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REVIEW

DERMATOLOGICAL AND COSMECEUTICAL BENEFITS OF *GLYCINE MAX* (SOYBEAN) AND ITS ACTIVE COMPONENTS

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Abstract: *Glycine max*, known as the soybean or soya bean, is a species of legume native to East Asia. Soya beans contain many functional components including phenolic acids, flavonoids, isoflavonoids (quercetin, genistein, and daidzein), small proteins (Bowman-Birk inhibitor, soybean trypsin inhibitor) tannins, and proanthocyanidins. Soybean seeds extract and fresh soymilk fractions have been reported to possess the cosmeceutical and dermatological benefits such as anti-inflammatory, collagen stimulating effect, potent anti-oxidant scavenging peroxyl radicals, skin lightening effect and protection against UV radiation. Thus, present review attempts to give a short overview on dermatological and cosmeceutical studies of soybean and its bioactive compounds.

Keywords: *Glycine max*, soybean, isoflavonoids, genistein, cosmeceutical, dermatological

The soybean (*Glycine max*) is an annual legume of the Fabaceae family. It is indigenous to East Asia and China but now is extensively cultivated in many temperate regions of the world (1). Traditionally, soybean has been an excellent source of proteins (2). Despite of proteins it is rich in dietary fiber and a variety of micronutrients and phytochemicals. Soybeans are unique among the legumes because they are a concentrated source of isoflavones (3). Soybean seeds extract and fresh soy milk is used in cosmetic dermatology for the improvement of skin tone, pigmentation and other photo-aging attributes (4). In this review, several cosmeceutical and dermatological studies of *Glycine max* commonly known as soybean and its bioactive compounds are described.

Active constituents

Phenolic acids

The term phenolics comprises of approximately 8000 naturally occurring compounds, all of which possess one common structural feature, a phenol (an aromatic ring bearing at least one hydroxyl substituent). Phenolics are plant secondary metabolites and they are commonly found in herbs and fruits, vegetables, grains, tea, coffee beans, propolis, and red wine as a color and flavoring agents and are an integral part of human diet (5). Naturally occurring phenolic acids contain two distinguishing constitutive carbon frameworks: the hydroxycinnamic and hydroxybenzoic acid structures. The phenolics, particularly polyphenols exhibit a wide variety of beneficial biological activities in mammals, including antiviral, antibacterial, immune-stimulating, antiallergic, antihypertensive, antiischemic, antiarrhythmic, antithrombotic, hypocholesterolemic, antilipoperoxidant, hepatoprotective, anti-inflammatory, and anti-carcinogenic actions. They are powerful antioxidants *in vitro* (6). In the past decade, the antioxidant activity of herbal phenolics, namely phenolic acids and flavonoids has been given much attention. Therefore, the phenolics may be beneficial in preventing UV-induced oxygen free radical generation and lipid peroxidation, i.e., events involved in pathological states such as photoaging and skin cancer (7). The concentration of phenolic com-

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pounds in the mature seeds is in ranges from 1–3 mg/g (8). Defatted soy flakes contained 4 mg of total phenolics/g of sample, which was distributed as about 28% of phenolic acids. The major phenolic acids present in soy bean are syringic, ferulic, and sinapic acids (9) (Fig. 1).

Flavonoids

Flavonoids is a collective term of polyphenolic compounds and ubiquitously exist in all parts of plants (10). They are categorized into flavonols, flavones, flavanones, isoflavones, catechins, anthocyanidins and chalcones in the light of chemical structures (11, 12). Isoflavones are a subclass of a large group called flavonoids. Because of its estrogenic activity, are also known as phytoestrogens (13). In soybean there are basically three types of isoflavones that are normally present in four different isoforms: glucosides (daidzingenistin and glycitin); acetylglucosides (acetyldaidzin, acetylgenistin and acetylglycitin) malonylglucosides (malonyldaidzin, malonylgenistin and malonylglycitin) and structure unconjugated aglycone (daidzein, genistein and glycitein) (14). Isoflavones are found in highest amounts in soybeans and soy foods, although they are also present in other beans and legumes. Soy foods generally contain 1.2–3.3 mg isoflavones/g dry weight, with the precise amount depending on numerous factors, including the type of soy food as well as soybean variety, harvest year and geographical location (15) (Fig. 2).

