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Review article

Plants used to treat hyperpigmentation in Iranian traditional medicine: a review

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Abstract
Skin hyperpigmentation is characterized as increased production and accumulation of melanin, which could be aesthetically unfavorable and develops serious skin diseases. There is a need to find new depigmenting agents, since many current natural and synthetic products present undesired side effects. In Iranian traditional medicine (ITM), plants have been used for the treatment of skin diseases such as hyperpigmentation. In this study, topical herbal medicines, for the treatment of hyperpigmentation were searched in ITM references, and their scientific names were identified, using different comprehensive glossaries. Thereafter, depigmenting mechanisms of these genera were reviewed in recent scientific literatures. Seventy-nine plants were made known as herbal remedies for skin hyperpigmentation. Furthermore, modern literatures have shown depigmenting effect of about 40% of these plants or their isolated compounds, with different melanogenesis inhibitory mechanisms with tyrosinase inhibition as the most revealed method. Regarding the new approach to medicinal plants in recent years, a large number of medicinal herbs that were mentioned in ITM references would be good candidates for exploring new herbal medicines for skin hyperpigmentation disorders.

Keywords: herbal medicine, hyperpigmentation, Iranian traditional medicine

Introduction
Skin pigmentation is a broad term, usually reflecting an increased and dispersion of melanin, the pigment that gives human skin, hair, and eyes their color [1,2]. Epidermal and dermal hyperpigmentation can be dependent to either increased numbers of melanocytes or activity of melanogenic enzymes [3]. Hyperpigmentary problems such as post inflammatory, hyperpigmentation, solar lentigo, and melasma, occur widely in the human population, and are considered to be skin disorders and cause psychological disturbances [4].
Since skin hyperpigmentation is related to the chemical nature of melanin, tyrosinase activity, tyrosinase-related protein-1 (TRP-1) and tyrosinase-related protein-2 (TRP-2) in the melanocytes, and the transfer of melanin in the keratinocytes, several treatment methods such as

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inhibition or attenuation of tyrosinase and related melanogenic enzymes catalytic activity, transcriptional regulation and post-translational modification of melanogenic enzymes, interruption of melanosome transfer, acceleration of epidermal turnover have been investigated [2,5].

Tyrosinase is the key enzyme of melanogenesis and the first in the conversion of tyrosine to melanin. It is a common target for therapeutic agents intended to alleviate cutaneous hyperpigmentation. By using purified mushroom tyrosinase or cell lysates of melanoma cells tyrosinase inhibitory effect could be determined [2]. Mushroom tyrosinase, the enzyme extracted from the champignon mushroom *Agaricus bisporus*, is highly homologous and commercially available, thus making it well suited as a model for studies on melanogenesis, and has been used by many studies carried out on tyrosinase inhibition [2,5].

Hydroquinone and its derivations, such as arbutin, and kojic acid are some of the common and effective whitening agents to treat hyperpigmentation disorders with mechanism of inhibition of tyrosinase [6,7]. In spite of their efficacy, the mentioned whitening agents would cause some adverse effects such as sensitization, contact dermatitis and erythema and also cytotoxic and mutagenic effect with prolonged exposures [4,8].

The long-term use of herbs, introduced in traditional medicines, confirms their value in drug discovery [9]. Surprisingly, many crude drug and plant extracts have been reported to inhibit the tyrosinase enzyme [4]. The “return to nature” trend of recent years had been accompanied by a thriving interest in whitening agents from herbal medicine [10] with most of the population still believing in traditionally crude drugs and medicinal plants to treat hyperpigmentation [4].

Iranian traditional medicine (ITM), which dates back to over 6000 years [11], was a combination of different medical traditions from Greece, Egypt, India and China. Iranian physicians such as Rhazes and Avicenna were merging all existing information on medicine at that time, and have also theorized their own examination and wise perception [12].

In ITM references, the most used terms denoting skin hyperpigmentation are ‘*Kalaf*’, ‘*Bahaq*’ and ‘*Namash*’ [13-16]. Review of Iranian Traditional Medicinal books showed that *‘Kalaf’* was a kind of skin darkness or brown to black pigmentation that usually occurred on the face with clinical manifestations similar to melasma [17,18]. ITM scholars believed that ‘*Bahaq*’ was similar to *‘Kalaf’* except that *‘Bahaq’* was associated with sloughing and roughness [15]. According to humoral theory in ITM, abnormal black bile congestion in skin layers and its increased concentration caused dark color spots on the face, known as *“Namash”* being equivalent to freckles [19].

There are many medicinal plants, which have been utilized for the treatment of hyperpigmentation by Iranian physicians, which are yet to be fully verified experimentally.

In this study, the medicinal plants used for the treatment of hyperpigmentation in ITM references via topical route of administration were reviewed. Subsequently, melanogenesis inhibitory effects of these species were searched in recent scientific literatures.

Methods

Traditional search

Three famous books including Liber continens, the Canon of medicine and *Makhzan-ul-adviah* were selected as the main references of ITM.

