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Review on oral plant extracts in Skin Whitening

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Abstract

Skin whitening has become one of the aesthetic problems among humans around the world, especially on women which is highly attention to skin beauty and whitening. Many of the plant extracts in oral energy drinks have whitening effects and good taste, which can support the health of the skin. We use the National Center for Biotechnology Information (NCBI) as a search engine to find literatures about skin whitening, oral plant extracts. This review mainly introduces the mechanism of skin whitening and the application of oral plant extracts in skin whitening. Skin whitening at melanin synthesis, melanosome transport, metabolism, oxidative stress, UV stimulation, other environmental stimulation inseparable. Many oral plant extracts are natural tyrosine inhibitors. The review concludes the melanin synthesis and transporting, pathway of melanin synthesis, whitening mechanism and the function of whitening on Green tea polyphenols, Rose Petal Extract (*Rosa gallica*), Pears, Peony, *Rosa roxburghii Tratt*, Olive (*Olea europaea* L.), Pomegranates, *Phyllanthus emblica* L., Mulberry extract, Açaí berry, saussurea involucrate flavonoids extract, etc. These will provide a strong foundation for the application of oral plant extracts in skin whitening. Furthermore, the mixture with function of skin whitening/ skin anti-aging / anti-inflammatory antioxidant oral plant extract can be a good candidate for further development on skin care product.

Keywords: skin whitening; oral plant extracts; melanin; melanosome; reactive oxygen species.

Practical Application: This review introduces the current mechanisms of skin whitening and analyzes abundant of oral plants that can promote skin whitening. In the functional food, whitening beauty is an important direction. In the future, after further research, it is hoped that oral extracts of these plants, which can prevent skin melanin formation or promote skin whitening, could be added to functional foods. At the same time, this review also provides some data support and summary for the subsequent application of plant oral extracts in skin health.

1 Introduction

Skin is the largest organ of the body. It represents 16% of our total body weight. Healthy skin can bring beauty to people. Therefore, humans make much account of a beautiful, whitening and healthy skin. Hence, skin is an important factor in human relationship.

Hyperpigmentation is that darkened patches or spots appear on the skin which occurs widely in the human population. Cosmetic products containing natural skin lightening ingredients are regarded as a safe alternative and effective approach to this hyperpigmentation problem (Searle et al., 2020). However, oral plant extracts as the novel and effective functional food that can also regulate the skin whitening (Fam et al., 2022; Hong et al., 2021; Song et al., 2020). What is oral plant extract? Qral plant extracts that are "medicine food homology", which means materials or extracts for both food and medicine (Gong et al., 2020). Plant-based foods or oral plant extracts including much of polyphenols, carotenoids, and select vitamins typically, which may protect the skin lonely or synergistically (Fam et al., 2022).

At present, there are more than 100 oral plant extract as tyrosinase inhibitors. Here, this review focus on oral plant extracts effecting the skin whitening. It involves the synthesis and transfer of melanin, factors affecting whitening, methods evaluating skin whitening and large amount of whitening oral plant extracts. It will afford a strong foundation for the application of oral plant extracts in skin whitening.

2 Materials and methods

Here, we use the National Center for Biotechnology Information (NCBI) as a search engine to find literatures about skin whitening, oral plant extracts. According to the research results in recent years, we summarize the contents of the mechanism of skin whitening and the relationship between oral plant extracts and skin whitening.

3 Results

3.1 The synthesis of melanin

Melanocyte is the epidermal melanin unit element in the skin. The whitening of the skin is closely related to the synthesis and transport of melanin in melanocyte and keratinocyte. Many

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researches indicate that the distribution of melanin goes through four stages: the formation of melanosome, the maturation of melanosome, the synthesis of melanin, and the transport of melanosome containing a large amount of melanin.