Soy proteins

Protein is the major constituent of the soybean (30 to 50 g/100 g) (16). It contributes to the supply of essential amino acids and nitrogen to human and animals (17). The major components of soy proteins are storage proteins known as β-conglycinin (7S) and glycinin (11S), which represent 65% to 80% of total seed proteins. Whole soybean contains about 7–9% of protease inhibitors that are in the grain cotyledon (18–20). The proteins STI, a Kunitz-type trypsin inhibitor or soybean trypsin inhibitor and BBI, the Bowman-Birk protease inhibitor (21, 22) were first isolated from soybeans in the early 1940's. STI (21) is a protein of 181 amino acid residues and a tertiary structure which is dependent on two disulfide bridges (23). BBI is an 8 kDa protein with 81 amino acid residues and seven disulfide bonds that is a weak trypsin inhibitor and a strong chymotrypsin inhibitor (24). STI is heat labile (23), while BBI has a stable conformation even after its disulfide bonds are broken by heating or treatment with acid and pepsin (21). STI and BBI are found

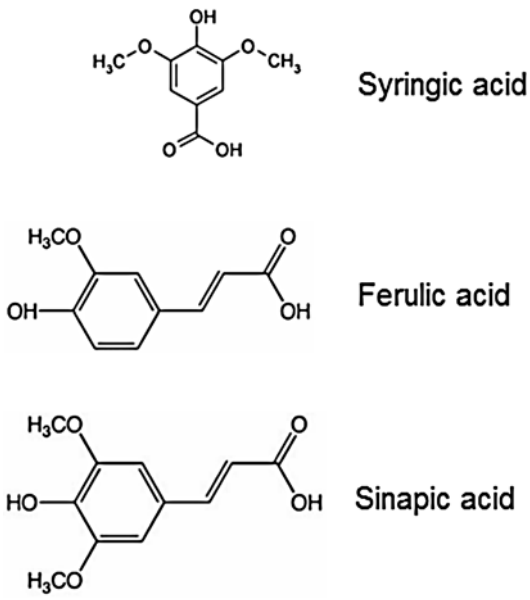

Figure 1. Chemical structure of major phenolic acids present in soy bean

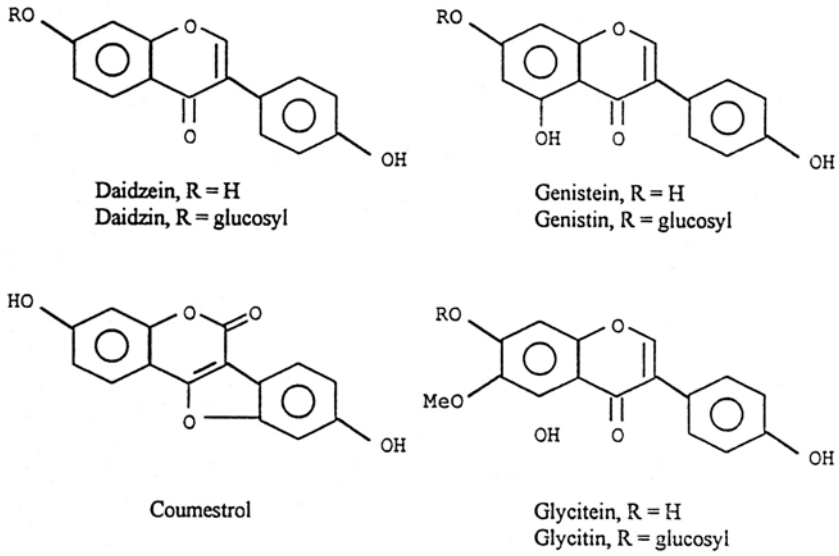

Figure 2. Chemical structures of soy isoflavones

only in the bean, and not in any other part of the soy plant (21).