Liber continens (*al-Hawi fi al-tibb*)

Abu Bakr Muhammad ibn Zakariya Razi (Rhazes), a renowned Iranian physician, chemist and philosopher (865–940 A.D.) wrote the book of *al-Hawi fi al-Tibb*. This book is the most important book of Rhazes, and was repeatedly printed in Europe during the 15^{th} and 16^{th} centuries, under the title ‘Liber Continens’. It had a major influence on the development of medical practices in Europe. Rhazes surveyed Greek and early Arabic medicine, as well as various Indian medical knowledge. Furthermore, during his work, he added his own considered judgment and medical experience as commentary [9].

The Canon of medicine

The Canon of medicine is the best work on traditional medicine, which was compiled by Abu Ali Al- Hussain ibn-e Abdullah- ibn-e- Sina, known as Avicenna, one of the most famous Iranian physician (980-1037 A.D.). The Canon of medicine was used in over half a century in European scientific centers as a medical textbook, and was later translated into different languages [20]. It consists of five books, and serves as a concise reference in traditional medicine. The second book contains an estimate of 800 individual drugs, mostly of medicinal plants (and some animal and mineral substances). Avicenna added his own comments, highlighting the differences between recipes from different sources, and occasionally, there were some disagreement regarding them. Thus, he gave his opinion of the effectiveness (or ineffectiveness) of some remedies [21].

Makhzan-ul-adviah

Makhzan-ul-adviah written by Aghili Alavi Khorasani, one of the prominent Persian physicians (1772 A.D.), is a significant reference about traditional medicine and medical terminology in Persian. About 1744 individual drugs of plant, mineral and animal origin used in traditional medicines, have been described in *Makhzan-ul-adviah.* It is a collection of his lifetime medical notes, summarized from everything he had read, as well as observations from his own medical experiences [22].

Plants to treat hyperpigmentation in ITM references

ITM references were searched in order to find a list of traditional names of medicinal plants, used for the treatment of hyperpigmentation, via topical route of administration with the main keywords: *'Bahaq'*, '*Kalaf*' and '*Namash*'. Thereafter, plants were identified by different comprehensive glossaries by matching their traditional names with scientific names [23,24].

Modern search

Plants with melanogenesis inhibitory effect in modern scientific databases

In order to find melanogenesis inhibitory effect of the plants, a substantial search of scientific databases such as 'Google Scholar', 'Scopus' and 'PubMed' was carried out, using the genera in combination with key terms such as 'hyperpigmentation', 'melanogenesis' and 'tyrosinase'.

Results and Discussion

Based on the ITM references, about 71 traditional names of medicinal plants, applied to treat skin hyperpigmentation ('*Bahaq'*, '*Kalaf*'and '*Namash'*) via topical route of administration were found. The plants have been listed based on their scientific names. Moreover, their repetition in the Canon of medicine, Liber continens and *Makhzan-ul-adviah* along with the traditional names of the plants, phonetic spellings, families and used organs have been shown (table 1).

In modern literatures, all of the plants mentioned in table 1 were searched for hyperpigmentation inhibitory effect, and the mechanisms of interference with melanin synthesis according to their genera. The results are as follows:

Tyrosinase inhibition

Quercetin-3'-*O*-*β*-D-glucoside was isolated from *Allium cepa* and inhibited melanogenesis without cytotoxicity. It inhibited melanin formation in B16 melanoma cells and mushroom tyrosinase [25].

In a study, among 67 tropical plants evaluated for anti-tyrosinase activity, *Althaea officinalis* demonstrated moderate mushroom tyrosinase inhibitory effect [26].

Aristolochia bottae Jaub.& Spach and magnoflorine, a compound isolated from *A. debilis,* had tyrosinase inhibitory activity via colorimetric method [27,28].

Table 1. Plants used for the treatment of hyperpigmentation via topical route of administration in ITM references; The Canon of medicine (C), Liber continens (L), *Makhzan-ul-adviah* (M)]