As we all know, tyrosinase plays an important role in the process of melanogenesis (Hushcha et al., 2021). Tyrosine can be catalyzed, oxidized and polymerized to be pheomelanin. Meanwhile, tyrosinase and TYRP1 may also turn into a light brown melanin (Susilawati et al., 2021). In the synthesis of melanin, TYR, TYRP1, Pmel17, MART-1 and MITF can identify melanocytes and specifically express (Zhou et al., 2021). Therein, MITF can also regulate the expression of TYR, TYRP-1, DCT, Pmel17, Rab27 and bcl-2. All these genes have an important function on melanocytes differentiation, dendricity, proliferation and apoptosis, as well as melanin synthesis (Hwang et al., 2017; Lee et al., 2022).

3.2 The Pathway of melanin synthesis

There are five major signaling pathways that are involved in melanin synthesis, but there are also some comparisons rare signaling pathways.

In melanocytes proliferation and differentiation signal pathway, the MAPK/ERK (mitogen-activated protein kinases/extracellular signal-regulated kinases) signaling is very important and essential. This signal pathway is that the kinases MEK and ERK ligand binding to their extracellular domain, activating Ras-Raf-MEK-ERK pathway and further to activate melanocyte receptors, as well as up-regulate the expression of MITF. Thus promoting the synthesis of melanin (Zhang et al., 2019a). The second signaling pathway is cAMP/PKA which called MC1R/α-MSH (cyclic adenosine monophosphate/protein kinase A). When the melanocyte receptors and their ligands are activated, the levels of intracellular cAMP and activity of PKA is increasing. Also, this pathway can improve the expression of MITF (Lee et al., 2016; Ostojic et al., 2021). Both pathways were mentioned MITF, indicating that it plays an important role in melanin synthesis. The third is PI3K/Akt (phosphatidylinositol 30-kinase/Akt). This signaling pathway plays a significantly role in melanocyte proliferation. It can also collaborate with MAPK/ERK pathway on regulating activity of melanocyte (Chaiprasongsuk & Panich, 2022; Zhang et al., 2019a). Wnt/b-catenin signaling pathway is another important pathway in pigmentation process and melanocytes differentiation, also for melanocyte stem cell (Zhang et al., 2019a). Another pathway is the NO signaling. The production of NO in keratinocytes is caused by ultraviolet radiation, and melanocytes and keratinocytes produce NO in response to inflammatory cytokines simultaneously. By activating the second messenger, NO increases tyrosinase activity and melanin production (Premi, 2020).

3.3 Melanosome transfer

The melanosome transfer which means melanocyte-to-keratinocyte transfer of melanosomes is an essential process on melanin pigmentation of skin. There are four models about melanosome transfer. In the first model, the tips of dendrites or filamentous processes protruding from melanocytes that contain melanophores are directly phagocytosed by neighboring keratinocytes. In the second model, melanocytes released the melanosome, which is subsequently incorporated into keratinocytes via phagocytosis. In the third model, melanin pigments are efflux into the extracellular space by fusion of melanosome membranes and plasma membranes. The fourth model is that the abscission phagocytic pattern is characterized by the shedding of closed vesicles containing melanosome and their recognition and phagocytosis by keratinocytes (Fukuda, 2021; Kim et al., 2020; Tadokoro et al., 2016).

3.4 Whitening mechanism

Hyperpigmentation becomes one of the aesthetic problems among humans including the male and female population. Besides determining human skin color, melanin also plays a vital protective role in human skin against the harmful impacts of ultraviolet (UV) radiation, drugs, chemical substances and other environmental factors. When melanocytes transport melanosome to neighboring keratinocytes, melanin will be deposited in keratinocytes and skin will show color (Allouche et al., 2021; Kim et al., 2020). The whitening mechanism is mainly carried out from the following three aspects: inhibiting the synthesis of melanin, regulating the melanin metabolism pathway and promoting the melanin metabolism.

