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 ORIGINAL ARTICLE

The Use of Botanical Extracts in East Asia for Treatment of Hyperpigmentation: An Evidenced-Based Review

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ABSTRACT

Recent years have seen a growth in the Asian cosmeceutical industry and an expanding worldwide marketplace with increasing consumer use of plant-based skin care products. The rising prevalence of Asian cosmeceuticals has led to research studies assessing the safety and efficacy of these products. We seek to review current evidence on safety and efficacy of key ingredients used in Asian cosmeceuticals to treat disorders of hyperpigmentation. A comprehensive search on PubMed was conducted to identify hyperpigmentation-related research studies on eight popular ingredients used in Asian cosmeceuticals: green tea, soy, orchid, licorice, rice water, ginseng, bamboo, and aloe. Both in vitro studies and clinical trials involving human subjects were included. Of the ingredients reviewed, soy and licorice had the most clinical evidence supporting their efficacy, while all other ingredients were supported by in vitro studies. More research is needed to further evaluate the safety and efficacy of Asian cosmeceutical ingredients in treatment of hyperpigmentation.

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INTRODUCTION

Cosmeceuticals, topical skin products containing bioactive ingredients purported to have medical benefits, are the fastest growing beauty industry in the world with an estimated $42.8 billion worth of sales in 2018.[1] The cosmeceutical industry is particularly robust in Asia, where skin lightening takes on cultural significance. This strive for aesthetic beauty has led to the formulation of naturally-based skin care products targeted at hyperpigmentation. Korea has been at the forefront of generating the newest and most innovative cosmeceutical products. Some of the most popular ingredients used in these cosmeceuticals include green tea, soy, orchid, licorice, rice water, ginseng, bamboo, and aloe. Since the rising popularity of Asian cosmeceuticals, there has been an increasing world-wide demand for skin care products utilizing exotic plant-based ingredients. Scientists have been conducting research studies on these plant extracts, their unique properties, and their evidence-based use in the current beauty industry. With increasing consumer use of cosmeceutical products, it is imperative that physicians understand the properties of these extracts and the scientific basis of their efficacy in order to better inform patients and ensure their safety. Few research articles have explored the effectiveness of plant-based Asian cosmeceuticals in treating hyperpigmentation, and even fewer have assessed the clinical evidence behind their efficacy. In this review, we seek to incorporate the most recent scientific literature to critically appraise in vitro studies and clinical trials investigating the natural ingredients found in Asian cosmeceuticals.

MATERIALS AND METHODS

A comprehensive review of the literature on natural ingredients most frequently used in Korean cosmeceuticals to treat hyperpigmentation was conducted on PubMed (U.S. National Library of Medicine). The search terms "green tea," "soy," "orchid," "licorice," "rice water," "ginseng," "bamboo," and "aloe vera" were input into the advanced search tool to identify all articles discussing hyperpigmentation or pigmentary disorders from both in vitro and in vivo studies with publications up to April 2019. Non-English language articles were excluded. A total of 50 studies were included for this study.

Studies Categorized by Active Ingredients

Aloe Vera

Aloe Vera is a popular succulent plant that has long been used for many dermatologic conditions such as eczema, burn wounds, skin infections, and acne vulgaris.[2] Inside the leaves of the aloe vera plant is copious amounts of gel that can be squeezed out and directly applied to the skin.[3] This gel has been used for its anti-bacterial and anti-inflammatory properties as well as to decrease hyperpigmentation of the skin. Aloesin, a natural hydroxymethyl chromone compound and the active ingredient in the aloe vera plant, competitively inhibits dihydroxyphenylalanine (DOPA) oxidation and non-competitively inhibits tyrosine hydroxylase activity.[4] Melanin is synthesized through tyrosine hydroxylase and oxidation of DOPA.[5] Thus inhibition of these steps in melanin biosynthesis has the potential to prevent overproduction of melanin and skin hyperpigmentation. A prior

study showed that the topical application of aloesin following ultraviolet (UV)-irradiation (210 mJ) on the inner forearm provided pigmentation suppression in a dose-dependent manner.[6] Another in vitro study showed that aloesin induced melanin aggregation in isolated tail melanophores of tadpoles, *B. melanostictus*, which lead to lightening of the skin.[7] More recently, aloe vera was tested in a double-blinded randomized clinical trial aimed at determining the clinical efficacy of a topical liposome-encapsulated aloe vera in the treatment of melasma in pregnant women. Researchers were able to show that this drug carrier system along with aloe vera decreased the severity of melasma in pregnancy when compared to aloe vera gel extract alone, as demonstrated by a 32% improvement in MASI scores in the treatment group compared to a 10% improvement in the control group.[2] When used topically, aloe vera is generally considered safe; however, some case reports of skin irritation and hypersensitivity to Aloe products have been reported.[8]

