

The Use of Botanical Extracts as Topical Skin-Lightening Agents for the Improvement of Skin Pigmentation Disorders

Wenyuan Zhu¹ and Jie Gao¹

Both physicians and dermatology patients are searching for long-term topical skin care solutions (both cosmetic and cosmeceutical) to address problems presented by skin hyperpigmentation. Specifically, some women often express a desire to “lighten” skin tone by achieving improved visible tone, reduction in yellowness (or sallow tone), and reduction in the appearance of hyperpigmented spots (“age” or “sun” spots). Traditional depigmenting agents, such as hydroquinone, corticosteroids, and kojic acid, although highly effective, can raise several safety concerns (for example, ochronosis, atrophy, carcinogenesis, and other local or systemic side effects) with long-term exposure. An understanding of the benefits of natural and botanical extracts provides opportunities to develop new products to address pigmentation problems. Active compounds isolated from plants, such as arbutin, aloesin, gentisic acid, flavonoids, hesperidin, licorice, niacinamide, yeast derivatives, and polyphenols, inhibit melanogenesis without melanocytotoxicity by different mechanisms. This review presents an overview of trends in the application of plant extracts as topical treatments for hyperpigmentation disorders. It highlights some of the most relevant natural extracts, providing *in vitro* screening results and relevant available clinical study trial findings supporting their efficacy.

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INTRODUCTION

Hydroquinone is often considered the gold standard among traditional topical treatments for hyperpigmentation. However, its use has been associated with a number of adverse effects, including skin irritation, contact dermatitis, and exogenous ochronosis in dark-skinned people. Other commonly available topical agents, such as corticosteroids, are either less effective or more likely to cause local or systemic side effects after long-term use. In the search for novel depigmenting agents, the investigation of natural plant extracts has led to the identification of many potentially active compounds (Table 1). Many plant extracts are more potent inhibitors of melanin formation than hydroquinone, kojic acid, or arbutin and are not associated with cytotoxicity or mutagenicity of melanocytes. Moreover, with natural sources offering a multitude of different extracts and isolated compounds, it is apparent that we are only beginning to realize the potential of natural extracts for skin-lightening applications.

DISCUSSION

Arbutin

Arbutin, a naturally occurring β -D-glucopyranoside derivative of hydroquinone, exists in the dried leaves of certain plant

species, such as bearberry. The mode of action appears to be by inhibition of melanosomal tyrosinase and DHICA (5,6-dihydroxyindole-2-carboxylic acid) polymerase activities at noncytotoxic concentrations rather than by suppression of the synthesis and expression of this enzyme (Maeda and Fukuda, 1996; Chakraborty *et al.*, 1998). It is thought that the activity of arbutin is driven by the structural homologies that it shares with the substrate tyrosine, which leads to the competitive inhibition of the catalytic function of tyrosinase. Studies have shown that α -arbutin (4-hydroxyphenyl α -glucopyranoside) demonstrates an even stronger inhibitory effect on human tyrosinase activity than arbutin itself. This effect was achieved without affecting mRNA expression of enzyme in cultured human melanoma cells and a three-dimensional human skin model (Sugimoto *et al.*, 2004). Deoxyarbutin (dA, 4-[tetrahydrofuran-2-yl-oxy]-phenol) has also demonstrated effective inhibition of mushroom tyrosinase *in vitro*. In a human clinical trial, topical treatment with dA for 12 weeks resulted in a significant or a slight reduction in overall skin lightness and improvement of solar lentigines in a population of light-skinned or dark-skinned individuals, respectively (Boissy *et al.*, 2005). α -Arbutin has widely replaced arbutin as the chosen skin-lightening agent in topical skin preparations because it is more

¹Department of Dermatology, First Affiliated Hospital of Nanjing Medical University, Nanjing, PR China

Correspondence: Dr Wenyuan Zhu, Department of Dermatology, The First Affiliated Hospital of Nanjing Medical University, Dermatology, No. 300, Guang Zhou Road, Nanjing 210029, PR China. E-mail: zhuwenyuan@yahoo.com