Inhibiting the synthesis of melanin

Tyrosinase is a copper ion containing metal enzyme, belonging to polyphenol oxidase, which exists widely in animals, plants and microorganisms. Inhibiting the activity of tyrosinase to inhibit melanin generation, so as to play the crucial role in skin whitening. Because, tyrosinase is a rate-limiting enzyme during the production of melanin in a series of chemical reactions. Kojic acid and its derivatives are good complexing agents for copper ions, which can act on tyrosinase. Kojic acid and its derivatives can inhibit catalytic activity via binding the active part of copper ions of tyrosinase (Zachary et al., 2020). α-Arbutin play a competitive inhibitory role of tyrosinase mainly due to their structural similarity to tyrosine or dopamine, as a competitive inhibitor (Rudeekulthamrong & Kaulpiboon, 2020). It has been reported that MITF that is the transcription factor can regulate TYR, TRP-1/2 and Pmel17 etc. genes in melanocytes and involved in melanocyte development, proliferation and survival. Furthermore, many signal pathways are involved in regulating MITF. Whitening active ingredients can affect the level of MITF by regulating the above signal pathways, further inhibit the expression of tyrosinase, so as to achieve skin whitening (Abrahamian & Grimm, 2021; Lee et al., 2022). DHA and EPA can inhibit the synthesis of melanin (Yamada et al., 2019). Another important protein is tyrosine-associated protein-2 (TRP-2), also known as DOPAchrome tautomerase. TRP-2 mainly regulates the production rate of DHICA, thus affecting the structure, type, and size of melanin molecules, so as to control melanogenesis (Enkhtaivan et al., 2022).

Meanwhile, the oxidation inhibitor is also the effective measure in inhibiting the synthesis of melanin. Melanin is a large amino acid derivative that can be converted to a colorless precursor by strong reductants, thereby reducing visible

pigmentation. At the same time, strong reductants can reduce the production of melanin by reducing or combining with the intermediates in the process of melanin production. Like vitamin C and VC-HG, which can inhibit the tyrosinase activity and comprehensively reduce the deposition of melanin on the skin surface through its own reduction, so as to achieve whitening effect (Taira et al., 2018).

Regulating the melanin metabolism pathways

Melanocyte signaling pathway is affected by a lot of cytokines, such as basic fibroblast growth factor (bFGF) and endothelin-1 (ET-1). All of these can affect the growth of the proliferation of melanocyte and pigmentation. Some factors also can stimulate the activity of tyrosinase, making melanocytes highly pigmented (Jeong & Yoon, 2021; Park et al., 2022).

Another important exogenous factor are UV and reactive oxygen species that effect the physiological process of melanin formation. Ultraviolet radiation is a most significant environmental factor that affecting skin whitening. Ultraviolet (UV) can negative effect the proliferation of melanocytes, melanin synthesis, long-term UV irradiation will cause slow metabolism, melanin deposition (Allouche et al., 2021). The researchers shown that UV exposure increased the expression of MITF and its downstream melanin-synthesizing proteins, such as PMEL17, Mart-1, Tyr, TRP1 and TRP2, finally enhancing the synthesis of melanin. UV exposure also up-regulated the level of protease activity receptor 2 (PAR2) on the surface of keratinocyte membrane, which increases the absorption and distribution of melanosome on keratinocytes. Simultaneously, many cytokines up-regulate, like bFGF, ET-1, IL-1α/1β, ACTH, NGF, α-MSH, PGE2/PGF2α, GM-CSF, TNF-α, BMP-4, NO, which affect the proliferation of melanocytes, melanogenesis and transferring (Cichorek et al., 2013; Nguyen & Fisher, 2019).

UVA, UVB, visible light, infrared spectrums, pollutants and psychological stress, etc. can damage the health skin. In damaged skin, inflammatory cells can generate or release reactive oxygen species (ROS), like superoxide, superoxide anion radical, hydroxyl radical, hydrogen peroxide and nitric oxide. These ROS are also stimulators for melanocytes and skin-aging (Chen et al., 2021b; Michalak, 2022). UV radiation generates ROS in the skin. At the last phase of melanogenesis, ROS accelerates the reactions among dihydroxyindoles and indole quinones and increases skin hyperpigmentation (Solano, 2020). During the process of melanogenesis, the level of ROS increased and GHS decreased. Low levels of H_2O_2 (≤0.3 mM) can activate tyrosinase for synthesis of melanin. O2 can mediate UV-induced melanogenesis in B16F10 mouse melanoma cells. Also, ROS may interplay with cytosolic and mitochondrial Ca^{2+} in human melanocytes during the process of melanogenesis (Lu et al., 2021). All these mean that ROS play an important role in skin whitening.