Dermatological and cosmeceutical benefits

Anti-inflammatory effects

Isoflavones, a major class of flavonoids mainly present in soybean, has been shown to possess antioxidant activity, reduce risk of cardiovascular disease, and inhibit cancer cell growth (25–28). Several recent studies also demonstrated that isoflavones may exhibit anti-inflammatory activity (29–31). Inflammation, a primary component of innate immunity, can result in killing or degradation of outer microorganisms by neutrophils in blood and macrophage in tissues through combination with polysaccharides on the microorganism's surface (32). Pus can thus be formed after the death of neutrophils that have entered damaged tissues because of infection. Meanwhile, macrophages can secrete several soluble proteins called cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-12 (IL-12), and tumor necrosis factor receptor (TNF-R). Among these cytokines, IL-1, IL-6, and TNF-R have attracted more attention as they can be localized to the infected tissue, manifested systemically throughout the body, and cause vasodilation as well as inflammation symptoms such as redness, swelling, heat and pain (32). Other cytokines, such as IL-8 and IL-12, were seldom investigated. Both IL-1 and TNF-R have been reported to increase expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), resulting in adhesion of neutrophils, monocytes and macrophages to vessel wall and subsequent inflammation of infected tissues (32). In addition to cytokines, macrophages can secrete inflammation mediators such as prostaglandin E_2 (PGE_2) and nitric oxide (NO), causing sepsis, septic shock and systemic inflammatory response syndrome (33). Chronic inflammation has been linked to numerous skin diseases and conditions, including skin aging (34) and many skin care products, therefore, contain anti-inflammatory agents. Additionally, inflammation has been linked to epithelial skin-tumors, and anti-inflammatory drugs are being studied for the prevention and treatment of non-melanoma skin cancers (35). Cyclooxygenase-2 (COX-2), the main UV-responsive COX isoform in human skin, is involved in UV-induced skin inflammation and carcinogenesis (36). UV-induced COX-2 expression plays a major role in UV-induced inflammation, edema, keratinocytes proliferation and epidermal hyperplasia, as well as in the generation of oxidative DNA damage. Repeated exposure to UV leads to chronic up-regulation of COX-2 expression and chronic inflammation, contributing both to accelerated skin aging and to an increased risk of skin can-

cer. The induction of COX-2 expression by UV is higher in aged human skin as compared to young human skin, and aged human skin produces higher amounts of prostaglandin E_2 (PGE_2, the product of the COX-2 pathway) relative to young skin (9). Aging of the skin may increase the susceptibility for developing both photo-aging and carcinogenic processes. Oral and topical COX-2 inhibitors have chemopreventive activity against chemically- and UV-induced skin cancer in numerous animal models (36). The topical applications of soy isoflavones to mouse skin before UVB exposure reduced the expression of COX-2 (37). Several studies dealing with the inhibition of inflammation by isoflavones are available in the literature (38). Several papers also suggested that genistein could activate peroxisomal proliferator-activated receptor-γ (PPAR-γ) and in turn, retard adhesion of monocytes to human vascular endothelial cells which may be associated with the A ring in the isoflavone structure (39, 40). It is found that with an isoflavone-containing diet intra-peritoneal lipopolysaccharide (LPS) injection in mice led to a decrease in the liver antioxidant glutathione level and prevention of the inflammation-associated induction of metallothionein in the intestine (40). In a later study, it was demonstrated that dietary isoflavones have beneficial effects on C-reactive protein (CRP) concentrations, but not on other inflammatory biomarkers of cardiovascular disease risk in postmenopausal women, and may improve VCAM-1 response in an ER gene polymorphic subgroup. Similarly, the CRP level could be raised in the blood of patients with end-stage renal disease, but both IL-6 and TNF-R were unaffected (41). In a recent study, it is further pointed out that isoflavones extracted from *Puerariathun bergiana* could suppress LPS-induced release of NO and TNF-R in primary cultured microglia and cell lines (42). Kao et al. reported the use of soybean cake as raw material for processing into powder and to evaluate the anti-inflammatory activity. Eleven treatments, including powders of malonyl-glucoside, glucoside, acetylglucoside, aglycone, as well as genistein standard, γ-PGA, control, normal, and PDTC (ammonium pyrrolidine dithiocarbamate), were used for evaluation. A total of 77 mice were provided daily with tube feeding for 4 weeks at a dose of 0.3 mL of aqueous solution from each treatment, and inflammation was induced with intraperitoneal injection of 1 mg/kg of body weight lipopolysaccharides (LPS). Results showed that all of the isoflavone powders and genistein standard were effective in inhibiting LPS-induced inflammation, lowering leukocyte number in mice blood and reducing production of IL-1, IL-6, NO, and PGE_2 in both peritoneal exudates, cell supernatant and peritoneal exudate fluid (43).

