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Skin hyperpigmentation and its treatment with herbs: an alternative method

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Abstract

Background: With an increasing number of patients, those who are facing a lot of skin-related complaints, often referred to as skin of pigmentation patients, are on the rise. Among all the most common complaints in patients with skin of color is hyperpigmentation. So, there is need of herbal formulation for treatment of hyperpigmentation.

Main body: This review article addresses the different types of hyperpigmentation, causes, and its treatment with herbs for the management of the skin hyperpigmentation. As uneven pigmentation of skin or hyperpigmentation is a common skin condition, which occurs when the skin produces more melanin. This can make spots or patches of skin appear darker than surrounding areas. Some forms of hyperpigmentation with post-inflammatory, melasma, and sun spots are more likely to affect areas of face, arms, and legs due to sun exposure and injury. Although the availability of multiple treatments for the condition which leads to some adverse effects, hyperpigmentation continues to present skin care management challenges for dermatologists.

Conclusion: Some plants and phytoconstituents, e.g., *Azadirachta indica*, *Glycyrrhiza glabra*, *Panax ginseng* and genistein, ellagic acids, quercetin, are very useful in herbal cosmetic as anti-hyperpigmentry agents in cosmetic industries. Some of flavonoids and triterpenoids present in plants also show their effect as antioxidant and skin whitening agents. It is expected that this review will compile and improve the existing knowledge on the potential utilization of herbs for the treatment of skin hyperpigmentation.

Keywords: Melanin, Hyperpigmentation, Tyrosinase, Age spot, Melasma

Background

Skin hyperpigmentation is a disorder in which patches of skin become darker in color than the normal surrounding skin. This occurs when melanin is overproduced in certain spots on the skin. Melanin is an important pigment in skin hyperpigmentation which is produced by the process called melanogenesis. Increased melanin pigment in epithelial cell is called melanosis. Epidermal melanosis is when melanocytes are in normal number but melanin is increased in hyper pigmented skin and dermal melanosis occur when melanin is present within the dermis between bundles of collagen [1]. Melanocyte cells (one melanocyte is surrounded by approximately 36 keratinocytes) produce two type of melanin pigment, eumelanin (Black or brown) and pheomelanin (yellow reddish) which are responsible for skin, hair, and eyes color in human. There is mainly three type of skin 3 hyper-pigmentation which are melsama [2, 3], post-inflammatory hyper pigmentation, and age spot or liver spot [4]. Skin hyper-pigmentation is caused by sun exposure, Addison's disease [5], hormonal imbalance, and vitamin B_{12} [6]. In skin cell, UV radiation produces reactive oxygen species (ROS) which activate the intracellular signaling pathways including mutagen-activated protein kinase. As human keratinocyte exposed to UV-B radiation shows higher p38 mitogen-activated protein kinase (MPAK) activity, which produce pro-inflammatory cytokines such as

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1L-1, cyclooxygenase (cox-2), and TNF-α expression [7]. There are two enzymes responsible for melanin production; one is tyrosinase and the other is dopachrome tatuomerase. Tyrsosinase is a main enzyme in melanin growth and over activity of tyrosinase enzyme causes hyper-pigmentation [8]. Tyrosinase involves amino acid tyrosine which on hydroxylation convert into L-3,4-DOPA that form DOPA-quinine by oxidation which is further oxidized by a free radical-coupling pathway to form melanin [9, 10]. The other enzyme dopachrome tatuomerase catalyze the transformation of dopachrome into 5,6-dihydroxyindole-2-carboxylic acid (DHICA) [11]. There are many herbs or chemical compound found which has tyrosinase inhibitory properties. Tyrosinase inhibitors demands are increasing on the industrial and clinical scale, so in-vitro assay and screening technique are also developed for tyrosinase inhibitor and other skin whitening agent [12]. Herbs like *Glycyrrhiza glabra*, *Panax ginseng*, *Embica officinalis*, *Azadiracta indica*, *Curcuma longa* [13], etc. have been used for treatment of skin hyperpigmentation as shown in Table 1. Also, phyto-constituents like ellagic acids, quercetin, and some whitening agent like kojic acid [72], arbutin [73], etc. are used for treatment as skin hyperpigmentation.

Main text

Type of skin hyperpigmentation

Post-inflammatory hyperpigmentation

It is the acquired hypermelanosis after the skin inflammation or injury that can occur in all skin types. It may occur due to infections such as dermatophytosis, allergic reactions such as mosquito bites, psoriasis, hypersensitive reactions due to medications, or injury from irritant (Fig. 1a), or cosmetic procedures. However, acne vulgaris (Fig. 1b), atopical dermatitis, and impetigo are very common causes of it. Indeed, post-inflammatory hyperpigmentation (PIH) is mainly common after acne in dark-skinned patients. PIH results from the overproduction of melanin or an irregular dispersion of pigment after inflammation. There may be rise in melanocyte activity which may be stimulated by inflammatory mediators as well as reactive oxygen species. Light to dark brown coloration in epidermal post inflammatory hyperpigmentation, whereas dermal PIH tends to be grey to black coloration [74].

Melasma

Melasma is an acquired hypermelanosis characterized by asymmetric, brown-colored, irregular, reticulated macules on sun exposed areas of the skin, especially the face (Fig. 1c, d). However, chronic ultraviolet (UV) exposure, female hormone stimulation, and predisposed genetic background have all been proposed to play a role in the development of melasma [74]. It is also noticed that a release of histamine from mast cells in response to UV irradiation has been demonstrated to stimulate melanogenesis, which is mediated by H2 receptors via protein kinase A activation. Sebocytes have been hypothesized to contribute to the development of melasma. Further studies are needed on the role of sebocytes in the pathogenesis of melasma [75].