Promoting melanin metabolism

Promoting melanin metabolism contain two directions, one is that inhibiting melanin transfer by melanosome, and another is that promoting exfoliation of epidermal cells. There are four main factors that affect melanosome transporting: the morphology of melanocytes; transport of melanosomes in melanocytes; transferring melanosomes from melanocytes to keratinocytes (Jo et al., 2020; Stephan et al., 2021).

3.5 Evaluation methods of skin whitening

At present, there are many methods to evaluate skin whitening. It can be mainly divided into in vitro experiment, in vivo experiment and human experiment.

In vitro experiment

In vitro experiment included enzyme biochemical assay, melanocyte assay and skin model assay. Enzymatic biochemical assay evaluated their whitening function by measuring the effect of the subjects on the tyrosinase activity. The commonly used enzyme material is mushroom tyrosinase. The constituent system of the enzyme solution contains mushroom tyrosase, tyrosine, L-dopa, etc. After the reaction with the addition of the subjects, the tyrosinase and dopa activities were calculated by measuring the absorbance at 305 nm and 475 nm, respectively (Micillo et al., 2018). The advantage of the enzyme biochemical method is that there is no cell culture, simple and fast. The disadvantage is that the system is too simple, the formation mechanism of melanin is very complex, and the whitening effect of the tyrosine-ase activity alone is relatively one-sided, which needs to be further verified combined with other experiments

In vitro cultured melanin cells can be used for tyrosinase activity assay and melanin content determination in cells, which is the most commonly used method to study whitening active substances. B16F10 melanoma cells are commonly used as melanocyte. In vitro cell experiments should be designed around the key steps in the formation of melanin. Traditional methods of detection indicators mainly include tyrosinase activity, the amount of melanin production, etc. Usually a certain concentration of subjects was applied on B16F10 cells for 24-96 h and cells were fully lysed with cell lysate, centrifuged at 4°C and 13000 r/min for 10 min, the supernatant as cellular protein extract and melanin precipitation at the bottom. The whitening efficacy of the subjects can be evaluated by NaOH lyses, tyrosinase activity by L-DOPA oxidation, and relevant mRNA and protein expression levels during the melanin synthesis by molecular biology (Lv et al., 2020; Zhou et al., 2018a). Cell assays have the advantages of simple operation, short experimental period, high reproducibility, and no animal ethical controversy, but cell experiments cannot completely simulate the growth environment of melanocytes in vivo, and the biological behavior of cultured melanocytes depends largely on the role of a series of cytokines, which is very different from the in vivo environment.

The 3D melanin skin model can be used for whitening efficacy detection. A number of 3D melanoid skin models have been successfully built in vitro: including SkinEthic RHPE in France, MelanoDerm in the United States, epiCS-M in Germany, and MelaKutis in China. Usually they contain 5% -10% unequal proportions of melanocytes that grow in the basal layer of the 3D melanoid skin model (Nakamura et al., 2018). The objects to be measured will be directly coated on

the epidermal surface with barrier function. After a period of time, the changes of deep melanocytes are detected by several detection indexes, including the quantification of melanin particles, tyrosinase activity measurement, western blot analysis, specific MART-1 immunofluorescence staining, QRT-PCR and pixel analysis software to evaluate the whitening efficacy of the subjects (Hatem et al., 2022; Myung et al., 2020). Melanin skin models exert their highly similar characteristics to skin structure and function, but 3D skin model tests are expensive and cannot fully mimic the growing environment of melanocytes in vivo.

