SPECIAL TOPIC: SKIN OF COLOR

- Chemical Peels for Facial Hyperpigmentation
- Microneedling in All Skin Types
- Biosimilars Perspectives
- HA Injection Technique
- Stem Cell Activation in Skin Rejuvenation
Evidence for Anti-Aging South Korean Cosmeceuticals

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ABSTRACT

As the market for South Korean skin care products grows in the U.S. and worldwide, consumers will increasingly seek advice from dermatologists regarding their efficacy. In this paper, the evidence behind the anti-aging and skin whitening activity of ingredients in the most popular South Korean skin care products was reviewed and critically evaluated. Industry profit data from Euromonitor was obtained to identify the top cosmeceutical brands by retail value in South Korea. The top selling products and their ingredients were then identified from individual brand websites. A comprehensive literature search was conducted using Pubmed to identify and grade the anti-aging and whitening efficacy for nine popular ingredients: licorice, niacinamide, beta-glucan, snail mucus, ginkgo biloba, ginseng, green tea, pomegranate, and soy. Of the various ingredients reviewed, niacinamide, green tea, licorice, and soy have the most published data for anti-aging and whitening activity. Although the literature shows modest results, small sample sizes limit interpretation. High-level evidence to support the use of South Korean skin care products in anti-aging and skin whitening is lacking.


INTRODUCTION

Patients are increasingly looking to natural ingredients to improve the appearance of their skin and delay the effects of aging. The aging process in the skin is due to a combination of intrinsic and extrinsic factors, among which ultraviolet (UV) radiation is believed to play an important role. UV radiation facilitates aging by increasing reactive oxidation species and cellular damage, epidermal hypertrophy, hyperpigmentation, degradation of extracellular matrix proteins and dermal collagen, and producing phototoxic effects such as erythema, edema, and inflammation. Skin care products promise anti-aging effects by counteracting these various factors.

Many of these natural anti-aging ingredients are emerging from Asian countries like South Korea, one of the world’s most innovative and fastest growing beauty markets. Although South Korea has a population of 50 million compared to the U.S. population of 300 million, the South Korea skin care market is worth $4.4 billion, rivaling the U.S. skin care market at $5 billion. South Korean skin care products focus on anti-aging and skin whitening using natural botanical and animal ingredients such as green tea, ginseng, and snail serum. As these products permeate the US market, patients are turning to dermatologists for advice on their efficacy, emphasizing the need for a critical understanding of the underlying evidence.

METHODS

We evaluated the scientific literature for the efficacy of nine natural active ingredients in the top selling brands emerging from the South Korean cosmeceutical industry. Available industrial profit data was obtained from Euromonitor to identify the top cosmeceutical brands by retail market value in South Korea (Figure 1). The top-selling products of these brands were then discovered on the brand websites, and a list of the products’ active ingredients was compiled (Table 1). The nine active ingredients were chosen based on frequency listed and availability of literature on PubMed. In vitro, preclinical in vivo, and clinical studies of the topical application of these active ingredients were identified, and the best available evidence was critically evaluated and is presented here within (Table 2). Exclusion criteria included other applications (i.e., oral) of these ingredients and popular ingredients with no available scientific studies at the time this paper was written.

Licorice

Licorice extract, also known as Glycyrrhiza uraleensis, is derived from the root of the Glycyrrhiza glabra plant, a legume native to Europe and Asia.

Licorice is frequently utilized in South Korean skin care products for its anti-inflammatory effects. Licochalcone A (LicA), an active ingredient in licorice extract, was shown in vitro to decrease prostaglandin E2, leukotriene B4, interleukin-6, and tumor necrosis factor-alpha in human keratinocytes. In a randomized, controlled clinical study, irritated skin treated with 0.025% of LicA-rich licorice extract was found to be less erythematous compared to vehicle alone by spectrophotometry. LicA may also effectively reduce sunburn erythema. Patients treated with 0.05% of the LicA-rich licorice extract and vehicle immediately and 5 hours after exposure to UVB irradiation had significantly less erythema where the LicA was applied. The erythema-reducing ability of LicA was also evaluated in patients with mild to moderate rosacea using 4 different types...
More recently, a double-blind placebo controlled study of 100 female subjects with melasma using *glycyrrhiza glabra* 2% cream showed significantly decreased hyperpigmentation as compared to control (P<0.001) per clinical evaluation by a dermatologist at 4 weeks.10