Effect of hormone on melasma Hormones play a role in the pathogenesis of melasma, estrogen, and progesterone have an impact in melasma development, because melasma is common in pregnancy, hormonal contraceptive use, estrogen therapy in prostate cancer patients, and conjugate estrogen use in women after menopause. In females, melasma is more frequent than in males. Melasma is an undesirable cutaneous effect of oral contraceptives. Melasma is commonly regarded as a physiological change in skin caused by hormone changes. Estrogens play a major role in both physiological and pathological conditions of the skin, including pigmentation. Estrogen and progesterone biological effects are regulated by their different receptors [75, 76].

Therapeutic implications The main method of treating melasma is still topical depigmentants. The most common anti-melanogic agent is hydroquinone, which inhibits the conversion of 1-3,4-dihydroxyphenylalanine to melanin via competitive tyrosinase inhibition, has also raised safety concerns such as exogenous ochronosis, permanent depigmentation, and potential cancer hazards [2]. The following are considered as alternatives to topical agents identified for having depigmenting properties with no adverse effects: resveratrol, azelaic acid, 4–n-butyl resorcinol, niacinamide, kojic acid, and ascorbic acid [75].

Age spot

The brown spots of the skin are aged marks (Fig. 1e). Skin regions, including the face and the back of the hands, grow primarily on that part of skin, which is often exposed to sunlight [9]. Age spots are brown because of lipofuscin bodies of the basal cells. Lipofuscin is the lysosome lipid and protein mixture in which lipids bind by malondialdehyde to protein fragmentations. Age spots vary in form, scale, color, and degree of protrusion in part of the skin. The skin's age spots are made up of the basal cells that bind to the basement membrane in epidermis. The basal cells are the stem cells responsible for the regeneration and repair of epidermis in new epithelial cells. Basal cells and chemical substances can be damaged by ultraviolet radiation and some injured cells can survive and grow old by

Table 1 Herbs used for treatment of skin hyperpigmentation

S.No	Herbs	Part used	Mechanism of action	Phytoconstituents	Reference
1	*Glycyrrhiza glabra* [Fabaceae]	Root	UVB protection Moisturing agent	Glycyrrhizic acid, Glycyrrhizin, Glabridin	[14, 15]
2	*Vitex negundo* [Verbenaceae]	Root	Tyrosinase inhibitory	Negundin A, [+]-lyoniresinol-3a-O-b-D-glucoside	[16]
3	*Aloe-barbadensis* [Asphodelaceae]	Leaf	Mosituring agent Tyrosinase inhibitory	Aloesin, 2"-Feruloylaloesin	[17, 18]
4	*Morus alba* [Moraceae]	Fruit	Tyr. 7 inhibitor ROS scavenger	Apigenin, umbelliferone, astragalin, Moranoline, 1-deoxynojirinmycin, resveratrol	[15, 19]
5	*Panax ginseng* [Araliaceae]	Root	Antioxidant, and skin whitening Agent	Ginsenoside, p-Coumaric acid	[20, 21]
6	*Gingko* [Ginkgoaceae]	Flower	Tyrosinasse inhibitor	Ginkgolide A, bilobalide	[13, 22]
7	*Azadirachta indica* [Meliaceae]	Leaf, Bark	Antioxidant Antibactrical	Oleic Acid, Azadirachtin, isomeldenin, nimbin, nimbinene, 6-desacetyl lnimbinene, nimbandiol	[17]
8	*Santalum album* [Santalaece]	Wood	Antioxidant, zskin whitening property	Alpha- and beta-santalol	[23, 24]
9	*Muntingia calabura* [Muntigaceae]	Flower, Leaf, Fruit	Antityrosinase and antioxidant activity	Stigmasterol, triglyceride, α-linolenic acid	[25, 26]
10	*Blumea balsamifera* [Asteraceae]	Leaves	Antityrosinase, lipid peroxidation inhibitory activities, liver-protective	3-O-7W-Biluteolin,	[25, 27]
11	*Magnolia officinalis* [Magnoliaceae]	Bark	Melanogenesis inhibition	Magnoloside I_a, crassifolioside, magnoloside V_a	[28, 29]
12	*Pueraria thunbergiana* [Leguminosae]	Root	Melanogenesisinhibition	Schaftoside, puerarin, genistin	[30, 31]
13	*Emblica officinalis* [Phyllanthaceae]	Fruit	Antioxidant, skin whitening property	Quercetin, Kaempferol, Gallic acid, Methyl gallate, Ellagic acid, Trigallayl glucose, Phyllantine, Phyllembein	[32, 33]
14	*Curcuma longa* [Zingiberaceae]	Root	Antioxidant, skin whitening property	Curcuminoids	[23]
15	*Camellia sinensis* [Theaceae]	Leaves	Antioxidant	Epigallocatechin gallate, epicatechin, gallocatechin	[23, 34]
16	*Nelumbo nucifera Gaertn* [Nelumbonaceae]	Flower	Antioxidant, tyrosinaseinhibotry activity	Pronuciferine, Armepavin, Kaempferol-3-o-glucoside, Luteolinglucoside	[35, 36]
17	*Crocus sativus L.*[Iridaceae]	Dried stigmas	tyrosinaseinhibotry activity	Crocin, picrocrocin, β- carotene, safranal.	[37, 38]
18	*Hemidesmus indicus* [Asclepiadaceae]	Root	Antioxidant, tyrosinaseinhibotry activity	Hemidesminine, Lupeal, vanillin	[39, 40]
19	*Vitis vinifera* [Vitaceae]	Seed and leaf	Tyrosinaseinhibotry activity	Gallic, protocatechuic, vanillic, syringic and ellagic acids	[17, 41]
20	*Euphorbia supina* [Euphorbiaceae]	Leave, flowers and tubers	Antioxidant, skin lighting agent	Protocatechuic acid, nodakenin, 3-*O*-glucoside	[42]
21	*Brillantaisia cicatricose Lindau* [Acanthaceae]	Leaves	Hyperpigmentation, leprosy, vermifuge, emetic, eczema, snakebite, lactogenic	Alkaloids, glycosides, terpenoids, steroids, flavonoids, tannins and saponins	[43, 44]
22	*Chenopodium uganda* [Chenopodiaceae]	Stem, leaves and flower	Tyrosinase inhibitory	Phenolics, flavonoids, saponins, and triterpenoids	[44]
23	*Sesamum angolense Welw.* [Pedaliaceae]	Leaves	hyperpigmentation, dysentery	Terpenoids and steroids	[43]