Animal test method

Common used whitening activities to screen animal models were zebrafish and guinea pigs.

Zebrafish (Danio rerio) has become a very practical vertebrate model as a tropical freshwater fish, with up to 87% similarity to the human genome (Frantz & Ceol, 2022). Zebrafish has the advantages of small size, transparent physical similarity to mammalian physiological functions, and enabling high-throughput screening (Zhou et al., 2018b). Zebrafish embryos are completely transparent early in development, and melanin begins to grow from the retinal epithelium at 24 h. Pigmented cells originate from differentiated neural crest cells in the dorsal epitoderm and then proliferate, migrate, and differentiate into pigmented blasts. It can be observed under a masa microscope and is an ideal living animal model for whitening active object screening with unique advantages (An et al., 2022; Yousaf et al., 2020). Intervention in the melanin formation process in zebrafish inhibited melanin formation, and the inhibition efficiency of the subjects can be calculated by comparison with the blank control group.

Yellow brown guinea pig's skin melanocytes and melanosome distribution approximates to humans. Ten yellow-brown guinea pigs were used, all shaved on both sides of the back into several 1 cm 2 cm size depilation areas. Cosmetics were coated twice a day with cotton sticks, and the blank area of depilation skin was set. After 28 days, guinea pig skin biopsies were taken for examination, fixed, embedded and sectioned, and granule cells containing melanin and dopa-positive cells in basal cells were compared with the blank area of depiliated skin (Ghorbanzadeh et al., 2019; Zhou et al., 2018c).

Human body test

The human trial method generally takes the human forearm skin as the test site, in order to avoid the impact of light on the skin chroma. The medial 2 cm×2 cm area of the forearm of healthy adult skin was randomly selected as the test site, one side is the pilot area and one side is the contrast area. The skin color meter was used to observe the change of skin color before and after the application of skin whitening agent, and detect the effect of skin whitening agent according to the degree of skin color reduction (Wang et al., 2019b).

3.6 The relationship of oral plant extracts and skin whitening

Epidemiological studies have reported that high intakes of specific plant-based foods were important for maintaining skin health, such as skin barrier and whitening function. Here, each food has regular nutrients and unique nutrient content that can provide a series of bioactive compounds which either alone or synergistically to protect the skin (Fam et al., 2022). Here, we pay close attention to oral plant extracts which are defined as medicine food homology (MFH) contains a variety of active contents in the function of skin whitening.

Nowadays, many of these oral plant-based natural sources extracts are mostly from Asian origin. These compounds of oral functional plant selected as tyrosinase inhibitors by extraction (Kim et al., 2022; Smit et al., 2009). Such as *Anacardium occidentale*, cashew fruit; *Morus alba L. and Morus rotundiloba Koidz*, Mulberry; *Glycyrrhiza glabra*; *Morus alba*; *Syzygium aromaticum*; *Citrus aurantifolia*; Pomegranates; *Cypreae moneta*; *Punica granatum*; *Citrus aurantium*; *Olea europaea* L.; *Phyllanthus emblica* L.; *rosa roxburghii tratt*; tomato Powder; Green tea polyphenols, pear, *Panax ginseng*; etc. (Avianggi et al., 2022; Chaikul et al., 2021; Chaiyana et al., 2020; Chen et al., 2022; Khettal et al., 2017; Kim et al., 2022; Lianza et al., 2020; Omar et al., 2018; Setyawati et al., 2018; Truong et al., 2017; Wang et al., 2021a; Zeitoun et al., 2020). At present, oral plant extracts are more studied on plant extracts with good taste and good effective. Here, we focus on some oral plant extracts that have function on skin whitening. Most of oral plant extracts are as tyrosinase inhibitors which have function on inhibiting tyrosinase activity or decreasing the expression of genes in four signal pathways on the above content.