**Ginkgo biloba**

*Ginkgo biloba (GB)* is one of the oldest species of tree on the planet11 and has been used in traditional herbal medicine for thousands of years. Its anti-aging benefits are derived from its anti-oxidant activity. EGB-761, the common standardized extract preparation of the ginkgo leaf containing mostly flavonoid glycosides has been shown to act as an anti-oxidant.12 A recent study demonstrated that EGB-761 photoprotects human dermal fibroblasts and mice skin against UVB light irradiation.13 In the human fibroblasts, the extract was found to inhibit the UVB-induced phosphorylation of MAPK pathway components and reduce the expression of the proinflammatory cytokines by suppressing reactive oxygen species generation. After mice were exposed to UVB radiation thrice weekly for 3 months, signs of photodamage, such as coarse wrinkle formation, epidermal hyperplasia, and elastic fiber degeneration were markedly reduced with the topical application of EGB-761 compared to control.14

These anti-aging effects of GB have been explored clinically but the evidence is not compelling. In a small study lacking a placebo group, application of ginkgo biloba gel increased skin moisturization and smoothness and reduced wrinkles compared to a mixture of tea and rociob.15 Another clinical trial assessed the anti-aging effect of GB in a formulation also containing Vitamin A, C, E and the red algae *Porphyra umbilicalis*.16 Although the formulation purportedly improved skin barrier function and

### TABLE 1.

<table>
<thead>
<tr>
<th>Select Products and Ingredients of Top South Korean Skin Care Brands</th>
<th>Example of products (ingredients)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand</strong></td>
<td><strong>Company name</strong></td>
</tr>
<tr>
<td>1</td>
<td>Sulwhasoo</td>
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<tr>
<td>2</td>
<td>The Face Shop</td>
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<tr>
<td>3</td>
<td>Hera</td>
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<tr>
<td>4</td>
<td>Missha</td>
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<td>5</td>
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<tr>
<td>7</td>
<td>The History of Whoo</td>
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</table>
reduced width and number of wrinkles, statistical significance was not achieved, and the efficacy of GB alone was not assessed.

**Beta-glucan**

Extracts from yeast species *Saccharomyces* or *Saccharomyces cerevisiae* contains the key active ingredient beta-glucan, a polysaccharide of D-glucose monomers linked by beta-glicosidic bonds. Beta-glucan can be extracted from oat, mushroom, and yeast.

Beta-glucan acts as an anti-oxidant and anti-wrinkle agent. One in vitro study showed that beta-glucan derived from the wall of *Saccharomyces cerevisiae* inhibits oxidation of human plasma proteins. Another in vitro study demonstrated that beta-glucan stimulates human fibroblast collagen biosynthesis through an NF-1-dependent mechanism.

Clinical support for topical beta-glucan as an anti-aging agent is limited. An 8-week treatment course of oat-derived beta-glucan showed a reduction of wrinkle depth and height and overall roughness per digital image analysis.

**Niacinamide**

Niacinamide is one of the best studied cosmeceuticals for anti-aging and is commonly found in many cosmeceuticals. Also known as nicotinamide, niacinamide is the precursor of niacinamide adenine dinucleotide (NAD) and its phosphate derivative, niacinamide adenine dinucleotide phosphate (NADP). These cofactors and their reduced forms (NADH and NADPH) serve as reduction-oxidation coenzymes in fundamental biological cellular processes in humans.

Niacinamide has shown whitening, anti-wrinkle, and anti-oxidant activity in numerous in vitro and preclinical in vivo studies (Table 2), as well as in clinical trials. In a randomized, split-faced trial of Japanese women, pigmentation change evaluated using high resolution digital images and subjective measurements found that 8 week application of 5% niacinamide resulted in significant lightening compared to vehicle (P<0.05). Another split-face clinical trial of Japanese women with application of 4% topical niacinamide and placebo twice daily for 8 weeks demonstrated a significant decrease in facial hyperpigmentation compared with placebo. Niacinamide was also found to significantly reduce wrinkles after 12 week application of 4% niacinamide compared to placebo.

