoaceae)	quercetin and kaempferol derivatives	anti- tyrosinase activity	Flower	[61-62]
4.	Aloe vera	<i>Aloe ferox</i> Mill. (Asphodelaceae)	Plicataloside and aloesin	anti- tyrosinase activity	Leaf	[63-66]
5.	Coffee berry	<i>Coffea arabica</i> L. (Rubiaceae)	caffeine, caffeic acid and chlorogenic acid	antioxidant property	Fruit	[67-68]
6.	Liquorice extract	<i>Glycyrrhiza glabra</i> L. (Leguminosae)	Glabridin	anti-inflammatory, moisturizing agent, UV-B protection, bleaching agent.	Root	[69-73]
7.	Chinese chaste tree	<i>Vitex negundo</i> L. (Lamiaceae)	Negundin A and [+] lyoniresinol-3a-O-b-D-glucoside	anti- tyrosinase activity	Root	[74-76]
8.	White mulberry	<i>Morus alba</i> L. (Moraceae)	Polyphenols	anti-tyrosinase activity and ROS scavenger	Fruit	[77-79]
9.	Turmeric	<i>Curcuma longa</i> L. (Zingiberaceae)	Curcuminoids	antioxidant property	Root	[3, 80]
10.	Korean Ginseng	<i>Panax ginseng</i> C.A.Mey (Araliaceae)	Ginsenoside, p-Coumaric acid	antioxidant property	Root	[81-82]
11.	Neem	<i>Azadirachta indica</i> A.Juss (Meliaceae)	Oleic acid, azadirachtin, isomeldenin, nimbin	Antioxidant, Antibacterial	Leaf, bark	[83-84]
12.	Strawberry	<i>Fragaria × ananassa</i> Duchesne (Rosaceae)	Procyanidin	anti-tyrosinase and antioxidant activity	Root	[85-86]
13.	Jamaica cherry	<i>Muntingia calabura</i> L. (Muntingiaceae)	Stigmasterol, triglyceride, α-linolenic acid	anti-tyrosinase and antioxidant properties	Flower, leaf, Fruit	[3, 87]

Results

A précised and organized tabular data based on natural bioactive compounds associated with melasma and their activities is collected.

Conclusion

Treatment for melasma still presents difficulties. Resistance occurrences or recurrences are frequent. Physical therapies like lasers can also cause rebound hyperpigmentation. Several important issues need to be solved before melasma can be treated. Firstly, it is still unclear if the alterations in the dermis of melasma patients are simple epiphenomena of prolonged sun exposure or primary events that activate melanocytes. If the primary disease is melasma, the dermal and epidermal pigments would be a therapy focus. Large-scale randomized, controlled clinical research, such as those on vascular laser therapy for melasma, may help address this matter. Second, as we have mentioned, there is an ongoing debate on the role and future of melanophages. It needs to be explored whether melanophages are required for the therapeutic outcome. The likelihood is that the number or activity of melanocytes will have a greater impact on how effectively melasma responds to therapy. RCM, which enables repetitive examination, might be a helpful method to address this problem. Finally, managing the fundamental genetic alteration in melasma may be quite difficult. However, more study is required to identify the potential genes responsible for melasma development.

Acknowledgements

The authors are thankful to the institute for providing the necessary facilities.

Authors' contributions

AR participated in the design of the study. JG conceived of the study and wrote the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Declaration : Authors do not have any conflict of interest to declare.

Ethical issues: None.

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