Bamboo

Bamboo is a type of flowering plant that belongs to the *Bambusoideae* subfamily and has been used as a healing treatment by Asian cultures for centuries.9 In vitro studies have shown bamboo to be an effective lightening agent. Water extract from bamboo shavings (WEBS) has demonstrated potent inhibitory effects against the activity of melanin-synthesizing enzyme, tyrosinase, in malignant melanoma B-16 cells of mice.[10] In this study, the effects were dose dependent and melanin content was significantly inhibited (65.05%) at 16 mg/ml with an inhibitory concentration (IC50) of 6 mg/ml. The application of the topical formulation was shown to be non-toxic and non-irritating to the skin. Another study examined the effects of bamboo extract on UVB-induced cell damage. Human keratinocytes were exposed to UVB in the presence of bamboo extract at varying concentrations and changes in cell viability were determined.[11] Bamboo extract diminished the generation of reactive oxygen species, inhibited matrix metalloproteinase 1 expression, and enhanced UVB-exposed cell survivability, as measured by apoptotic assays. These results suggest that bamboo extract may have the ability to attenuate the process of skin photoaging. Few clinical trials on human subjects have been conducted on bamboo extract. The only clinical trial to date utilized a skin cream formulated with flavonoids and extracts from bamboo leaves.[12] Results showed that addition of 1.5% topical bamboo extract resulted in sun screening efficacy and protection against UVB damage as indicated by an SPF of 1.27. A UV Index reading of 0 to 2 indicates low risk of harm from unprotected sun exposure for the average person. No irritation was reported by participants with topical application to the skin.

Ginseng

Ginseng has been used for centuries in Asian traditional medicine to treat many chronic diseases.[13] The popularity of the ingredient has led to its formulation in high-end Asian skin care products. In vitro studies demonstrate that P-coumaric acid extracted from the fresh leaves of Panax ginseng inhibits tyrosinase activity and melanin content in B16 melanoma cells, suggesting that this ingredient may be an effective skin lightening agent.[14] Furthermore, ethanol extract from ginseng seeds reduced melanin production in melan-a-cells (melanoctyes originating from mice) by 35.1% without cytotoxicity.[15] Among the active metabolites isolated, picrionoside A was shown to be effective in reducing body pigmentation in zebrafish in addition to decreasing the rate of melanin synthesis in melan-a-cells by 17.1% without cytotoxicity.[16] These in vitro studies suggest that different active ingredients in ginseng may be efficacious skin lightening agents. No clinical trials have studied the effects of topical application of ginseng. However, one study evaluated the effectiveness of oral administration of ginseng on patients with melasma. A cohort of 25 female patients consumed 3 grams of Korean red ginseng powder over a 24 week period.[17] Skin pigmentation was assessed using the melasma area and severity index (MASI), melasma quality of life scale (MELASQoL), and patient/investigator-rated improvement scales. After 24 weeks, the MASI score decreased from 8.8 to 5.6, and the MELASQoL showed improvement in 91% of patients ($P<0.05$). The mean level of pigmentation decreased from 184.3 to 159.7 and erythema levels decreased from 253.6 to 216.4 ($P<0.05$). The regimen showed good tolerability overall with minimal adverse events.

Green Tea

Green tea is known for its potent antioxidant and anti-inflammatory properties.[18] Among the many polyphenols in green tea extract, epigallo-catechin-3-gallate (ECGC) is the primary active ingredient.[19] One study using immortalized melanocytes showed that camellia sinensis water extracts containing green tea inhibited melanogenesis and tyrosinase activity in a concentration-dependent manner.[20] The skin lightening effects of green tea may be due to chelating properties at the active site of tyrosinase.[21] In a randomized controlled trial, 60 women with melasma were treated with a 2% analogue of green tea in a hydrophilic cream.[22] Hyperpigmentation lesions were significantly reduced in 60% of the experimental group relative to the control group as measured by a reduction of mean number of hyperpigmented lesions, as determined by dermatologic and photographic evaluations. In addition to treating melasma, green tea extracts were shown to reduce skin pigmentation in healthy Asian subjects.[23] The lightening effects of green tea may be due to the prevention of sun damage accumulated over time. The skin of normal volunteers was treated with green tea or one of its main ingredients.[24] After thirty minutes, the treated areas were exposed to solar-simulated UV radiation and subsequent UV-induced erythema was monitored. Skin areas with green tea extract showed a dose-dependent inhibition of erythema response caused by UV radiation. Further histology showed that areas of skin treated with green tea extract had a reduced num-

ber of sunburn cells and epidermal Langerhans cells damaged by UV radiation. With the emerging popularity of green tea extract-formulated skin care products, more clinical trials are needed to evaluate the lightening effects of green tea on human skin.