Finally, a randomized, double-blind, split-face, placebo-controlled clinical trial of white females found that 12 weeks of twice daily treatment of 5% niacinamide significantly improved fine lines, wrinkles, hyperpigmentation, redness, yellowing, and skin elasticity compared to vehicle (P<0.05).

**Snail mucus**

Secretions from the mollusk *Cryptophallus aspera* (SCA) have recently become a popular ingredient in Asian skin care products. SCA are composed of glycosaminoglycans, which have been shown to function as growth factors. SCA has been proven beneficial in the regeneration of burnt skin and in the management of open wounds, and now recent studies suggest its role as an anti-aging agent.

In vitro studies indicate that SCA is a powerful antioxidant and plays an important role in promoting cell survival against insults like UVB (Table 2). The clinical efficacy of SCA as an anti-aging is also promising. A nonrandomized, open-label clinical study using topical SCA on females exhibiting facial photodamage demonstrated significant reduction in fine lines, deep wrinkles, and improvements in elasticity, dyspigmentation, and roughness after 90 days. Silicone replica assessments also reported improvements in wrinkle depth by as high as 30% as well as cutaneous microroughness. Biopsies showed significant reduction of both epidermal thickness and solar elastosis after 90 days of SCA application. In addition, a 2-center, double-blind, randomized split-face 14 week study of patients with moderate-severe photodamage treated with an emulsion (8% SCA) and liquid serum (40% SCA) versus placebo showed significant improvement in skin texture and rhythms based on physician assessments and silicone skin impression.

**Pomegranate**

*Punica granatum*, also commonly known as pomegranate, is a small tree of the Punicaeae family grown mainly in Iran, India, Spain, Israel, and the US, and is rich in polyphenols.

The polyphenols from pomegranate are believed to have powerful antioxidant, cell survival, and whitening activity. They have been shown to scavenge free radicals and decrease macrophage oxidative stress and lipid peroxidation in vitro and in vivo in mouse models. In vitro study demonstrated pomegranate juice and seed extracts have 2-3 times the antioxidant capacity of either red wine or green tea. In addition, pomegranate fruit extract was shown to enhance collagen synthesis and to protect human skin fibroblasts from cell death following UV exposure.

In vitro studies have shown that it may inhibit melanogenesis by downregulation of tyrosinase, Tyrp1, and Mc1r.

However, evidence for clinical benefit is lacking. The only clinical study to date is a single-blinded, placebo-controlled split-face study in which male volunteers used topical microemulsion of pomegranate extract on one cheek for 12 weeks. Significant improvement was noted in erythema and in skin melanin content compared to control.