Table 1 Herbs used for treatment of skin hyperpigmentation *(Continued)*

S.No	Herbs	Part used	Mechanism of action	Phytoconstituents	Reference
24	*Proteamadiensis Oliv.*[Proteaceae]	Root, bark	Skin disease, hyperpigmentation	Terpenoids and steroids	[43]
25	*Carica papaya L.* [Caricaceae]	Leaves	Moisturing agent, antioxidant,	Papain, chymopapain A and B	[45]
26	*Acacia catechu* [Mimosaceae]	Bark	Antioxidant activity, Skin whitening property	Catechin, catechutannic acid.	[46]
27	*Arnica Montana* [Asteraceae]	Flower	Inhibitor in B16 melanoma cells	Triterpene, essential oils, fatty acids, thymol, pseudoguaianolidesesquiterpene lactones	[47]
28	*Artemisia dracunculus* [Asteraceae]	Leaves	inhibit melanocyte-stimulating hormone	Isobutyl and piperidiyl	[48]
29	*Glycine max* [Fabaceae]	Seed	Antioxidant, tyrosinase inhibitory activity	Kunitz-type trypsin inhibitor and Bowman-Birk protease inhibitor	[49]
30	*Thymelaea hirsuta* [Thymelaeaceae]	Leaves, Stem and flower	Antioxidant property, antimelanogenesis effect	Genkwadaphnin, gnidicin	[50]
31	*Betula pendula* [Betulaceae]	Bark, leaves	tyrosinase inhibitory activity	Phenolics, flavonoids, tannins, saponins, glycosides, sterols and terpene derivatives	[51]
32	*Caesalpinia sappan* [Fabaceae]	Wood	Inhibit melanogenesis and cellular tyrosinase activity	Homoisoflavanone, sappanone A	[52]
33	*Callicarpa longissima* [Lamiaceae]	Leaves	Inhibits melanin production		[53]
34	*Carthamus tinctorius L.* [Asteraceae]	Seeds	Melanogenesis inhibitory activity	Essential oils contains palmitic acid, palmitoleic acid, margaric acid, margaroleic acid	[54, 55]
35	*Coccoloba uvifera* [Polygonaceae]		Antioxidant and anti-tyrosinase activities, inhibited the production of IL-1a, TNF-a and a-MSH in melanocytes	Titratable acid Ascorbic acid	[56, 57]
36	*Colocasia antiquorum* [Araceae]	Root and bark	Inhibits the melanogenesis	Colocasinol A	[58]
37	*Crataegus azarolus L.* [Rosaceae]	Leaves	Effect on B16F10 melanoma cells	vitexin-200-O-rhamnoside	[59]
38	*Juniperus chinensis L.* [Cupressaceae]	Fruit	Inhibition of tyrosinase and melanogenesis	Amentoflavone-7-*O*-D-glucoside	[60]
39	*Glechoma hederacea L.* [Lamiaceae]	Stem	Reduced the cellular melanin content and tyrosinase activity	Germacrene D Ursolicacid, oleanic acid	[61, 62]
40	*Garcinia livingstonei T* [Clusiaceae]	Bark	Inhibit melanin production	Amentoflavone 3βhydroxyeupha-5 ,22-diene O-methylfukugetin Morelloflavone Volkensiflavone	[63, 64]
41	*Viola odorata* [Violaceae]	Leaves	Anti-melanogenic activity	Vitamin C, methyl salicyte	[65, 66]
42	*Passiflora edulis* [Passifloraceae]	Seed	Inhibits melanogenesis	Piceatannol	[67]
43	*Stewartia pseudocamellia* [Theaceae]	Bark and fruit	anti-melanogenic activity	deoxystewartianol-40 -O-arabinoglucoside stewartianol-3-O-glucoside	[68]
44	*Cyperus rotundus* [Cyperaceae]	Rhizomes	TRPV1 Channel Inhibition and ORAI1Channel Inhibition.	Valencene camphene	[69]
45	*Cudrania tricuspidata* [Moraceae]	Fruit	Inhibition of L-DOPA Auto-Oxidation	Flaniostatin	[70, 71]

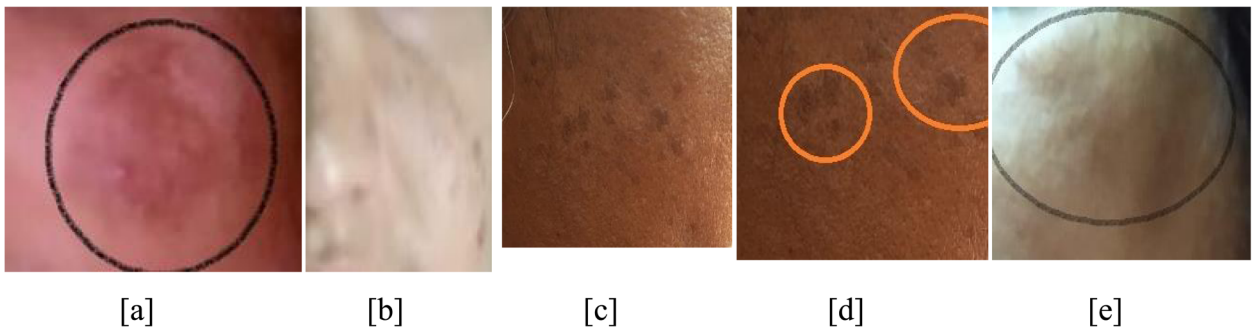


Fig. 1 Symptoms of skin hyperpigmentation. **a** Post-inflammatory hyperpigmentation. **b** Acne produced PIH. **c** Melsama on face. **d** Melsama spot. **e** Age spots on face

misrepairs [77]. Age spot are treated by some skin lighting agents like kojic acid [78].