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Table 1. Overview of botanical extracts with depigmenting activity

| Component | Plant source | Depigmenting mechanism | <i>In vitro</i> research | <i>In vivo</i> research | Potency |
|-------------------------------------|---|---|-------------------------------------|--|---|
| <i>Arbutins</i> | | | | | |
| Arbutin | Pear, cranberry, blueberry, bearberry shrub | ↓ Tyr. ↓ DHICA polymerase | MT B16 NHM | | Arbutin < HQ < dA (Boissy <i>et al.</i> , 2005) |
| α-Arbutin | Pear, cranberry, blueberry, bearberry shrub | ↓ Tyr. ↓ DHICA polymerase | MT ⁺ human melanoma cell | 100 mg g ⁻¹ 15 days 15 Koreans | Arbutin < α-arbutin (Funayama <i>et al.</i> , 1995); reduced pigmentation by 43.5% (Choi <i>et al.</i> , 2002) |
| Deoxyarbutin | Pear, cranberry, blueberry, bearberry shrub | ↓ Tyr. ↓ DHICA polymerase | MT NHM | 3% 12 weeks 34 Caucasian 16 ethnic | Improved skin tone, significant in Caucasians (Boissy <i>et al.</i> , 2005) |
| Aloesin | Aloe | ↓ Tyr. Competitively ↓ DOPA oxidase | MT B16 NHM | 100 mg g ⁻¹ 15 days 15 Koreans | Arbutin < aloesin < kojic acid (Jones <i>et al.</i> , 2002); reduced pigmentation by 34% (Choi <i>et al.</i> , 2002) |
| <i>Flavonoids</i> | | | | | |
| Flavones | Most plants | ↓ Tyr. Uncompetitively | MT | | Chrysin < apigenin < luteolin (Kubo <i>et al.</i> , 2000) |
| Flavonols | Most plants | Copper chelation | MT | | Morin < galangin < quercetin (Xie <i>et al.</i> , 2003) |
| Hesperidin | Citrus fruits | ↓ Tyr. Antioxidant of collagen | MT B16 NHM | 1%, 3% 30 females UV-induced pigmentation | Hesperidin (200 μg ml ⁻¹) ≈ kojic acid; significantly reduced pigmentation in 1 week (Zhang <i>et al.</i> , 2008) |
| p-Coumaric acid | Panax ginseng | ↓ L-tyrosine oxidation | MT B16 | | Significant suppress melanogenesis (Im <i>et al.</i> , 2003) |
| Niacinamide | Root vegetables, yeast | ↓ Melanin transfer, antioxidant of collagen | MC-KC coculture PREP | 8 weeks 5%, 18 facial stain 2%, 40 facial tone | ↓ 35–68% melanin transfer; significant improvement in 4 weeks (Bissett <i>et al.</i> , 2004) |
| <i>Licorice extracts</i> | | | | | |
| Glabridin | Licorice | ↓ Tyr. ROS scavenger | B16 | | Significant ↓ Tyr. at low concentrations (Yokota <i>et al.</i> , 1998) |
| Liquiritin | Licorice | Melanin dispersibility Epidermal remove | MT | 20% 4 weeks 20 melasma | 80% excellent (Amer and Metwalli, 2000) |
| Mulberry | <i>Morus alba</i> | ↓ Tyr. ROS scavenger | Melan-a | | < kojic acid (Lee <i>et al.</i> , 2002) |
| <i>Polyphenols</i> | | | | | |
| Procyanidins | Grape seeds, cranberry | ↓ Tyr. ROS scavenger | MT B16 | | Kojic acid, arbutin < EA (Shoji <i>et al.</i> , 2005) |
| Ellagic acid | Strawberry, geranium | Copper chelation ↓ MC proliferation | MT B16 | | Kojic acid, arbutin < EA ≈ HQ (Shimogaki <i>et al.</i> , 2000) |
| <i>Traditional Chinese medicine</i> | | | | | |
| 18α-GL | Licorice | ↓ Tyr. | MT S91 | 3% 30 female UV-induced pigmentation | Significantly reduced pigmentation in 1 week (Zhang <i>et al.</i> , 2008) |
| Sophorcarpidine | Kuhseng | ↓ Tyr. | MT Melan-a | | < HQ (Lu <i>et al.</i> , 2006) |

↓, inhibit; 18α-GL, ammonium glycyrrhizinate; B16, murine B16 melanoma cell; DHICA, 5,6-dihydroxyindole-2-carboxylic acid; DOPA, 3,4-dihydroxyphenylalanine; HQ, hydroquinone; KC, keratinocyte; MC, melanocyte; MT, mushroom tyrosinase; NHM, normal human melanocytes; PREP, pigmented reconstructed epidermis model; S91, Cloudman S91 melanoma cells; Tyr., tyrosinase.

effective and stable in producing the desired effects on human skin.

Aloesin

Aloesin, a compound isolated from the aloe plant, has been proven to competitively inhibit tyrosinase from human,

mushroom, and murine sources. Studies have shown that tyrosine hydroxylase and DOPA (3,4-dihydroxyphenylalanine) oxidase activities (of tyrosinase from normal human melanocyte cell lysates) are inhibited by aloesin in a dose-dependent manner (Jones *et al.*, 2002). The topical application of aloesin on UV-irradiated (210 mJ) human volar

forearm (four times a day for 15 days) showed pigmentation suppression in a dose-dependent manner (Choi *et al.*, 2002). Aloesin, along with arbutin, was observed to synergistically inhibit melanin production by combined mechanisms of noncompetitive and competitive inhibitions of tyrosinase activity (Jin *et al.*, 1999).