Green tea polyphenols

Green tea polyphenols contain catechin (C), epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), epigallocatechin-3-gallate (EGCG), and gallocatechin-3-gallate (GCG) (Kochman et al., 2020). The catechin was proposed to be due to the direct inhibition of tyrosinase activity and down-regulation of tyrosinase expression (Lee et al., 2021; Lim et al., 2021; Zhang et al., 2020). ECG, GCG and EGCG are most potent inhibitor that inhabiting the tyrosinase activity effects in green tea polyphenols (Roh et al., 2017). The tea catechins significantly inhibited tyrosinase activity and melanin synthesis via down-regulating of cAMP/CREB /MITF signaling pathway in B16F10 cells, where the effects of ECG > EGCG > GCG (Zhang et al., 2020). Meanwhile, in B16 melanoma cells, EGCG inhibited a-MSH-induced production of melanin (Roh et al., 2017). UV Pigmented Spot (PS) scores reduced by the consumption of green tea (Fukushima et al., 2020). Thus, Green tea polyphenols can be considered as inhibitors of tyrosinase activity and expression of melanocyte, thereby inhibiting melanin synthesis

Pears

Pears are widely used worldwide as a sweet and nutritious food. Pear has a history of more than 2,000 years as a folk medicine. Pears contain naturally abundant source of arbutin, which was discovered as a skin whitening active constituent (Hong et al., 2021). In melanocytes of mice, stimulating with α-MSH, four of Korean pears extracts can inhibit the tyrosinase activity down to 50% (Hong et al., 2021).

Rose petal extract (Rosa gallica)

The Rosaceae was one of the most widely distributed plants in the world. Rose Petal Extract (*Rosa gallica*) species belonged to the family of Rosaceae. Rose Petal Extract (RPE) inhibit production of melanin mainly via tyrosinase inhibition. It has been reported that RPE inhibited tyrosinase activity in a dose-dependent manner. The inhibitory rate was higher than arbutin and vitamin C at 50–100 μM of RPE. Meanwhile, RPE (100 and 200 μg/mL) significantly reduced melanin in α-MSH-stimulated melanocytes (Song et al., 2020).

RPE treatment can also phosphorylate the MEK-ERK, MKK4/7-JNK, and MKK3/ 6-p38 MAPK pathways, shown a dose dependent in B16F10 cells. MAPK pathway is an important signaling pathway that is involved melanin synthesis. RPE can also down-regulates MITF expression by inducing MAPK activation in B16F10 melanoma cells. That means RPE suppress the expression of MITF and tyrosinase transcription, which get involved in activation of the MAPKK-MAPK signaling pathways (Song et al., 2020). The flavonoids, glycosides and quercetin have the function of skin whitening (Chen et al., 2021a; Lu et al., 2019, 2022).. A Rosa centifolia petal extract (ROSE CRYSTA®-70: ROSE-70) has been shown to have function of skin whitening (Kaneda et al., 2022).

Peony

Peony is an economic and visual crop that has been cultivated in China for more than 1,600 years (Yan et al., 2021). As a potential functional oral raw material, flavonoid of fengdan peony are natural plant antioxidants which can effectively clean free radicals inside our body, and free radicals can cause hyperpigmentation. An significant regulating melanin metabolism pathway is free radical that effect the physiological process of melanin formation (Chen et al., 2021b). The DPPH scavenging effect of peony flavonoids was significantly strengthened with the increase of flavonoid concentration, shown a dose dependent. The result show that the peony flavonoids have better antioxidants. In turn, peony flavonoids may have function on skin whitening (Lu et al., 2022).