Scientific name	Family	Traditional name	Phonetic spelling	Used Parts	*kalaf*	*bahaq*	*namash*
Achillea ptarmica L.	Asteraceae	Oodo-ul-otas	/uːdɔːlɔːtæs/	Root	-	M	-
Alcea digitata Alef. *Althaea officinalis* L.	Malvaceae	Khatmi	/χætmɪ/	Seed	-	LCM	-
Alkanna tinctoria (L.) Tausch	Boraginaceae	Abukhalsa	/æbuːχælsɑː/	Leaves, root	-	LCM	-
Allium sp.	Alliaceae	Korath	/kɔːrɑːθ/	Seed, root	C	-	-
Allium cepa L.	Alliaceae	Basal	/bæsæl/	Seed	M	CM	-
Alyssum sp.	Brassicaceae	Alooson	/æluːsɔːn/	-	LCM	-	-
Amygdalus communis L. (*Prunus amygdalus* L.)	Rosaceae	Louz	/ləʊz/	Seed, root, oil	L	-	L
Apium graveolens L.	Apiaceae	Karafs	/kæræfs/	Leaves, branches	-	-	L
Aristolochia sp.	Aristolochiaceae	Zaravand-e-Modahraj	/zærɑːvændemɔːdæhrædʒ/	Root	CM	-	-
Arum italicum Mill.	Araceae	Loof	/luːf/	Root	CM	CM	C
Astragalus sp.	Fabaceae	Katira	/kætiːrɒː/	Gum	M	M	M
Beta vulgaris L.	Chenopodiaceae	Selgh	/selɢ/	Leaves	CM	M	CM
Brassica nigra (L.) K.Koch	Brassicaceae	Khardal	/xærdæl/	-	LCM	C	
Brassica oleracea L.	Brassicaceae	Karnab	/kærnæb/	Seed, leaves	ML	L	ML
Bryonia sp.	Cucurbitaceae	Fashara	/fɑːʃærɑː/	Root	CM	-	-
Caesalpinia bonduc (L.)Roxb	Caesalpiniaceae	Rateh	/ræte/	-	C	-	-
Capparis sp.	Capparaceae	Kabar	/kæbær/	Fruit	-	ML	-
Carthamus tinctorius L.	Asteraceae	Ehriz	/əhrɪz/	Fruit	C	CM	M
Cicer arietinum L.	Leguminosae	Hemmas	/hemmæs/	-	CM	L	CM
Citrus medica L.	Rutaceae	Otroj	/əʊtrəʊdʒ/	Fruit	CM	-	-
Convolvulus scammonia L.	Convolvulaceae	Saghmoonia	/sæɢmuːnɪɒː/	Sap	CM	CM	M
Costus sp.	Costaceae	Quost	/ɢoʊst/	Root	CM	-	-
Cucumis colocynthis L. *Cucurbita mexicana* Dammann	Cucurbitaceae	Qar	/ɢær/	The rind	-	M	-
Cucumis melo L.	Cucurbitaceae	Bettikh	/bettɪχ/	Seed, Peel	CM	CM	-
Cucumis sativus L.	Cucurbitaceae	Qessa	/ɢessæ/	Fruit	-	L	-
Curcuma zedoaria (Christm.)Roscoe	Zingiberaceae	Jadvar	/dʒædvɑːr/	Root	M	M	-
Daphne mezereum L.	Thymelaeaceae	Mazarioon	/mɒzærɪʊn/	Leaves	L	L	-
Dorema sp.	Apiaceae	Oshagh	/ɔːʃæɢ/	Gum	M	M	-
Ecballium elaterium (L.) A. Rich.	Cucurbitaceae	Qesa-ul-hemar	/ɢesɑːəʊlhəmɑːr/	Fruit	M	M	-
Eruca sativa Mill.	Brassicaceae	Jerjir	/dʒerdʒɪr/	Seed	CM	M	CM
Ficus carica L.	Moraceae	Teen	/tiːn/	-	M	LCM	-

Table 1. Continued

Scientific name	Family	Traditional name	Phonetic spelling	Used Parts	***kalaf***	***bahaq***	***namash***
Flemingia grahamiana Wight &Arn.	Acanthaceae	Varas	/væræs/	Fruit	CM	M	CM
Gentiana lutea L.	Gentianaceae	Gentiana	/dʒentɪɑːnɑː/	Root	-	CM	-
Gypsophila struthium Loefl.	Caryophyllaceae	Kondosh	/kɔːndɔːʃ/	Root	CM	CM	-
Hemerocallis sp.	Hemerocallidaceae	Sousan	/suːsæn/	Root	CM	M	-
Hypericum sp.	Clusiaceae	Houfariqun	/huːfɑːrɪɢuːn/	Flower, arial parts	M	M	-
Hyssopus officinalis L. *Nepeta* sp.	Lamiaceae	Zoofa-ye-yabes	/zuːfɑːjejæbes/	Arial parts	CM	-	-
Indigofera tinctoria Mill. *Chrozophora tinctoria* (L.) A.Juss.	Fabaceae	Nil	/niːl/	-	CM	CM	-
Iris sp.	Iridaceae	Irsa	/iːrsɒː/	Seed, root	CM	M	CM
Jasminum sp.	Oleaceae	Yasmin	/ jæsmɪn/	Leaves, fruit	CL		-
Laurus nobilis L.	Lauraceae	Qar	/ɢɒːr/	-	M	CM	-
Lepidium draba L. *Plumbago europaea* L.	Brassicaceae Plumbaginaceae	Qonabari	/ɢɔːnɒːbærɪ/	Arial part	CM	CM	-
Lepidium sativum L.	Brassicaceae	Horf	/hɔːrf/	Seed	M	M	M
Linum sp.	Linaceae	Katan	/kætɑːn/	Seed	C	-	-
Lolium temulentum L.	Poaceae	Shailam	/ʃæjlæm/	Seed	-	CM	-
Lupinus termis L.	Fabaceae	Tormes	/tɔːrmes/	Seed	CM	LCM	-
Lycium afrum L.	Brassicaceae	Hozoz	/hɔːzɔːz/	Leaves, seed	LC	-	-
Mandragora officinarum L.	Solanaceae	Yabrooh- os-sanam	/jæbruːhɔːssænæm/	Sap	CM	-	CM
Moringa arborea Verdc. *M. oleifera* Lam.	Moringaceae	Ban	/bɒːn/	Seed	LC	LC	LC
Muscari comosum (L.) Mill.	Hyacinthaceae	Balboos	/bælbuːs/	Bulb	CM	M	
Myrtus communis L.	Myrtaceae	Ass	/ɒːs/	Leaves	CM	LC	CM
Narcissus sp.	Amaryllidaceae	Narjes	/nærdʒes/	Flower, seed	CM	CM	-
Nerium sp.	Apocynaceae	Defli	/deflɪ/	Leaves	-	M	-
Nymphaea sp.	Nymphaeaceae	Niloofar	/nɪluːfær/	Root	-	L	-
Persicaria hydropiper (L.) Delarbre	Polygonaceae	Zanjabil-ul-kelab	/zændʒæb iːləʊlkelɑːb/	Arial parts	CM	-	-
Pistacia sp.	Anacardiaceae	Habbat-ul-khazra	/hæbbætəʊlχæzræ/	Fruit	CM	-	-
Polygonum hydropiper L.	Polygonaceae	Felfel-ul -ma	/felfelɔːlmɒː/	Fruit	L	-	L
Portulaca oleracea L.	Portulacaceae	Khorfah	/χɔːrfæ/	Leaves	-	-	M
Raphanus sp.	Brassicaceae	Fojl	/fəʊdʒl/	Seed, leaves	-	CM	-
Rheum sp.	Polygonaceae	Ravand	/rɒːvænd/	Root	LCM	-	-
Ricinus communis L.	Euphorbiaceae	Karchak	/kærtʃæk/	Seed	CM	-	-