An aged cell has two effects on a tissue, i.e., reduced neighborhood cell productivity in resolving environmental changes and enhanced damage fragility; and decreased local tissue repair performance. The adjacent cells in an old cell are thus at increased risk of injury and misrepairs. Through this process, an aged cell causes neighboring cells to age [77].

Causes of hyperpigmentation

Hyper pigmentation is caused by many factors. These may be exogenous and endogenous factor like endocrinologic factor: Addison's disease, Cushing's syndrome, Nelson syndrome, Pheochromocytoma, Carcinoid, Acromegaly, Hyperthyroidism, Acanthosis nigricans, Diabetes. Nutritional factor: Kwashiorkor, Vitamin B_{12} deficiency [5, 79], Folic acid deficiency, Niacin deficiency, Tryptophan deficiency, Vitamin A deficiency. Melasma is an undesirable skin effect on contraceptive use hormonal [76].

Treatment skin hyperpigmentation by herbs

In addition to photosafety, there are several medications and treatments to treat hyperpigmentation of the skin of darker skin patients safely and efficiently with some adverse reactions. So, herbs and phytoconstituents are better choice for treatment for skin hyperpigmentation. Some herbs with their mechanism of action for treatment of skin hyperpigmentation are given in Table 1. Hydroquinone, azelaic acid, kojic acid, liquoric extract, retinoids, etc., and treatments like chemexfoliation and laser therapy may be effective on their own properties, or in combination with other drugs [78, 80].

The possible mechanisms of actions by which herbs are used for the treatment of skin hyper pigmentation are namely tyrosinase inhibitory, antioxidant, and skin whitening effects.

Tyrosinase inhibitory effect

Tyrosinase is a copper-containing enzyme which performs various functions, glycosylated, and found exclusively in melanocytes [81]. It catalyzes conversion of L-tyrosine into L-DOPA which further converted into dopaquinone then dopachrom e[82]. Dopachrome polymerizes to form melanin. Inhibition of tyrosinase enzyme inhibit the melanin production which help to remove the skin hyperpigmentation. Extract of herbal drugs like licorice, *Aloe vera*, *Vitex negundo*, *Morus alba*, and many other drugs are used for inhibition of tyrosinase activity.

Tyrosinase inhibitory effects were calculated by the formula:

$$\text{Percentage inhibitory effect} = \left[(\text{Control}-\text{Control blank})-(\text{Test}-\text{Test blank}) \times 100/(\text{Control}-\text{Control blank})\right]$$

Antioxidant

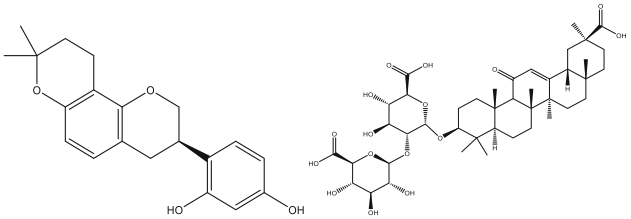
Antioxidants are substances that used to neutralize reactive oxygen species to prevent (for preventing) cells and tissues from oxidative damage. The cutaneous antioxidant system includes enzymatic and non-enzymatic substances. Some enzymatic antioxidants like vitamin E, vitamin C, resveratrol, and lipoic acids. These molecules perform removal of free radicals; neutralization of singlet oxygen in the cell membrane; prevent lipid peroxidation, oxidative and mutagenic action to DNA inhibition; and repair of endogenous antioxidant systems [83]. IC_{50} for resveratrol was 57.05 μg/mL, which demonstrated a great tyrosinase inhibitory potency. But analog of kojic acid shows the most powerful tyrosinase inhibitor [IC_{50} = 28.66 μg/mL], two times more active than resveratrol [84]. Some herbs also show antioxidant effect which are used for the treatment of skin hyperpigmentation are *Asphodelus microcarpus* [42], *Euphorbia supine* [85], and *Panax ginseng* [42].

Skin whitening drugs

Potency of skin whitening agents is due to phenolic component present in the herbs. Arbutin is a natural occurring tyrosinase inhibitor which has skin whitening property with IC_{50} value of 3.0 mM in HEMn cells [81]. The most commonly used chemical agents are hydroquinone [HQ], arbutin, kojic acid, liquid nitrogen, laser treatment, chemical skinning, and super natural dermabrasion [28]. Also, ascorbic acid and its products and there are many of herbs or herbal extract used as skin whitening agents are *Syzygium aromaticum*, *Magnolia officinalis*, and *Holarrhena antidysentrica*.

Glycyrrhiza glabra

Glycyrrhiza glabra extracts play a large role on the skin mainly as a result of its antioxidant activity, especially its strong antioxidant glycyrrhizin, triterpene saponins, and flavonoids. The main attributes are skin whitening, skin depigmentation, lightening of skin, anti-aging, anti-erythemic, emollient, anti-acne, and photoprotective effects [86]. Gabridin is present in the hydrophobic part of the root extract of *Glycyrrhiza* and it can reduce tyrosinase activity in culture on melanocytes and inhibit UVB induction [86].

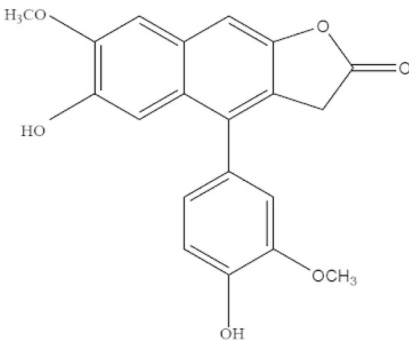


Glabridin **Glycyrrhizin**

The extract of licorice inhibits the tyrosinase activity by inhibiting oxidation of L-DOPA to an IC_{50} value of 53 μg/mL. Glabridin content has highest inhibition activity on tyrosinase. The highest inhibitory activity was reported on the first oxidation of tyrosine with IC_{50} value of 0.9 μg/mL [87].