Licorice

Licorice, also known as Glycyrrhiza glabra, has long been used for its medicinal value and anti-inflammatory components.[25,26,27] However, licorice also contains the active ingredient Glabridin that may have value in reducing pigmentation. Glabridin works by inhibiting UVB-induced pigmentation and tyrosinase, thus disrupting the pathway of pigment production.[28] In vitro studies have shown that Glabridin has 16 times the skin lightening effects of hydroquinone, a known skin lightening agent.[28,29] In line with this, in a single-center, double-blind clinical study of 18 subjects comparing the efficacy of a hydroquinone-free formula, containing Glabridin, there was a significant reductions in ultraviolet-induced hyperpigmentation when compared to both the negative control as well as 4% hydroquinone cream.[30] Furthermore, in a single-blinded study comparing the efficacy of belides, embilica, and licorice 7% to 2% hydroquinone in the treatment of melasma, the degree of depigmentation in both groups was not statistically different.[31] Another active ingredient present in licorice, liquirtrin, has also demonstrated depigmention properties. In fact, in one double-blind, split-face study of 20 subjects comparing 2% and 4% liquirtin to 4% hydroquinone for the management of melasma, both concentrations of liquirtin were significantly more effective in decreasing pigmentation when compared to hydroquinone.[32]

Orchid

Orchid extract contains plant pigments called anthocyanins, a group of phytochemicals known for their antioxidant and anti-inflammatory properties.[33] These flavonoids combat reactive oxygen species (ROS) and are capable of soothing and enhancing skin tone while minimizing oxidative stress.[33,34] In vitro studies suggest that orchid extract is effective in suppressing WNT1 expression by downregulating a transcriptional activator of the gene.[35] Increased expression of WNT1 stimulates melanocyte stem cell differentiation. A double-bind, comparative, split-face clinical trial in 48 female patients with melasma and/or solar lentigines to evaluate the in vivo efficacy of a cosmetic formulation containing orchid extract compared to 3% vitamin C derivative.[36] After 8 weeks of topical use, the orchid extract group showed similar efficacy as vitamin C group in lightening melasma and lentigines by colorimetric measurements and subjective questionnaire. Importantly, the study found little risk associated with the use of topical orchid extract. No instances of contact dermatitis, pruritis, or irritation were reported during the 8 weeks of treatment.

Rice Water

Rice (*Oryza sativa*) extract is a key ingredient in many Asian hair and skin treatments.[37] It contains high levels of bioactive phenolic compounds (p-coumaric, ferulic, and caffeic acids) that display anti-tyrosinase and photoprotective properties.[38] The anti-melanogenic peptides found in rice bran protein were shown to significantly inhibit melanogenesis in mouse B16 melanoma cells without causing cytotoxity.[39]The suppression of melanogenesis can be attributed to its anti-tyrosinase and TRP-2 inhibitory effects, which protect the cell from oxidative stress in a dose-dependent manner. It is proposed that the potent skin lightening effects of the extract result from the synergistic activities of the active phenolic ingredients.[38] A double-blind randomized control trial of 24 volunteers demonstrated that rice extract cream (0.1% or 0.2%) resulted in a significant decrease in melanin index ($P< 0.001$) post-treatment (28 days) compared to baseline.[38] Furthermore, no subjects reported adverse effects over the study period. To confirm the safety of the topical treatment, patch testing in a separate cohort of 25 healthy subjects showed no signs of skin irritation on exposure to rice extract cream. Another clinical trial using semi-purified rice bran extract entrapped in niosomes formations demonstrated skin lightening in 30 human subjects within a 28-day period.[40] Both gel and cream formulations resulted in a sustained skin lightening effect post-treatment even after continued application was forgone for 7 days. No skin irritation was noted in this clinical study.

Soy

Soybean is a legume commonly grown in East Asia.[41] It consists of many biologically active ingredients including isoflavones.[42] There are a number of in vitro studies attesting to the pigment-reducing properties of soybean extract.[42,43,44] Equally significant is the large amount of clinical trials supporting its efficacy as skin lightening agent. A 16-week, double-blind, placebo-controlled clinical study of African-American, Hispanic, and Asian patients with Fitzpatrick skin types III–V showed that a soy-containing topical formulation resulted in a reduction in post-inflammatory hyperpigmentation caused by acne. Assessments of acne severity and hyperpigmentation were measured by expert clinical evaluations, global acne asessments, and spectroscopic measurements evaluating changes in redness and melanin over time.[46] Another double-blind, vehicle-controlled study enrolled 65 women with facial photodamage and monitored their skin condition over a 12-week period with the use of a soy extract-containing moisturizer.[47] Using colorimetric measurements, digital photography, and clinical evaluation, the soy moisturizer was significantly more efficacious in reducing mottled pigmentation blotchiness and overall skin tone compared to the vehicle. No adverse events were reported. In a study of 16 Hispanic women with melasma, subjects applied a stabilized soy extract once daily for 3 months to areas of dyspigmentation with untreated dyspigmented areas serving as controls.[47,48] Fourteen of the sixteen subjects had a 12% reduction in hyperpigmentation as measured by colorimetric evaluations. No side effects were noted. In fair-complexioned men of Celtic origin,

TABLE 1.