Table 1. Continued

Scientific name	Family	Traditional name	Phonetic spelling	Used Parts	*kalaf*	*bahaq*	*namash*
Rosa canina L. *Rosa moschata* Herrm.	Rosaceae	Nasrin	/næsrɪn/	Flower	M	-	-
Rubia tinctorum L. *R. cordifolia* L	Rubiaceae	Fovvah	/fɔːvvæh/	Root	-	M	-
Ruta graveolens L.	Rutaceae	Sodab	/səʊdɒːb/	Leaves	C	CM	-
Senna sp.	Caesalpiniaceae	Sena-e-makki	/senɑːmækkɪ/	Leaves	M	M	-
Trachyspermum copticum (L.) Link	Apiaceae	Nankhah	/nænχɒːh/	Seed	CM	CM	
Trigonella foenum-graecum L.	Fabaceae	Holbah	/həʊlbæ/	Seed	LCM	-	-
Triticum vulgare Vill.	Poaceae	Hentah	/hentæ/	Seed	CM	-	-
Urginea maritima (L.) Baker	Hyacinthaceae	Eshghil	/eʃɢiːl/	Root	-	-	M
Vicia faba L.	Fabaceae	Baghela	/bɒːɢelɒː/	Bark, fruit	LCM	LC	LCM
Vicia ervilia (L.)Willd.	Fabaceae	Karasnah	/kæræsnæ/	Seed	CM	C	C

-: not mentioned

Choi *et al.* investigated the effects of whitening, anti-wrinkling and safety of acetone extract of *Astragalus sinicus* Linne seeds and reported that it may be useful as a potential agent for functional cosmetic products [29]. Hee Kim *et al*. suggested that calycosin isolated from *A. membranaceus* (Fisch.) Bunge might be an effective skin-lightening agent. According to the studies, calycosin demonstrated tyrosinase inhibitory activity with melanin biosynthesis inhibition zone in a culture plate of *Streptomyces*. Moreover, it dramatically reduced melanin synthesis of Melan-a cells, without any apparent cytotoxicity, and reduced expression of tyrosinase [30].

The inhibitory effect of brazilein (a compound isolated from the methanol extract of *Caesalpinia sappan*) on tyrosinase activity was evaluated using multi-spectroscopic and molecular docking techniques. The results showed a dose dependent inhibitory effect of brazilein against tyrosinase activity, which was significant to kojic acid as the positive control. In addition, the inhibitory effect of brazilein on cellular tyrosinase and melanin synthesis in B16 cells was found to be in a dose dependent manner [31].

The active principle compounds isolated from the seeds of *Carthamus tinctorius* demonstrated a significant inhibition for mushroom tyrosinase. It was also found that N-feruloylserotonin and N-(*p*-coumaroyl) serotonin strongly inhibited the melanin production of *Streptomyces bikiniensis* and B16 melanoma cells, in comparison with a known melanogenesis inhibitor, arbutin [32].