Vitex negundo

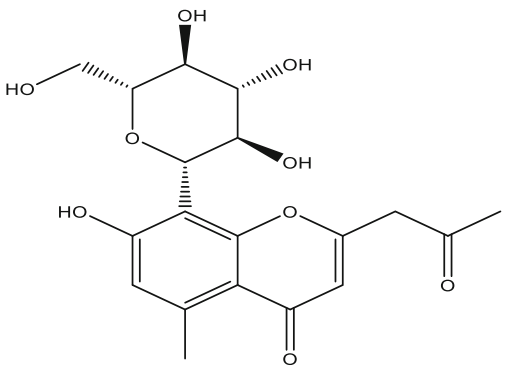
A poultice of this plant is used for the diagnosis of hyperpigmentation as melasma or ephelides by local cosmetic practitioners. Negundin contains lactone functionally at C-2 position with potent IC_{50} value of 10.06 mM against tyrosinase enzyme [16]. *Vitex negundo* is used as skin whitening agent, tyrosinase inhibitor, and inhibit the synthesis of post inflammatory pigmentation [88]. *Vitex negundo* contains a number of chemical constituents, one of them is negundin A.



Negundin A

Aloe

The leaf gel is used as a cure for minor burns and sunburns [7] and *Aloe vera* gel mainly has antifungal, anti-inflammatory, and hepatoprotective potential [89]. The isolates of *Aloe vera* are barbaloin, aloesin, aglycone of aloenin, 2′′-*O*-feruloyl aloesin, isoaloeresin D, and aloe resin E shows potent tyrosinase inhibitory properties. Lyophilized gel shows IC50 = 10.53 and 6.08 mg mL^{-1} is for methanolic extract. Aloesin shows highest inhibition value than other molecules extracted form aloe [90].



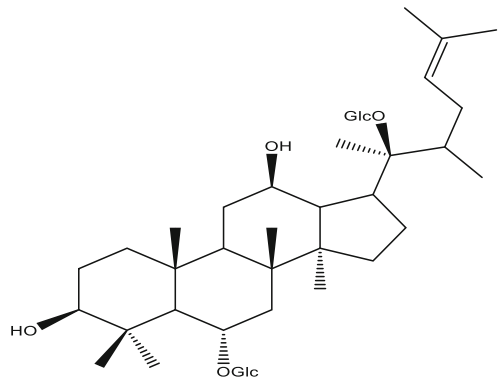
aloesin

Morus alba

Flavonoids present in *Morus alba* extract shows antioxidant and tyrosinase-inhibiting properties. Tyrosinase-inhibiting activity of mulberry extract is comparable with HQ and kojic acid [29]. Oxyresveratrol and Mulberroside-A derived from *M. alba* root which strongly inhibit the monophenolase production and inhibit mushroom tyrosinase activity in melanin synthesis [44]. They have properties of fever reduction, liver protection, and blood pressure lowering. The polyphenols in the leaves have properties for depigmentation [86]. Mulberroside F have 51.6% inhibition at 1 μg/mL concentration on 0.29 μg/mL IC_{50} value [91].

Panax ginseng

Panax ginseng is a herb containing various therapeutically active ginsenosides. P-Coumaric acid isolated from *Panax ginseng* fresh leaves was used to inhibit L-tyrosine oxidation catalyzed by mushroom tyrosinase. The *Panax ginseng* berry isolates are Floralginsenoside [FGA], Ginsenoside [GRd], and Ginsenoside Re [GRe].



Ginsenoside Re [GRe]

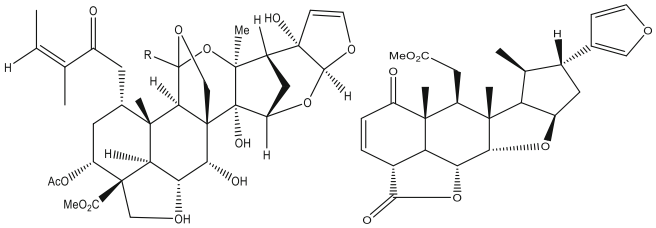
Of these 3, floralginsenoside [FGA] has been observed to have a powerful inhibitory effect on melanogenesis by means of reduced expression of the microphthalmic-associated factor [3]. Ginseng's importance lies in its many pharmacological roles, such as anticancer activity, as well as shows activity like antioxidant, aging, antistress, and anti-fatigue. Due to the free radical activity of DPPH, the potent antioxidant activity of PgAuNPs has been observed. *Panax ginseng* leaves also have skin whitening, skin-protective and moisture retention properties [13, 21, 22]. Extract of panax ginseng shows 3.65mM IC_{50} value [92].

Gingko biloba

Ginkgo biloba is a member of the Ginkgoaceae family. The *G. biloba* extract EGb 761, which contains, most of it, quercetin and Kaempferol derivatives, and terpens [6%] from tree leaves, containing flavone glycosides [33%] which has shown capacity to minimize sunburn cells in mice from ultraviolet B (UVB) [93]. Gingko shows anti-inflammatory, anti-vasculature, antioxidant, and tyrosinase properties [8]. Gingko is used to treat various medical problems such as poor circulation of the blood, hypertension, poor memory, and depression [93]. The water extract of *Gingko biloba* inhibit 50% of tyrosinase activity at 2.25 mg/mL IC_{50}. Also, ethanol and ethanol-ether mixture extract shows 50% inhibitory activity at IC_{50} value 75 and 0.32 mg/Ml respectively [94].

Azadirachta indica

Azadirachta indica shows activity against tyrosinase enzyme and also shows antioxidant and antibacterial properties [95]. It contains isomeldenin, nimbin, nimbinene, 6-desacetyllnimbinene, nimbandiol, and Azadirachtin.