Rosa roxburghii Tratt

Chestnut rose (*Rosa roxburghii Tratt*), also known as Chinquapin rose or Burr rose, is a rare wild fruit crop in southwest, Central South and Northwest China. Fruit of Chestnut rose contains account of vitamin C, polysaccharides, trace elements and essential fatty acids, etc. (Chen & Kan, 2018; Wang et al., 2021a). Vitamin C itself is an effective antioxidant and skin whitening oral and topical active substance. A novel polysaccharide (RRTP1-1) in Chestnut rose is a good scavenger of hydroxyl radical and a moderate scavenger of superoxide radical. The DPPH scavenging activity increased with the increase the concentration of the polysaccharide from 0.02 mg/mL to 0.6 mg/mL. RRTP1-1 groups could add the activity of CAT, SOD and GSH-Px in serum sample (Chen & Kan, 2018). Reducing ROS can effectively restrain the activity of tyrosinase and promote skin whitening. *Rosa roxburghii Tratt* also contain flavonoids which inhibited tyrosinase (Wang et al., 2021a).

Olive (Olea europaea L.)

In Europe and Mediterranean countries, Olives are widely used in folk medicine and herbal tea. Olive extract and oleuropein can significantly reduce the increase in the area of melanin granules in the stratum basale that belong to epidermis which simulated by the UV irradiation via Fontana-Masson staining (Uchiyama et al., 2019).

Pomegranates

Polyphenols contained in a variety of plants play an important role in the diet, can effectively remove free radicals and antioxidant activity, thus playing a role in skin whitening. Pomegranates is a deciduous tree, the fruit is rich in ellagic acid and polyphenols, which contain flavonoids and hydrolyzable tannins that can improve skin whitening (Lu et al., 2022; Vucic et al., 2019). Therefore, Pomegranates have strong anti-oxidant effects. Pomegranate as a functional supplement and cosmetic ingredient can inhibit the mushroom tyrosinase activity and scavenge free radicals (Chan et al., 2022). After consuming pomegranate, melanin formation has a trend to decrease (Henning et al., 2019). Pomegranate extract reduced the number of DOPA which as an intermediate in the synthesis of melanin in the melanocytes of the epidermis by irradiating UV on guinea pigs (Henning et al., 2019). In B16F10 cells, compared with α-MSH-stimulated treatment, Pomegranate concentrate powder (PCP) can up-regulate the expression of glutathione peroxidase-1 (GPx-1) and down-regulate the expression of genes that involved in melanin synthesis, such as phospho-p38, phospho-PKA, phospho-CREB, phospho-GSK3β, MITF, and TRP-1 (Kang et al., 2015). Drinking fixed Polypodium leucotomos/ pomegranate combination can reduce the melanin index and skin sebum content (Emanuele et al., 2017). Some Assay also test on the 3D skin pigmented model to prove its function (Wang et al., 2021b). Otherwise, Fermented pomegranate extracts can clean free radicals and have an anti-oxidation function and have a whitening function via NO signaling pathway (Chan et al., 2022). Therefore, Polyphenols extract as the oral plant extract can be useful for inhibiting melanin synthesis and improving skin whitening.

Phyllanthus emblica L.

Medicinal plants can be used as a source of food and medicine for humans, which are precious gifts of nature. Amla (*Phyllanthus emblica* L.) is an economic resource plant with medicine food homology (Chan et al., 2022; Saini et al., 2022). Amla (*Phyllanthus emblica* L.) Fruit Extract is rich in vitamin C, alkaloids, ellagitannins, gallic acid, flavonoids (especially rutin and quercetin) which plays a crucial role in lightening skin tone, so as to an established anti-oxidant. Amla has good effect on lessening erythema induced by ultraviolet. Amla can also protect against oxidative stress caused by transition metals, free radicals, non-radicals. All of these are important to skin whitening (Saini et al., 2022).