Adhikari *et al.* have stated that fresh peel of *Citrus aurantifolia* (Christm.) Swingle and *C. aurantium* L. exhibited mushroom tyrosinase inhibitory activity [4]. In another study, *C. sinensis* (L.) Osbeck showed tyrosinase inhibitory activity alone, and in combination with other extracts such as *Capparis spinosa*, *Olea europaea* and *Oryza sativa,* evaluated by *in vitro* and *in vivo* models. The skin whitening effect and the skin tolerance of this combination in comparison with kojic acid and hydroquinone, demonstrated more extensive effect [33]. Wu *et al*. evaluated the whitening properties of six different varieties of Taiwanese pummel (*C. grandis* Osbeck). One of the varieties, known as Touyu inhibited tyrosinase, which was almost similar to the inhibition shown by kojic acid. They claimed that *C. grandis* had high potential for using as ingredients in products that prevent skin pigmentation [34]. Several researchers have reported the tyrosinase inhibitory effect of some by-products, flavonoids and essential oils extracted from citrus family. Based on the results, citrus hydrosols demonstrated better inhibitory effect than L-ascorbic acid, a well-known tyrosinase inhibitor compound [35]. It has been revealed that nobiletin, a polymethoxy-flavonoid occurring exclusively in citrus fruits, appeared to be more powerful than kojic acid in reduction of tyrosinase activity [36]. In another study, *C. sinensis* flavonoid fraction from fruits showed about 60% tyrosinase inhibition [37]. The essential oils, extracted from fruit peels of *C. grandis* and *C. hystrix* DC, showed IC_{50} comparable to the kojic acid as the positive control [38].

In a research, Baurin *et al*. have screened anti-tyrosinase activity of sixty-seven tropical plants. According to the results, *Costus spicatus* exhibited moderate tyrosinase inhibitory activity [26].

A topical cream containing 4% concentrated extract of *Ficus carica* fruit (w/o emulsion), significantly reduced the skin melanin, trans-epidermal water loss and skin sebum, and increased the skin hydration. It also showed insignificant effects on skin erythema and sebum content and could possibly be used against hyperpigmentation, acne, freckles and wrinkle [39]. Nerya *et al*. realized that 3-(2,4-dihydroxyphenyl propionic acid), DPP acid, isolated from the leaves of *F. carica,* might increase shelf life of intact mushrooms by treatment with H_2O_2, followed by DPP acid or for cut mushrooms by licorice extract or DPP acid alone [40].

Curto *et al*. showed that methyl gentisate, an alkyl ester of gentisic acid, derived from *Gentiana lutea* roots was effective on melanogenesis inhibition using mammalian melanocyte cell cultures and cell-free extracts. Moreover, the compound appeared to be non-mutagenic as a topical skin-lightening agent [41].

Tumen *et al*. screened the dichloromethane, acetone, ethyl acetate and methanol extracts of the leaves along with the berries of *Myrtus communis,* against tyrosinase. The dichloromethane extract demonstrated the most tyrosinase inhibition [42].

Hyun *et al*. reported that tyrosinase inhibition activity of 70% methanol and pressurized liquid extracts of *Persicaria filiformis*. was more than 90% [43].

In a study, Kilic et al. evaluated the antioxidant and tyrosinase inhibitory activities of the methanol extracts of immature and mature shell skins of *Pistacia vera*. The results showed that although the immature shell skin was rich in phenolic and flavonoid compounds and also demonstrated higher antioxidant activity in all test systems compared to the mature one, the tyrosinase inhibitory effect of the mature shell skin was more potent [44].

Miyazawa *et al*. introduced one of the isolated compounds from *Polygonum hydropiper* L., [(2R,3R)-(+)-taxifolin)], by a guided fractionation method as a new tyrosinase inhibitor alternative to cosmetic agents such as arbutin and kojic acid [45]. In another research, *P. cuspidatum* Siebold & Zucc. extract obtained by supercritical fluid carbon dioxide extraction, suppressed tyrosinase function and melanin content via mushroom and B16-F10 cellular based assay platforms which could be considered as skin anti-tyrosinase agent [46]. In addition, piceid (5,4′-dihydroxystilbene-3-*O*-*β*-D-glucopyranoside), one of the stilbenes found in *P. cuspidatum* root, has shown hypopigmentation activity and tyrosinase inhibitory effect in melanocytes, which were more considerable than those of arbutin [47]. Leu *et al*. stated that among the examined anthraquinones of *P. cuspidatum*, physcion with great tyrosinase inhibitory activity and impressive skin permeability activity was the most potent anthraquinone and could be a powerful candidate for dermal use [48].

In a study, 67 tropical plants were evaluated for their tyrosinase inhibition activity, and stated that *Portulaca pilosa* demonstrated strong inhibition of tyrosinase, which could be selected for identifying new active phytochemical constituents in the development of skin-