Azadirachtin Nimbolide

Santalum album

Sandalwood has many medicinal properties like anti-inflammatory, antiphlogistic, antiseptic, antispasmodic, carminative, diuretic, emollient, hypotensive, memory booster, sedative, etc. [96]. Sandalwood oil has protecting, smoothening, moisturizing, hydrating, and skin anti-wrinkling properties. The oil inhibits the oxidative enzyme 5-lipoxygenase and has DPPH radical scavenging activity [24]. Alpha-santalol is the major ingredient of sandalwood oil. In comparison to kojic acid and arbutin, it is a potent inhibitor of tyrosinase [IC_{50} = 171 μg/mL].

Muntingia calabura

Muntingia calabura extracts are prepared in different solvents such as ethanol, aqueous, hydro-ethanol, petroleum ether using decoction methods with various parts of plant including leaves, flora, and fruits. This results in optimum anti-thyrosinase and antioxidant activity in the leaf extract of *Muntingia calabura* in hydroethanol [25]. Plant extracts have an inhibitory effect on melanogenesis. The human body's reactive oxygen species increases the damage done to DNA, the melanin biosynthesis, and the melanocyte proliferation. *M. calabura* leaf hydroethanol shows 94.00 ± 1.97% inhibition of tyrosinase enzyme

Blumea balsamifera

Blumea balsamifera is a medicinal plant that belongs to the Asteraceae family. The leaves are used for certain conditions such as rheumatism and high blood pressure. As part of the plant with different physiological activities, its leaves have attracted attention, including plasmine inhibitory, antifungal, and hepatroproof, antidiabetic, wound cure, angiogenic. In addition, antibacterium, free radical scavenging, inhibitory activity of lipid peroximization, xanthine ojidase inhibition, superoxide scavenging activities, and antityrosinase activity were identified in the methanol extracts of the leaves of

the plant [97]. Nine flavonoids are isolated from *Blumea balsamifera* from ethyl acetate extract [25].

Magnolia officinalis

Magnolia officinalis [Magnoliaceae] has antispasmodic, anticancer, antioxidative, and antidiabetic activities. The extract of plant Magnolia officinalis inhibits melanogenesis by a pre-translational regulation on tyrosinase gene expression. It also exhibits depigmenting activity. The fermented methanol bark extract shows antityrosinase activity and at a conc. of 200 μg/mL, it reduces 99.8% of melanin formation [98, 99].

Pueraria thunbergiana

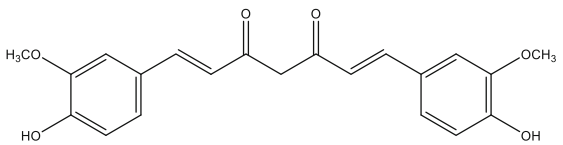
P. thunbergiana root and flower have various medicinal properties. EtOAc-soluble extract fractions were more effective than kojic acid, a whitening agent used for positive control for a MSH-induced melanin synthesis. Tyrosinase specifically affected by the aerial portion of *P. thunbergiana* [30]. Extraction of root have % inhibition of tyrosinase at 1 mg/mL, 2 mg/mL, and 4 mg/mL are 10.36%, 0.78%, 13.22%, and 3.13% respectively [100].

Emblica officinalis

E. officinalis is recognized for its nutritional content. A wide range of chemicals are present, including flavonol-glycosides, carbohydrates, mucic acids, amino acids, sesquiterpenoids, alkaloids, flavone glycosidses, phenolic glycosides, phenolic acids, and tannins. *E. officinalis* fruit juice contains the highest amount of vitamin C and vitamin E as compared to other fruit juice. The extract could inhibit tyrosinase, by inhibiting microphthalmia-associated transcription factor (MITF) and Trp-1 gene expression, but under low concentration of the extract treatment would induce Trp-2 gene expression. EPE has higher IC_{50} than the MPE; *emblica* fruit shows IC_{50} 4346.95 ± 166.23 μg/mL. Ethanolic extract has higher antioxidant and anti-melnogenesis effect [101, 102].

Curcuma longa

Curcuma longa contains some active ingredient which have tyrosinase inhibitory or depigmentry activity like curcumin, demethylcurcumin, and bisdemethyl curcumin. Among these, curcumin has the highest percentage of tyrosinase inhibition [23].



curcumin

Natural curcuminoides show potent inhibitory activity as compared to synthetic curcumin analog. Curcumin analog has higher tyrosinase activity with compound o-diphenols and m-diphenols than other compound. Tyrosinase activity is inhibited by curcuminoids by inhibiting L-dopa oxidation [103]. Partially purified curcuma longa [PPC] inhibits the level of tyrosinase protein like MITF, TRP1, and also suppress the α-MSH stimulated cells. Activation of ERK or PI3k/Akt in signaling pathway by suppressive mechanism of PPC on melanogenesis [104].

Camellia sinensis

It is commonly known as green tea. It belongs to the Theaceae family. Green tea is made of steamed, dried, rolling leaves to inactivate endogenous polyphenol oxidase [PPO]. The activities of *Camellia sinensis*, melanin synthesis, and expression of melanogenic enzyme at the protein and mRNA levels in melan-A cells were evaluated by researchers [105]. Green tea contains active ingredients like -[-]-epigallocatechin-3-gallate[EGCG], [-]-epigallocatechin[EGC], [-]-catechin[C], [-]-gallocatechingallate [GCG], and [-]-epicatechingallate [ECG]. EGCG inhibit melanin production in mouse melanoma cells. All active ingredients do not show potent inhibitory activity but EGCG and gallic acid show higher tyrosinase inhibitory activity by cell proliferation. EGCG and GA also inhibit cell proliferation in cell line of K562 [human leukemia cell] and 293T [human embryonic kidney] [106]. Further, 6.2% of IC50 of methanol extract of seed [644.93 ± 1.44 μg/mL]. Methanol extract of pericarp shows 12 time stronger IC_{50} value than the methanol extract of seed which is IC50 = 57.77 ± 0.34 μg/mL [107].