Skin lightening effects

Skin pigmentary abnormalities are seen as esthetically unfavorable and have led to the development of cosmetic and therapeutic treatment modalities of varying efficacy. Hence, several putative depigmenting agents aimed at modulating skin pigmentation are currently being researched or sold in commercially available products (44). Melanocytes, the pigment producing cells of the follicular and interfollicular epidermis, produce a specialized lysosomal related organelle termed the melanosome. Within the melanosome, biopolymers of the pigment melanin are synthesized to give hair and skin, as well as other tissue, its color. This melanin synthesis involves a bipartite process in which structural proteins are exported from the endoplasmic reticulum and fuse with melanosome-specific regulatory glycoproteins released in coated vesicles from the Golgi apparatus. Melanin synthesis ensues subsequent to the sorting and trafficking of these proteins to the melanosome (45). Each melanocyte resides in the basal epithelial layer and, by virtue of its dendrites, interacts with approximately 36 keratinocytes to transfer melanosomes and protect the skin from photo-induced carcinogenesis. Furthermore, the amount and type of melanin produced and transferred to the keratinocytes with subsequent incorporation, aggregation and degradation influences skin pigmentation (46). Hyperpigmentary disorders of the skin such as melasma, age spots or solar lentigo can result from the overproduction and accumulation of melanin (47). The protease-activated receptor 2 (PAR-2) (48–50) is a seven transmembrane G-protein-coupled receptor that is activated by a serine-protease cleavage, creating a tethered ligand. Trypsin and mast cell tryptase are the only known natural activators of PAR-2 (51, 52). PAR-2 is expressed in keratinocytes (53) but not in melanocytes (47) and is involved in the regulation of pigmentation (54–56). The pigmentary effect of PAR-2 modulation by serine protease inhibitors is possible only when keratinocyte-melanocyte contact is established (57).

Melanocytes alone do not respond to PAR-2 modulating agents with pigmentary changes (54). PAR-2 activation was shown to increase keratinocyte phagocytosis (57) resulting in increased melanosome ingestion and transfer (55) even in the absence of melanocytes. Serine protease inhibitors that interfere with PAR-2 activation were shown to

reduce melanosome transfer and ingestion by keratinocytes, resulting in depigmentation both *in vitro* and *in vivo* (54, 55).

For medical and cosmetic reasons, it is often desired to alter skin color. Currently available topical agents used to treat hyperpigmentation include tyrosinase inhibitors, retinoids, hydroquinones, and melanocyte-cytotoxic agents. Unfortunately, the results of these treatments are sometimes disappointing (58) and there is a need for more effective, safer, and less irritating depigmenting therapies. Moreover, a move towards natural therapies created a demand for a natural, safe, and efficacious depigmenting treatment.

Soybean seeds have been used in Asia for centuries as a dietary source of protein (57). Soymilk and the soymilk-derived proteins STI and BBI inhibit PAR-2 activation and thus induce skin depigmentation by reducing the phagocytosis of melanosomes by keratinocytes, thus reducing melanin transfer .Such agents may serve as an alternative, natural treatment for hyperpigmentation (57). The depigmenting activity of these agents, as well as their ability to prevent UV-induced pigmentation, was demonstrated both *in vitro* and *in vivo* (57). Importantly, the non-denatured soybean extracts were superior to either STI or BBI alone in their depigmenting effect, even though the concentrations of STI and BBI within these extracts were much lower than when tested individually (57).

Soybean trypsin and Bowman-Birk inhibitors inhibit activation of the protease-activated receptor-2 (PAR-2) and therefore, inhibit the melanosome transfer. PAR-2 is expressed in keratinocytes but not in melanocytes, and is involved in the regulation of pigmentation (58). PAR-2 is a phagocytic receptor and inhibition of PAR-2 results in impaired melanosomes transfer from the melanocytes to the keratinocytes. The inhibition of PAR-2 by serine protease inhibitors results in reduced pigment deposition and skin color lightening (59). Non-denatured soybean extracts contain two serine protease inhibitory proteins, i.e., soybean trypsin inhibitor and Bowman-Birk inhibitor. Soybean trypsin inhibitor, Bowman-Birk inhibitor, and non-denatured soybean extracts inhibit PAR-2 activation, resulting in skin depigmentation *in vitro*, *in vivo* and in human skins transplanted onto immune-compromised mice (60). The first documentation of a clinical skin lightening activity by the non-denatured soybeans extracts was published in 2000 (61), with a follow-up study in 2002 (62). A study of skin color suggests that these extracts are excellent choice for the treatment of post-inflammatory hyperpigmentation and melasma (63). In a recent review, these non-denatured soybean extracts were discussed as topical alternatives to hydroquinone (64, 65).

Elastin and collagen stimulating effects

Elastin fiber production is reduced with aging (66, 67). The age-induced decline in skin elasticity results from slower tissue regeneration, from lower elastin synthesis levels and from the increased production and secretion of elastases. UV exposure further decreases the functionality of the elastic fiber network, as excessive elastin production and abnormal cross-linking create elastotic material ("solar elastosis") with reduced elastic capacity (67, 68). Preventing or reversing skin ageing includes the use of sunscreens and sun avoidance behavior, the use of anti-oxidants, and the use of agents like retinoids, which inhibit collagenases and promote collagen production (69). Only a few agents are available to directly enhance the balanced synthesis and assembly of the elastic fiber network. The inhibition of fibroblast-derived elastases following chronic UVB irradiation was found to protect the dermal elastic network of the skin from fragmentation and to reduce wrinkle formation in rodents (70, 71).