Flavonoids

Bioflavonoids can be divided into flavones, flavonols, isoflavones, and flavanones. The effects of many flavonoids on the oxidation of L-DOPA have been studied. Isoflavones, including glycitein, daidzein, and genistein, showed little antityrosinase activity, but 6,7,4'-trihydroxyisoflavone has been identified as a potent tyrosinase inhibitor stronger than kojic acid. Flavanones, such as hesperidin, eriodictyol, and naringenin, have a structure that is similar to that of hydroquinone. When concentrated in nanocapsules, they are protected until they reach the active site of melanin synthesis, where they exert a powerful reducing action and antiradical activity, and act as a substrate competitor for tyrosinase (Tiedtke *et al.*, 2004).

Hesperidin

Hesperidin is a bioflavonoid existing extensively in the peel and membranes of citrus fruits. Studies by Zhu and colleagues have demonstrated hesperidin's potent ability to inhibit melanin synthesis without cytotoxicity. This work found dose-dependent inhibition of tyrosinase activity (vs control) of hesperidin in melanoma B16 cells and human primary melanocytes (Figure 1, Zhang *et al.*, 2008). In addition, hesperidin was found to protect against UVA-induced damage of fibroblasts and oxidative damage of collagen (Proteggente *et al.*, 2003). Thus, hesperidin offers potential skin-lightening benefits, including improved overall skin tone and antiyellowing effects.

Niacinamide

Niacinamide is a biologically active form of niacin (vitamin B3) found widely in many root vegetables and yeasts, and it is also an important precursor of NADH (nicotinamide adenine dinucleotide) and NADPH (nicotinamide adenine dinucleo-

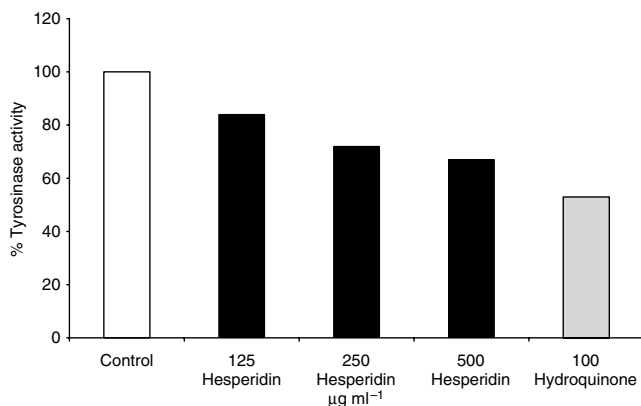


Figure 1. Inhibitory effect of hesperidin on tyrosinase activity in human primary melanocyte.

side phosphate). The large number of cellular enzyme reactions in which these cofactors participate may be the basis for the variety of cosmetic benefits, including barrier enhancement observed from the topical use of niacinamide (Hakozaki *et al.*, 2002). Using cocultures of human melanocytes and keratinocytes, investigators have shown that niacinamide inhibits the transfer of melanosomes from melanocytes to keratinocytes. Results of clinical studies using topically applied niacinamide have demonstrated a reversible reduction in hyperpigmented lesions and increased skin lightness compared with vehicle alone after 4 weeks of use. In a separate clinical study, topical niacinamide was also shown to decrease collagen oxidation products and improve aging-induced yellowing or sallowness (Bissett *et al.*, 2004).

Licorice extracts

Licorice extracts have several active compounds that may stimulate or suppress melanogenesis. Glabridin, the main ingredient in the hydrophobic fraction of licorice extract, inhibits tyrosinase activity in cultured B16 murine melanoma cells, at concentrations from 0.1 to 1.0 $\mu\text{g ml}^{-1}$, without affecting DNA synthesis. Other active compounds, such as glabrene, isoliquiritigenin licuraside, isoliquiritin, and licochalcone A, isolated from licorice extracts, were also shown to inhibit tyrosinase activity (Fu *et al.*, 2005; Nerya *et al.*, 2003). Liquiritin has no effect on tyrosinase; however, it causes depigmentation by other mechanisms, and studies demonstrate that a 20% liquiritin cream applied at 1 g day^{-1} for 4 weeks is therapeutically effective in melasma (Amer and Metwalli, 2000).