Nelumbo nucifera Gaertn

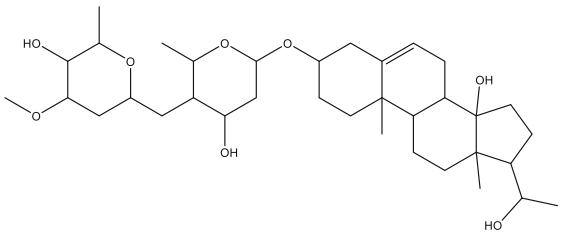
Family of *Nelumbo nucifera Gaertn* is Nelumbonaceae. Commonly, it is known as Indian lotus. Its seed and leaves extract contain alkaloids, saponine, and phenols which shows antioxidative activity against tissue oxidation. Lotus seed and leaves show protective effects on skin against UVB irradiation, anti-wrinkle effect, and skin whitening effect [35, 108].

Crocus sativus L

It is commonly known as saffron belonging to family Iridaceae. The antioxidant activity of extract was 81% using 70% ethanol. *Crocus sativus* decreases the melanin pigment from the skin. Emulsion is use in the cosmetic or medicine preparation to treat skin hyperpigmentation and used as skin whitening agent [40]. Isorhamnetin-3, 49-diglucoside has 55.7% at 2666.7 μm/mL concentration with 1.84 mm IC_{50} [109].

Hemidesmus indicus

It belongs to family Asclepiadaceae and commonly known as Anantmul. *H. indicus* decreases the monophenols and diphenols activity of tyrosinase by inhibiting L-dopa to dopachrome synthesis in melanin production. Monophenolase activity inhibition by 2-hydroxy-4-methoxybenzaldehyde MBALD was studied with a substratum l-tyrosin e[39]. Hemidesminine, Lupeal, and vanillin are the active constituents which shows antioxidant effect [40].



Heminine

Vitis vinifera

The main active ingredients of which are red vine leaf extract (RVLE), contains many flavonoids. Deionized water was the solvent used in RVLE preparation. The solution RVLE showed the possibility of inhibiting dopachrome formation that can be observed at wavelength of 475 nm with a spectrophotometer. The bioactive components of RVLE included gallic acid, chlorogenic acid, epicatechin, rutin, and resveratrol. RVLE solution is also used in cosmetic formulations as natural whitening agent [52]. Extract of VVC is more potent then arbutin to inhibit tyrosinase activity and its has30 휇g mL^{-1} IC_{50} value [110].

Euphorbia supina

The ES extract has a non-cytotoxic effect on the proliferation of B16F10 cells. Clear cytotoxicity is observed in B16F10 cells at a concentration of 1000 μg/mL. The ES extract showed an occurrence of 93.05 ± 0.6% at 200 μg/mL almost equivalent to ascorbic acid. ES extracts had a relatively high ABTS+ radical scavenge activities of 8 and 40 μg/mL [14]; protocatechuic acid, nodakenin, and 3-*O*-glucoside are the chemical constituent present in the *Euphorbia supina* [111].

Acacia catechu

The extract has recorded high tyrosinase inhibition activity at a concentration of 120 μg/ml, with an inhibition percentage of 61.58 compared to a positive kojic acid regulation [98.73% inhibition] at a concentration equivalent to 120 μg/ml. Without preservative, *A. catechu* whitening cream has maintained strong stability for 3 months [46].

Carica papaya

It contains papain, chymopapain A and B which shows antioxidant activity. It also contains calcium, sugar, fiber, vitamin C, thiamine, riboflavin, niacin, amino acid, carotene, and malic acids. It also includes proteins and fats [45]. It has been found that carica fruit extract is having 87% of antioxidant activity. The phenolic compounds in papaya fruit contained two major groups. The most important natural antioxidant groups are these phenolic compounds [111].

Arnica montana

3β,16β-Dihydroxy-21a-hydroperoxy-20[30]-tariaxasten is a compound present in *Arnica montana* that is found to be 50 times stronger than 4-methoxyphenol, a commonly used depigmenting agent; it inhibited in the melanin biosynthesis, without affecting cells production and much stronger than arbutin as well. At 0.125 mg/mL, Arnica flowers inhibit melanin synthesis in 80% ethanol extract [47].

Artemisia dracunculus

Undeca-2E,4E-dien-8,10-dynoic acid isobutylamide and piperidylamide are two active compounds found in *Artemisia dracunculus*. These compounds inhibit mediated melanin production in B16 cells of mouse melanoma potently by inhabitation of melanocyte-stimulating hormone [-MSH]. Consequently, the cytotoxicity was not related to the inhibitor activity of compounds 1 and 2 against melanin biosynthesis [48].

Thymelaea hirsuta

T. hirsuta extract shows a time-dependent decrease in cytoplasmic accumulation of melanin and do not show any cytotoxicity effect. Genkwadaphnin and gnidicin are the active constituents in the extract of *T. hirsuta* which shows effect against melanin synthesis. By ERK1/2 phosphorylation, melanogenesis effect on B16 cells are decreases. Inhibition of melanin production by downregulation of tyrosinase by *Thymelaea hirsuta* [112].