Mulberry extract is rich in phenol, arbutin, tannin, which can act as antioxidants and tyrosinase inhibitors on hyperpigmentation (Austin et al., 2019; Jung et al., 2021; Yuan

& Zhao, 2017). Proanthocyanidin-rich grape seed extract that orally administered can increase the L* value and decrease the melanin index (Babbush et al., 2021). Korean red ginseng powder have beneficial effects for melasma (Babbush et al., 2021). Pulp extracts of Açaí berry can be an inhibitor of tyrosinase activity, down-regulating the expression of MITF and protect skin cells against oxidative stress that irritated by UV. Besides the antioxidant activity, Açaí berry extract also have anti-inflammatory, anti-cancer, immunomodulatory. That means Açaí berry exhibited extraordinary antioxidant and skin whitening power (Petruk et al., 2017; Pirozzi et al., 2020). The saussurea involucrate flavonoids extract (SIFs) inhibit tyrosinase activity that result in decreasing in the melanin synthesis and suppress expression of melanin synthesis genes in the human melanoma A375 cell (Dai et al., 2020). A new oral multi-plant extracts containing cucumis melo extract, acerola extract, olive fruit, aloe vera gel, grape seed extract can be an anti-tyrosinase factor (Xie et al., 2022).

4 Discussion

The skin is a complex and multifunctional organ of the human body, which protects the body from external physical, chemical and infectious attacks and plays a crucial role in many biological and biochemical processes (Csekes & Rackova, 2021). In China, "MFH" means that some food themselves are drugs, and there is no absolute boundary between food and drugs (Gong et al., 2020). Nutrition and particularly oral plant extracts that are MFH could help to fight against skin degradation. Among them, skin whitening increasingly value by both women and men.

Here, we summary the synthesis and transfer of melanin, factors affecting skin whitening, methods evaluating skin whitening and review the function of skin whitening on large amount of oral plant extracts. Together, studies provide evidence of the potential benefits of oral administration of plant extracts for skin whitening and antioxidant benefits. There are four signal pathways that effect the melanin synthesis. Among them, tyrosinase activity and expression, MITF are particularly important. Melanosome transport of melanin also directly affects melanin deposition in the skin. ROS in oxidative stress can promote the synthesis of melanin. So skin whitening and antioxidant have close relationship. At present, in vivo and in vitro methods that evaluate skin whitening are focus on tyrosinase activity, synthesis and transport of melanin.

In the age of personalized nutrition, this review can help us find oral plant extracts which have function of skin whiten and inhibition of reactive oxygen species. We find that most fruit extracts can be used as raw materials for oral plant whitening products because they inhibit tyrosinase activity or participate in the expression of pathway genes, and have excellent taste (Fam et al., 2022; Hong et al., 2021; Song et al., 2020; Uchiyama et al., 2019). Skin whitening products that contain oral plant extracts are commercially available in order to achieve a lighter skin.

In addition to skin whitening, many oral plant extracts also have antioxidant, skin anti-aging and anti-inflammatory effects. Oral of lingonberry and *P. emblica* fruit extract (amla) fruit extract can improve skin conditions contain elasticity and thickness (Uchiyama et al., 2019). Olive is strongly related to the ability of the molecule to scavenge free radicals which have the function of skin anti-aging and antioxidant. Olive also have the function of the anti-neuroinflammatory (Gorzynik-Debicka et al., 2018; Michalak, 2022; Zhang et al., 2019b). Amla powder not only reduced oxidative stress damages, but also inhibited inflammation (Wang et al., 2019a). Mulberries may be a good source of antioxidants. Meanwhile, it has antibacterial effect on several pathogenic bacteria causing gastrointestinal infection (Suriyaprom et al., 2021). Black raspberry extract have high antioxidant activity which can be valuable food additives for functional food (Staszowska-Karkut & Materska, 2020). *Chenopodium formosanum* may be a good source for anti-aging via promoting collagen synthesis and attenuating AGEs-induced ROS production (Lyu et al., 2022). In the future, the mixture with skin whitening/ skin anti-aging / anti-inflammatory antioxidant oral plant extract can be a good candidate for further development on skin care product.

Conflict of interest

The authors declare no conflict of interest.

Data availability statement

Reported results were taken from already published papers.

Author contributions

All authors agree with the manuscript content. Bo Wang, Liping Qu and Feifei Wang led study design. Bo Wang and Xiaohong An write the paper. Bo Wang and Xiaohong An consult the literature. Liping Qu and Feifei Wang provided suggestions and modified the manuscript.

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