whitening agents [26].
Matsuda *et al*. showed that the ethanol extracts of *Prunus x yedoensis* Matsum., *P. zippeliana* Miq., *P. amygdalus* Schltr., *P. persica* (L.) Batsch and *P. armeniaca* L., have potential tyrosinase inhibitory effect *in vitro*, while *P. x yedoensis* and *P. zippeliana* leaves reduced the melanin amount by auto-oxidation [49]. The clinical efficacy evaluation of one herbal formulation for facial blemishes containing *P. amygdalus* oil showed that after applying it twice daily for 6 weeks, a significant decrease in blemishes (p<0.05) was observed with no significant adverse reactions [50].
The whole plant extracts including: ethyl acetate and 50% propylene glycol of *Raphanus sativus* had over 50% tyrosinase inhibitory effect, while ethyl acetate extract demonstrated more potent ability [51].
Based on studies, *Rheum palmatum* L. and *R. officinale* L. have demonstrated tyrosinase inhibition properties (68% and 60%, respectively) [52,53].
Silveira *et al*. agreed with the inclusion of *R. rhaponticum* L. rhizome extract into cosmetic, sunscreen and skin care products, for the prevention or reduction of photo damages. This was because *R. rhaponticum* rhizome extract demonstrated inhibitory effect on tyrosinase via mechanisms such as mushroom tyrosinase method, tyrosine kinase activity in melanocytes, as well as inhibition of IL-1α, TNF-α and α-MSH production. In addition, *in vitro* antioxidant properties of the plant extract against lipid peroxidation and free radical scavenging has been revealed [54]. In addition, a number of isolated potent compounds such as 3,4',5-trihydroxystilbene-4'-*O*-beta-D-(2''-*O*-galloyl) glucopyranoside and 3,4',5-trihydroxystilbene-4'-*O*-beta-D-(6''-*O* galloyl) glucopyranoside (from *R. officinale*), rhapontine (from *R. undulatum)* and its converted compound, rhapontigenin, exhibited a competitive inhibition against tyrosinase and also inhibited the biosynthesis of melanin [53,55].
The results of melanogenesis evaluation by *in vitro* and *in vivo* methods in foods revealed that *Rosa canina* (dog rose) extract could potentially be used as a natural inhibitor of polyphenol oxidase and tyrosinase to preserve the quality of fresh-cut vegetables and fruits [56]. In 2009, Fujii and Saito reported quercetin isolated from the ethyl acetate fraction of *R. canina.* It carries out inhibition by two particular mechanisms including tyrosinase inhibitory activity (reduced 31.6% melanin content) and protein expression by *in vitro* method [57]. On the other hand, in another study in 2011 by Fujii *et al*., it was claimed that due to its very low content in *R. canina*, quercetin would contribute only slightly to the inhibition of melanogenesis and procyanidin glycosides would be the main compound which could reduce the production of melanin [58].
In a research carried out by Muñoz *et al*., it was suggested that the extraction method strongly affected tyrosinase inhibition activity and the cytotoxicity data. Among the different extracts obtained from *Ruta graveolens* with water:EtOH (1:1) using several methods, the one prepared by percolation demonstrated the best mushroom tyrosinase inhibition (44.99 ± 0.25%) and no cytotoxicity effect was observed by *in vitro* model (IC_{50}< 1000 mg/ mL) [37].
Trigonella foenum-graecum L. was one of the fifty-two Nepalese crude drugs traditionally used for the treatment of hyperpigmentation, and was screened for mushroom tyrosinase inhibitory activity primarily. It showed 24.3% ± 8 tyrosinase inhibition with 91.4% inhibitory activity of kojic acid [4].
In order to find a safe and permeable compound for whitening against hyperpigmentation and sunburn, Ookubo *et al*. performed intracellular screening for melanogenesis inhibitors with 11-arginine (11R), a cell membrane-permeable peptide as a transdermal delivery system, fused with several kinds of tyrosinase inhibitory peptides from natural sources. According to the study, one of the natural peptides found in gliadin protein (a *Triticum vulgare* Vill. component)

could exhibit potent inhibition on melanin synthesis via melanin content measurement in B16 4A5 melanoma cells with no cytotoxicity. In addition, the whitening effect of the fused peptide with pyrenbutyrate, a skin delivery enhancer, was measured in a UV-induced sun-tanning guinea pig model, and the results demonstrated a significant inhibition of melanogenesis in Masson-Fontana staining through histology study [59].

Yao *et al*. investigated the tyrosinase inhibitory effect of various legumes such as *Vicia faba* in China, and claimed that its tyrosinase inhibition activity significantly correlated with total phenolic content and DPPH assays ($p < 0.01$) [60].

Table 2 has shown a list of plants or their isolated compounds with mushroom tyrosinase inhibition activity (MTIA) based on modern researches.

Transcriptional regulation of melanogenic enzymes

According to the study of Peng *et al*., the aerial part of *Achillea millefolium* essential oil could suppress melanin production, by the attenuation of tyrosinase activity via the regulation of the c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinase (ERK) signaling pathways. In addition, linalyl acetate was found as the major functional component of the essential oil [61].

The ethyl acetate extract of *Citrus unshiu*- press cakes, by-products of the juice industry was evaluated, for the anti-melanogenic potentials, through the measurement of tyrosinase, tyrosinase related protein (TRP-1, TRP-2) and microphthalmia associated transcription factor (MITF) in B16F10 cells, using Western blot analysis. The results indicated that it inhibited tyrosinase, TRP-2 and MITF expressions in a dose dependent manner. Furthermore, HPLC fingerpriningt of the extract revealed the presence of rutin, arirutin, and hesperidin in different quantities in the cakes [62].

It has been demonstrated that the methanol extracts of *Cucumis sativus* leaves and stems had the potential to inhibit melanin production in B16 cells at concentration of 100 µg/mL by reducing, tyrosinase expression at the protein level. In addition, among 8 compounds isolated from the plant leaves, lutein was more potent in reducing the expression levels of tyrosinase and wasfound to suppress melanogenesis with IC_{50} value of 170.7 µM compared to the other compounds [63].