**Green Tea**

Green tea (GT) is derived from the tea plant, *Camellia sinensis*, which is native to the tropical or subtropical climates of South East Asia and has been used in traditional Chinese medicine for centuries. The main active ingredients are polyphenols.
<table>
<thead>
<tr>
<th>Component</th>
<th>Active ingredient</th>
<th>Mechanism of action</th>
<th>In vitro and preclinical in vivo studies</th>
<th>Clinical studies</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Licorice</td>
<td>Licochalcone A</td>
<td>Anti-inflammatory</td>
<td>Human keratinocytes</td>
<td>Randomized controlled studies: 46 patients, ↓ erythema after 3d on irritated skin; 12 patients, ↓ sunburn erythema at 5 and 24 hrs; No control: 62 patients with roseacea, ↓ erythema compared to baseline at 8 wks</td>
<td>Level 1B</td>
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<tr>
<td></td>
<td></td>
<td>↓ PE2, LKB4, II,6, TNPα</td>
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<tr>
<td>Glaabridin</td>
<td></td>
<td>Whitening</td>
<td>B16 murine melanoma cells, guinea pig</td>
<td>Unblinded controlled study: 20 patients with melanoma, 70% ↓ pigmentation intensity at 4 wks</td>
<td>Level 2B</td>
</tr>
<tr>
<td>Liquiritin</td>
<td></td>
<td>Whitening</td>
<td>Mushroom tyrosinase</td>
<td>Double blind placebo controlled study: 100 patients with melanoma, ↓ hyperpigmentation at 4 wks</td>
<td>Level 1B</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Egb-761</td>
<td>Anti-oxidant Inhibit UVB-induced phosphorylation of MAPK, suppress ROS generation</td>
<td>Human dermal fibroblasts, BALB/c mice skin</td>
<td>Controlled study: 20 patients, ↑ moisturization and smoothness, ↓ roughness and wrinkles</td>
<td>Level 2B</td>
</tr>
<tr>
<td>Beta-glucan</td>
<td>Beta-glucan</td>
<td>Anti-oxidant</td>
<td>Human plasma proteins</td>
<td>No control: 27 subjects ↓ wrinkle depth and height, ↓ roughness at 8 wks</td>
<td>Level 2B</td>
</tr>
<tr>
<td>Niacinamide</td>
<td>Niacinamide</td>
<td>Anti-oxidant ↑ NADPH</td>
<td>Human keratinocytes</td>
<td>Controlled studies: 18 Japanese females, ↓ hyperpigmentation with 5% formulation after 6 wks (p&lt;0.05); 18 Japanese females, ↓ hyperpigmentation with 5% formulation after 6 wks</td>
<td>Level 1B</td>
</tr>
<tr>
<td>Snail mucus (Cryptophalus aspera (SCA))</td>
<td>Anti-oxidant</td>
<td>Human keratinocytes and fibroblasts</td>
<td>Nonrandomized open label clinical study: 15 females, ↓ Fine lines, deep wrinkles, elasticity, ↓ dryness, roughness</td>
<td>2 Center double blind split-face controlled study: 26 patients, improvement in texture and rhytides</td>
<td>Level 2B</td>
</tr>
<tr>
<td>Polyphenols</td>
<td>Polyphenols</td>
<td>Antioxidant Scavenge free radicals, ↓ macrophage oxidative stress and lipid peroxidation</td>
<td>Mouse models, immortalized HaCat keratinocytes</td>
<td>Single-blinded placebo-controlled split face study: 11 males, topical pomegranate extract for 12 weeks improved erythema and decreased melanin content</td>
<td>Level 2B</td>
</tr>
<tr>
<td>Component</td>
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<tr>
<td>Green tea</td>
<td>Polyphenols (catechins)</td>
<td><strong>Anti-oxidant</strong> ↓UVB-induced depletion of antioxidant enzymes, ↓lipid peroxidation and protein oxidation <strong>Anti-inflammatory</strong> Inhibit UV-induced MAPK and NFκB activation, ↓Leukocyte infiltration and edema <strong>Hydration</strong> ↓Transdermal water loss, ↑moisture capacity</td>
<td>Mouse models</td>
<td>Human skin punch biopsies: pretreatment with EGC, ↓leukocytes, ↓lipid peroxidation, and total glutathione levels, ↓UV-induced H2O2 and NO</td>
<td>Level 1B</td>
</tr>
<tr>
<td>Panax ginseng (red ginseng, Asian ginseng, Korean ginseng)</td>
<td>Saponins (or ginsenosides)</td>
<td><strong>Skin remodelling</strong> ↑Type I collagen synthesis, ↓MMP expression, ↓apoptosis <strong>Anti-oxidant</strong> Ginsenoside RB2: ↓UVB-induced ROS elevation and MMP-2 expression <strong>Whitening</strong> ↓tyrosinase activity, ↓melanocyte proliferation, ↓GM-CSF expression</td>
<td>Human dermal fibroblasts and keratinocytes</td>
<td>Clinical study: 23 females, topical ginseng extract prevented eye wrinkle formation, ↓global photodamage, ↓roughness, ↑moisturization and softer skin</td>
<td>Level 2B</td>
</tr>
<tr>
<td>Soy</td>
<td>Phytoestrogens, Isoflavones, Genistein, Daidzein</td>
<td><strong>Antioxidant</strong> ↓Free radicals (H2O2), ↑glutathione, glutathione-S-transferase, antioxidant enzyme activity <strong>Skin remodelling</strong> ↑Collagen, elastin, MMP inhibitors, ↓MMPs <strong>Protease inhibitors</strong> Soybean trypsin inhibitor, Bowman-Birk protease inhibitor <strong>Phytoestrogen effects</strong> ↓UV-induced apoptosis, ↑skin elasticity, ↑type 1 procollagen, ↓wrinkle depth <strong>Whitening</strong> ↓Transfer of melanosomes into keratinocytes</td>
<td>Mouse skin, human keratinocytes</td>
<td>12-week double-blind randomized vehicle-controlled clinical study: 65 females, soy moisturizer with protease inhibitors improved pigmentation, blotchiness, dullness, fine lines, overall texture and skin tone, overall appearance.</td>
<td>Level 1B</td>
</tr>
</tbody>
</table>