Comparison of Properties of Active Ingredients in Asian Topicals

Name of Topical	Evidence Behind Use	Skin Condition(s) Treated	Dosing & Formulation*	Mechanism of Action	Adverse Events**	Market Availability in U.S.***
Aloe Vera	Double-blinded RCT2,6-7	PIH, melasma, eczema, burn wounds, skin infections, acne vulgaris	Liposome-encapsulated leaf gel extract (0.5 wt % concentration)	Competitive inhibition of DOPA oxidation, non-competitive inhibition of tyrosine hydroxylase	Skin irritation, hypersensitivity, hives	Yes
Bamboo	Uncontrolled observational study[12]	Hyperpigmentation, UVB-damaged skin, photoprotection	Cream formulation with 1.5% mass fraction of bamboo leaf extract	Dose-dependent inhibition of tyrosinase activity	No reported incidences of skin irritation	Yes
Ginseng	Uncontrolled observational study[17]	Melasma, hyperpigmentation	Oral formulation w/1 gram red ginseng powder	Inhibition of tyrosinase activity	No reported cutaneous effects with oral administration	Yes
Green Tea	Multiple RCTs[21-24]	Melasma, hyperpigmentation, photoprotection	2-5% green tea extract in hydrophilic cream	Concentration-dependent Inhibition of tyrosinase activity via chelation at active site	No reported incidences of skin irritation	Yes
Licorice	Single and double-blind clinical studies[28-32]	Hyperpigmentation, melasma	Topical formulation of 7% licorice extract or 2-4% liquiritin	Inhibition of tyrosinase	No reported incidences of skin irritation	Yes
Orchid	Double-blind comparative split-face clinical trial[36]	Melasma, solar lentigines	5% orchid extract cosmetic formulation or serum	Reduction of reactive oxygen species (ROS), downregulation of transcriptional activity of WNT1 gene	No adverse events including irritation, itching and contact dermatitis	Yes
Rice Water	Several double-blind RCTs[38,40]	Hyperpigmentation	0.1-3% rice bran in oil-based cream or niosomal dispersion	Dose-dependent inhibition of tyrosinase and TRP-2, photoprotective properties	No reported incidences of skin irritation	Yes
Soy	Multiple RCTs[46-48,50]	PIH, photodamage, melasma, facial hypermelanosis	Active moisturizer with stabilized soy extracts	Inhibition of melanosome phagocytosis by keratinocytes via protease-activated receptor 2 (PAR-2)	No reported incidences of skin irritation	Yes

PIH = post-inflammatory hyperpigmentation; RCT = randomized control trial
*Dosing and formulation based on efficacious activity of the topical(s) with observable results and definable endpoints.
**Adverse events as reported in current scientific literature. More studies are needed to further elucidate adverse events and appraise the long-term side effects of these topical formulations.
***Market availability in U.S includes but is not limited to over-the-counter products and cosmeceuticals available in stores or online platforms.

soybean extract had a skin lightening effect in treating facial hypermelanosis in 44 individuals.[50] Overall, promising results from multiple randomized-control trials and the well-tolerability of soy extract supports the use of soybean extract in treating hyperpigmentation.

DISCUSSION

Asian cosmeceuticals containing natural plant-derived ingredients are increasing in popularity in the U.S. and worldwide. As the market for these skin care products continue to grow, consumers will increasingly seek advice from dermatologists regarding their efficacy. The scientific and clinical evidence supporting some of the most popular ingredients formulated in Asian skincare products used to treat hyperpigmentation, as reviewed here have shown them to overall be safe and well-tolerated. Although, well-controlled, robust clinical studies evaluating the safety and efficacy of plant extracts for treatment of hyperpigmentation are continuing to evolve, as reviewed

here, soy and licorice had the most clinical evidence to date. Nonetheless, all the ingredients have been substantiated to some degree by scientific research, through in vitro and/or in vivo studies, and appear to be well-tolerated.

With the mounting popularity of Asian skin care products, we anticipate an increasing number of clinical studies in the future to further evaluate the efficacy and safety of these ingredients in human subjects, allowing clinicians to better understand and counsel patients, and perhaps offer alternative, non-hydroquinone based topical lightening therapy to their patients.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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