It has been demonstrated that the ethanolic extract of *Lepidium apetalum* seeds reduced UV-induced skin pigmentation in brown guinea pigs with no obvious side effects. In addition, it could act as a hyperpigmentation inhibitor via a mechanism involving IL-6-mediated down regulation of MITF, a transcription factor implicated in tyrosinase gene expression and melanocyte differentiation, rather than a direct inhibition of tyrosinase activity [64].

Wing-Ki Cheung *et al*. demonstrated the inhibitory effect of 2,3,5,4′-tetrahydroxystilbene-2-*O*-β-D-glucopyranoside, isolated from dried tubers of *Polygonum multiflorum*, on tyrosinase in cell-free kinetics. They demonstrated that the anti-melanogenic activity of the compound was mediated probably via a noncompetitive inhibition on tyrosinase, down-regulation of the expression of melanogenic proteins, and reduction of tyrosinase/tyrosinase-related protein 1 (TRP-1) complex formation [65].

Inhibition of melanosome transfer

In a study, although combination of extracts of *Curcuma zedoaria* and *Aloe ver*a demonstrated very low tyrosinase inhibition activity in extract treated cells (50% to 90% for 1-5 µL extract combination); it decreased melanogenesis without altering the cell proliferation, and acted as melanin transfer inhibitor to the keratinocytes [66].

Skin hyperpigmentation is characterized by increased production and accumulation of melanin, which could be aesthetically unfavorable, and develops serious skin diseases. Nowadays, attention has been drawn to develop cosmetic products with depigmenting effect [67].

Table 2. Plants or their isolated compounds with mushroom tyrosinase inhibition activity (MTIA) based on modern researches

Plant /Compound	Plant organ	Extract	MTIA		Reference
			Inhibition %	IC_{50}	
Allium cepa **quercetin-3′-*O*-*β*-D-glucoside**	Ds	*	-	6.5 µM	[25]
Althaea officinalis	L	Propylene glycol 50%	48	-	[26]
Aristolochia bottae	Ap	Hexane	-	117.8 µg/mL	[27]
Aristolochia debilis **Magnoflorine**	St	Methanol	36.5 (100µg/mL)	-	[28]
Astragalus sinicus	S	Acetone	93.8 (20 mg/mL)	-	[29]
Astragalus membranaceus **calycosin**	R	Methanol	-	38.4 µM	[30]
Caesalpinia sappan **brazilein**	Hw	Methanol	-	21.21 mM	[31]
Carthamus tinctorius **N-feruloylserotonin**	S	Methanol 80% (Ethyl acetate fraction)	-	0.02 mM	[32]
Carthamus tinctorius **N-(p-coumaroyl) serotonin**	S	Methanol 80% (Ethyl acetate fraction)	-	0.07 mM	[32]
Carthamus tinctorius **acacetin**	S	Methanol 80% (Ethyl acetate fraction)	-	0.78 mM	[32]
Citrus aurantifolia	*	*	69.4 (50 µg/mL)	-	[4]
Citrus aurantium	*	*	53.4 (50 µg/mL)	-	[4]
Citrus sinensis	F	Ethanol 50%	22.0	-	[33]
Citrus grandis	F	Methanol	90.8 (10 mg/mL)	-	[34]
	Fp	*	-	2.07 µg/mL	[38]
Citrus sp. **Nobiletin**	Fp	Methanol	-	46.2 µM	[36]
Citrus hystrix	Fp	Essential oil	-	2.08 µg/mL	[38]
Costus spicatus	L	Propylene glycol 50%	39	-	[26]
Myrtus communis	L, B	?	40.53 (200 µg/mL)	-	[42]
Persicaria filiformis	St, L	Methanol 70%	93.1	-	[43]
Polygonum hydropiper **[(2R,3R)-(+)taxifolin)]**	Sp	Methanol	70 (0.50mM)	-	[45]
Polygonum cuspidatum **Physcion**	*	Ethanol	~70 (10 µM)	-	[48]
Portulaca pilosa	L	Propylene glycol 50%	93	-	[26]
Prunus x yedoensis	L	Ethanol 50%	80.6	-	[49]
Prunus zippeliana	L	Ethanol 50%	79.3	-	[49]
Prunus amygdalus	L	Ethanol 50%	43 (500µg/mL)	-	[49]
Prunus persica	L	Ethanol 50%	42.6 (500µg/mL)	-	[49]
Prunus armeniaca	L	Ethanol 50%	42.1 (500µg/mL)	-	[49]
Raphanus sativus	W	Ethyl acetate	88.50 (5mg/well)	-	[51]
		Propylene glycol 50%	68.73 (5mg/well)		
Rheum palmatum	Rh	Methanol	68 (333µg/ml)	-	[52]
Rheum officinale	Rh	Methanol	~ 60	-	[53]
Rheum rhaponticum	Rh	Methanol	-	0.06 µg/ml	[54]
Rosa canina	M	Distilled water	98.45	-	[56]
Rosa canina **quercetine**	F	*	68.4	-	[57]
Ruta graveolens	L	Ethanol 50%	44.99 (2.5%W/V)		[37]
Trigonella foenum- graecum	S	Methanol	24.3	-	[4]
Vicia faba	Lg	Ethanol 70%	67.73	-	[60]