Also known as catechins, which comprise 30 to 35 percent of the dry weight of the green tea leaf. Of the four major GT catechins, epigallocatechin-3-gallate (EGCG) is the most abundant catechin and the most powerful antioxidant. GT polyphenols have multiple anti-aging properties, including anti-oxidation, anti-inflammation, and decreased collagen breakdown. In vitro studies of topical GT catechins to mouse skin demonstrated protection against UVB-induced...
depletion of antioxidant enzymes, lipid peroxidation, and protein oxidation. An in vivo study using human skin punch biopsy samples demonstrated topical EGCG inhibited UV-induced infiltration of inflammatory leukocytes, epidermal lipid peroxidation, and H2O2 and NO production. A mouse study demonstrated topical treatment with EGCG resulted in decreased leukocyte infiltration and UVB-induced activation of MAPK and NF-kappaB cell signaling pathways. Mouse models demonstrated that GT extracts diminished epidermal thickness, increased collagen and elastic fiber content, and reduced expression of MMPs.

Clinical evidence for GT’s anti-aging properties is still limited. A small clinical study of human volunteers treated with application of GT extract, especially the EGCG and ECG fractions, to skin thirty minutes prior to UVR exposure resulted in a dose-dependent inhibition of UV radiation-induced erythema as measured by chromameter. On histology, GT extract-treated skin had reduced number of sunburn cells and protected epidermal Langerhans cells and DNA from UV damage. A controlled clinical study on the effect of 6% Camellia sinensis glycolic leaf extracts compared to vehicle on the forearm found increased skin moisturization, with significant improvements in skin texture and viscoelasticity at 30 days compared to vehicle.

Ginseng
Panax ginseng (P. ginseng), also known as Red ginseng, Asian ginseng, and Korean ginseng, is a traditional oriental medicinal herb plant indigenous to Far Eastern countries. The main bioactive ingredients are the saponins, also called ginsenosides, which function as agonists to steroid receptors.

Topical formulations of P. ginseng may have an anti-aging effect through inhibition of UVB-induced skin remodeling. Topical P. ginseng ginsenoside Rb1 has been shown to suppress MMP expression in human dermal fibroblast cells, increase type I collagen production, and inhibit UVB-induced increase in skin thickness and wrinkle formation in mouse models. Clinical studies show promising results for reducing wrinkle formation as topical application of enzyme-modified ginseng extract demonstrated reduction in global photo-damage and total roughness, and increase in moisturization.

Several studies have shown that P. ginseng may also have whitening effects by inhibiting melanogenesis via several steps of melanogenesis regulation. In vitro studies of P. ginseng components significantly inhibited melanogenesis by inhibiting tyrosinase (Table 1). They also exert antimelanogenic activity by blocking melanocyte proliferation and decreasing expression of GM-CSF, which is known to stimulate melanogenesis. Unfortunately, no randomized controlled studies on humans or intact skin could be found to date for these whitening effects.

**CONCLUSION**

As summarized herein, high-level evidence for the efficacy of these natural cosmeceuticals is lacking. Studies assessing the ingredients beta-glucan, snail mucus, pomegranate, ginkgo biloba, and ginseng were uncontrolled with small sample sizes and short follow up. The randomized controlled studies for niacinamide, green tea, licorice, and soy do qualify as Level 1B evidence, and the results are modest; however, the power of the studies is limited by the small sample sizes. Understanding the available data and its limitations for these ingredients is important so that dermatologists are better equipped to educate patients.

**DISCLOSURES**

The authors have no potential conflicts of interest or relationships with industry.

**REFERENCES**


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