Betula pendula

In addition to metal chelating, *Betula pendula* is a significant source of strong depigmentants with an effect on tyrosinase to decrease and scavenge properties. Chlorogenic acid, Catechin, p-Coumaric acid, Isoquercitrin, Chrysoeriol, and Quercetin-3-O-glucuronide are the active constituents present in the extract. The power of chain-breaking antioxidants, phenolic compounds, including flavonoids, which scavenge lipid peroxyl radicals,

Table 2 Phytoconstituents for the treatment of skin hyperpigmentation

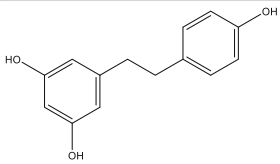
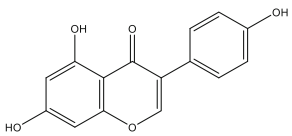
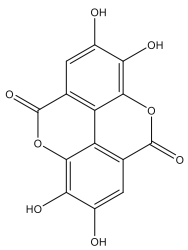
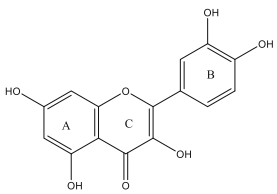
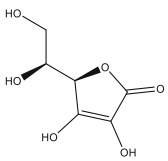
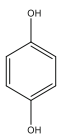
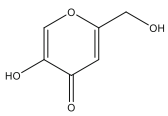
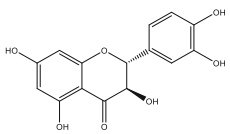
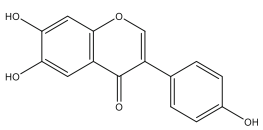
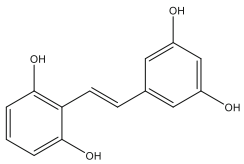
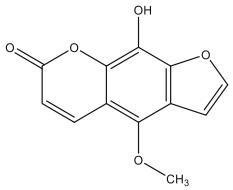
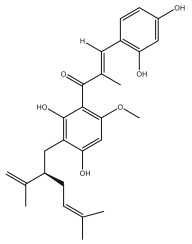
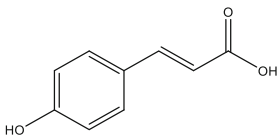
S.No.	Phytoconstituent	Common source	Structure	Traditional use	Reference
1	Resveratrol	*Vitis vinifera*		Inhibition of melanin synthesis, tyrosinase inhibitor	[84, 114]
2	Genistein	*Glycine max*		Antioxidant, inhibit melanogenesis pathway	[115]
3	Ellagic acid	*Rubus idaeus*		Antioxidant, suppresses melanogenesis	[116]
4	Quercetin	*Citrus aurantium*		Anti-melanogenesis effect, tyrosinase inhibitor	[117]
5	L-ascorbic acid	*Embelica officinalis*		Skin lightening effect	[118]
6	Hydroquinone	*Agaricus hondensis*		Epidermal-type melasma inhibitor, tyrosinase inhibitor	[119]
7	Kojic acid	*Aspergillus oryzae*		Tyrosinase inhibitor	[120]
8	Taxifolin	*Cedrus deodara*		Inhibit melanin synthesis	[121]
9	6-Hydroxydiadzein	*Glycine max*		Inhibit melanin synthesis	[122]
10	Gnetol	*Gnetum gnemon*		Tyrosinase inhibitor	[123]

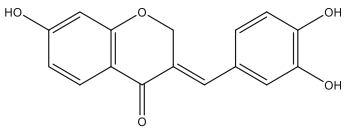
Table 2 Phytoconstituents for the treatment of skin hyperpigmentation *(Continued)*

S.No.	Phytoconstituent	Common source	Structure	Traditional use	Reference
11	9-Hydroxy-4-methoxypsoralen	*Angelica dahurica*		Tyrosinase inhibitor	[124]
12	Kuraridin	*Sophora flavescens*		Tyrosinase inhibitor	[125]
13	*p*-Coumaric Acid	*Arachis hypogaea*		Antioxidant, inhibit melanin synthesis	[126]

break through chain sequences with the same mechanism as radical hydroxyl scavenging. Then, 30.21 ± 0.23% of tyrosinase inhibitory effect were observed at 80 μg/mL concentration on 119.08 ± 2.04 μg/mL IC_{50} [113].

Caesalpinia sappan

Homoisoflavanone, sappanone A are isolated from the extract of *Caesalpinia sappan*. The crude extract has demonstrated highest melanogenesis inhibitory activity in mouse B16 melanoma cells and crude extract of *C. sappan* has been evaluated in a previous study for antiproliferating activity in B16 melanoma cells. Homoisoflavanones are a small class of oxygen that occur naturally. Sapanone A shows a dose-dependent inhibition of melanogenesis [52].



Sapanone A

Callicarpa longissima

Callicarpa longissima inhibits the development of melanin by suppressing the MITF [microphthalmia-associated transcription factor] gene expression of the B16F10 mouse melanoma cells. Carnosol is present in the extract of *Callicarpa longissimi* which has oxidative property and carnosol and carnosic acid are responsible for inhibiting melanin synthesis [53].

Phytoconstituents used for the treatment of skin hyperpigmentation are given in Table 2.

Conclusion

In this review, we discussed many of herbs and phytoconstituent which are used as tyrosinase inhibitor and also as skin whitening agents. Skin is the most important part of our body. The colour of skin is determined by the presence of melanin in the skin. Melanin is a pigment present in skin which is responsible for the skin color in plants and mammals. When the amount of melanin is increased in the skin, then it causes hyperpigmentation on the skin. Synthesis of melanin depends mainly on tyrosinase enzyme. It convert L-tyrosine in L-DOPA and L-DOPA to dopaquinone by which melanin is produced in the epidermis layer of skin and affect the skin color. Plants like *Azadiracta indica*, *Glycyrrhiza glabra*, *Panax ginseng* and genistein, ellagic acids, quercetin, and many other phytoconstituents which are used in herbal cosmetic as anti-hyperpigmentry agents in cosmetic industries. Some of flavonoids and triterpenoids present in these herbs show their effect as antioxidant and skin whitening agents.

Abbreviations

MITF: Microphthalmia-associated transcription factor; ROS: Reactive oxygen species; MPAK: Mitogen-activated protein kinase; COX: Cyclooxygenase; DHICA: Dihydroxyindole-2-carboxylic acid; HQ: Hydroquinone; PPC: Purified curcuma longa; RVLE: Red vine leaf extract; PPO: Polyphenol oxidase

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Authors' contributions
We declare that this work was done by the authors named in this article: SK conceived and designed the study. PR carried out the literature collection of the data and writing of manuscript. SSY helped in writing of the manuscript. DK and BK assisted in the data analysis and corrected the manuscript. All the authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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