Mulberry

Dried mulberry (*Morus alba*) leaves (85% ethanol extract) have been shown to inhibit tyrosinase activity. Additionally, several phenolic flavonoids, such as gallic acid and quercetin, and fatty acids, such as linoleic acid and palmitic acid, have been isolated from its leaves. Mulberroside F (moracin M-6, 3'-di-O-beta-D-glucopyranoside), the active component, showed inhibitory effects on tyrosinase activity and on melanin formation in melan-a cells. This compound also exhibited superoxide scavenging activity that is involved in the protection against auto-oxidation (Lee *et al.*, 2002; Katsube *et al.*, 2006), suggesting a role for *Morus alba* as a component of lightening cosmetics.

Polyphenols

Polyphenols are a class of compound that have antioxidant capacity and are found widely within plants. The inhibition of melanogenesis has been observed with many types of polyphenol plant extracts. Proanthocyanidins or procyanidins, classified as polyphenols, exist in red wine and cranberry juice; grape seeds are another especially rich source. The antioxidative activities of proanthocyanidins were found to be much stronger than the activity of vitamin C or E in aqueous systems. Ellagic acid is another natural polyphenol that is widely found in fruits and vegetables. The extract of the rinds of pomegranate contains 90% ellagic acid and showed inhibitory activity against mushroom tyrosinase

in vitro. The mechanism of action may be inhibition of the proliferation of melanocytes and melanin synthesis by tyrosinase in melanocytes (Yoshimura *et al.*, 2005).

Ginseng

P-coumaric acid, extracted from the fresh leaves of Panax ginseng, was shown to inhibit the oxidation of L-tyrosine more strongly than the inhibition of tyrosinase demonstrated by L-DOPA (Lim *et al.*, 1999). Treatment with Radix ginseng in the presence of various concentrations of Radix trichosanthis suppressed tyrosinase activity and melanin content but increased cell proliferation slightly in B16 melanoma cells, raising the possibility that this combination may be effective as a skin-lightening agent (Im *et al.*, 2003).

Ginkgo

Extracts from the leaves of the ginkgo tree have shown potent free radical scavenger activity when applied to the skin. Ginkgo flavone glycosides, mostly quercetin and kaempferol derivatives, can inhibit tyrosinase activity by chelating copper in the enzyme (Hibatallah *et al.*, 1999; Xie *et al.*, 2003).

Herbs used in traditional Chinese medicine

There are many kinds of traditional Chinese medicine prescriptions aimed at the treatment of hyperpigmentary disorders. The inhibitory actions of the extracts of 219 different traditional Chinese medicine herbs on tyrosinase activity were studied, and 11 ethanolic extracts and 8 aqueous extracts showed inhibitory effects on tyrosinase superior or similar to that of arbutin (Lei *et al.*, 1999; Zhang *et al.*, 1999; Wang *et al.*, 2000). Further research investigated the effects and mechanisms of action of screened herbs. Ammonium glycyrrhizinate (18 α -GL), aloesin, icariin, piceid, salidroside, and epigallocatechin-3-gallate were found to significantly inhibit melanogenesis without cytotoxic effects *in vitro*. Most of these worked primarily by inhibiting tyrosinase activities competitively or noncompetitively (Lei *et al.*, 2002; Rlu *et al.*, 2003; Wang *et al.*, 2004; Yue *et al.*, 2005). A human trial is currently underway to study the effects of treatment with hesperidin and glycyrrhiza cinnamic acid, a naturally occurring aromatic fatty acid of low toxicity, which has a long history of human use. It is known that cinnamic acid does not influence fungal growth but decreases the yield of pigment from the mycelium. Cinnamic acid and aloesin are mixed-type inhibitors of tyrosinase activity, and sophorcarpidine functions as an uncompetitive inhibitor. Tan *et al.* (2002) demonstrated that sophorcarpidine, aloin, and cinnamic acid can bind not only to the enzyme but also to the enzyme-substrate complex, leading to inactivation of tyrosinase.

CONCLUSION

During the past decades, thousands of plant extracts have been screened, and hundreds of compounds were identified as potential skin-lightening ingredients. It is clear that natural sources and extracts represent a repository of ingredients that can be used in topical treatments to achieve improvement of

hyperpigmentation and the overall appearance of skin. More and more *in vitro* studies are showing that these ingredients may also provide additional potential for protective cosmetic use, through antioxidant efficacy and protection of macromolecules, such as collagen from UV irradiation. However, only a few have been incorporated into topically applied cosmetics or cosmeceuticals, often due to lack of parallel human clinical trials. The results of the research by these authors and others indicate the real possibility that natural plant extracts may offer the potential to significantly expand the choices for skin-lightening ingredients and address the need for better ways to treat hyperpigmentation.

CONFLICT OF INTEREST

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