* Not mentioned, -: Not done, ?: Not found, Ap: aerial part, B: berries, Ds: dried skin, Dt: dried tubers, F: fruit, Fp: fruit peels, Hw: heart wood, J: juice, L: leaves, Lg: legumes:, M: mature fruit, R: root, Rh: rhizome, S: seed, Sp: sprout, St: stems, W: whole plant

Depigmentation can be achieved by regulating the activity and transcription of tyrosinase, tyrosinase related melanogenesis enzymes, the uptake and distribution of melanosomes in recipient keratinocytes, melanin and melanosome degradation, and the turnover of pigmented keratinocytes [2].Despite their benefits, a number of current natural and synthetic ingredients utilized in cosmetic products for the treatment of hyperpigmentation would cause some harmful and undesired side effects. Hence, there is need to find new depigmenting agents with intense, rapid and optional whitening effect, no harmful side-effects which lead to elimination of unfavorable pigments [2,68].

In this regard, there are several reviewed studies, regarding the natural depigmenting agents and the mechanisms of melanogenesis inhibitory effect of herbal medicine. In 2008, Lin et al. summarized natural skin whitening products involving tyrosinase blockers and the products blocking the upstream regulation points of melanogenesis [10]. In two separate studies, in 2009 Chang and Smith *et al*. surveyed and presented an overview of tyrosinase inhibitors from natural and synthetic sources [5,69]. In 2012, Loizzo *et al*. reviewed studies on tyrosinase inhibitors of natural and synthetic origins, and also provided the information for enhancing the quality of food in industries, utilizing potential tyrosinase inhibitors [70]. Furthermore, in 2015, Chen *et al*. introduced natural and synthetic melanogenic inhibitory agents [8].

As the use of plant extracts and herbs has its origins in ancient times [71], in the present study, topical used medicinal plants, for the treatment of hyperpigmentation were searched in Iranian traditional medicine (ITM) books. Based on the results, 71 traditional names with depigmenting effects were introduced in table 1. It should be noted that the scientific names represented 79 plant names, because some traditional names were matched with more than one scientific name based on the used botanical text references. Furthermore, among the plant families, Brassicaceae accounted for most plants found followed by Fabaceae and Cucurbitaceae, respectively. In addition, 44% of the introduced plants have been mentioned in two ITM references as shown in table 1. Studying modern literatures revealed that about 40% of the traditional plants had been investigated for hyperpigmentation inhibitory effect with different mechanisms in order of priority such as controlling the tyrosinase activity, transcriptional regulation of melanogenic enzymes and inhibition melanosome transfer. In addition, *Astragalus membranaceus*, *Citrus unshiu*, *Polygonum multiflorum* and *Rosa canina* have exhibited more than one melanogenesis inhibitory pathway.

Although many mechanistic points can be targeted, tyrosinase inhibition is still the most common approach in achieving skin whitening agents [5]. Using kinetic analyses, tyrosinase activity could not be easily examined. Furthermore, controversial results were obtained when purified mushroom tyrosinase or cell lysates of melanoma cells were used [2]. According to articles reviewed in our study, the applied concentration of plants for determining mushroom tyrosinase inhibition was mentioned in a few studies; therefore, it would be a bit difficult to compare the tyrosinase inhibitory effect of all plants in Table 2. On the other hand, among the studied plants with high repetition in ITM, *Astragalus sinicus*, *Rosa canina* and *Vicia faba* with high scores in ITM, exhibited over 50% inhibitory activity against tyrosinase compared to ascorbic acid as the positive control (68, 98.45 and 93.8%, respectively). In addition, some isolated compounds from *Allium cepa*, *Astragalus membranaceus* and *Carthamus tinctorius* have demonstrated tyrosinase inhibition activity.

With regards to Table 2, the compounds isolated from some of the traditional used plants, including quercetin-3′-*O*-β-D-glucoside, magnoflorine, calycosin, nobiletin, brazilein, N-feruloylserotonin, N-(p-coumaroyl) serotonin, acacetin, [(2R,3R)-(+)taxifolin)], physcion and quercetine, have exhibited tyrosinase inhibitory effects similar to or more potent than the applied positive controls in the studies. It is so important that in some cases, the mentioned compounds were introduced as depigmenting agents of cosmetic products.

Some of the plants mentioned in table 2, exhibited inhibitory effects lower than 50% on mushroom tyrosinase that may act through different melanogenesis inhibitory pathways, which is not based on tyrosinase activity.

Conclusion

In the present review, among the 79 plants introduced, over 50% are yet to be investigated for depigmenting activity. Hence, these plants would be good candidates for exploring new herbal medicines, for skin hyperpigmentary disorders.

Regardless of the fact that tyrosinase inhibitory activity was the main applied method in this review; several mechanisms could be involved in investigating the whitening effect of these plants. Due to the different modes of interference, it seems that combined methods could be a better approach for achieving new depigmenting agents.

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Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the content of the paper.

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