Searching for botanical extracts for anti-aging skin care use, the non-denatured soybean extracts were found to have elastase-inhibitory activities (72). In addition, non-denatured soybean extracts were found to induce the synthesis of collagen and elastin, and to promote the correct assembly of new elastin fibers, providing a complete protection and restoration to the dermal extracellular matrix (73). *In vitro* studies using both purified elastases and cultured fibroblasts demonstrated that non-denatured soybean extracts could affect the extracellular matrix. The enzymatic activity of several elastases was inhibited by these extracts, and, to a lesser extent, by STI or BBI, while soy isoflavones did not show any elastase-inhibitory activity (72). The non-denatured soybean extracts also protected elastic fibers produced by cultured fibroblasts from degradation by exogenously-added elastases (72). Additionally, these extracts exhibited elastin-enhancement activities. A dose-dependent induction of expression of the elastin gene was documented using an elastin promoter-luciferase reporter gene, and was confirmed by mRNA analysis of treated fibroblasts. The synthesis of new tropoelastin monomers, as well as of elastin-accessory proteins, and the assembly of new elastin fibers, was documented by histological staining (72). The elastin-enhancing activity of the non-denatured soybean extracts was confirmed *in vivo*. Histological analysis

of mice and swine skins topically treated with non-denatured soybean extracts showed a significant increase in the elastic fibers network, with an accompanied increase in elastin mRNA and in desmosine content (72). When human skins, transplanted onto immuno-deficient mice, were topically treated with these extracts, an increase was documented in the expression of elastin, elastin-accessory proteins, and collagen (72). Human skin explants treated *ex-vivo* with non-denatured soybean extracts and analyzed by histological staining and immune histochemistry showed an increase in elastin, fibrilin-1 and collagen production (73). These data suggest that non-denatured soybean extracts not only protect extracellular matrix from degradation, they also induce collagen and elastin synthesis, and increase the total amount of stable, cross-linked elastin fibers.

Protection against UV radiation

Chronic exposure of human skin to UV radiation is known to damage the structure and function of the skin. These changes are referred to collectively as photo-aging, which is characterized by wrinkles, laxity, roughness and irregular pigmentation (74). Photo-aged skin displays prominent alterations in the cellular component and extracellular matrix of the connective tissues such as an accumulation of disorganized elastin fibers (elastosis), a marked increase in glycosaminoglycans (GAGs), and a loss of interstitial collagens (75). The unifying pathogenic agents responsible for these changes are UV-induced reactive oxygen species (ROS) that deplete and damage the non-enzymatic and enzymatic antioxidative defense systems of the skin, leading to oxidative damage of the cellular and non-cellular components and ultimately skin cancer, immune-suppression and premature skin aging (76). ROS are believed to activate the cytoplasmic signal transduction pathways in the resident fibroblasts, which are related to growth, differentiation, senescence and connective tissue degradation, as well as causing permanent genetic changes (77). Considering that UV induces oxidative stress-mediated adverse effects in the skin, the regular intake of antioxidants and antioxidant nutrients as well as an antioxidant topical treatment is suggested to be a useful way to reduce the harmful effects of UV radiation (78).

In recent years, isoflavones have attracted increased attention owing to their health-related beneficial aspects. In addition to its diphenolic structure-based estrogen-like effect, isoflavones are associated with a broad range of biological activities that include antioxidant properties and inhibitory effects on the several enzymes of the estrogen receptor-independent signal pathways (79). Genistein, the primary isoflavone from soy products, is known to enhance the antioxidant enzyme activities such as superoxide dismutase, catalase and gluthathione reductase in various mouse organs (80), and it has also been shown to inhibit tyrosine kinase and topoisomerase (81, 82). Therefore, an investigation into the protective effects of dietary soy isoflavones on UV-damaged skin in the nutritional aspect is warranted. Also several experimental studies have suggested that the topical treatment of soybean isoflavone genistein inhibits UVB-induced skin tumorigenesis in a hairless mice model (83).

Potent anti-oxidant scavenging peroxyl radicals

Intracellular and extracellular oxidative stress initiated by ROS promotes skin-aging, which is characterized by wrinkles and atypical pigmentation. Because UV enhances ROS generation in cells, skin aging is usually discussed in relation to UV exposure. The use of antioxidants is an effective approach to prevent symptoms related to photo-induced aging of the skin (84). Several bioactive compounds, including phenolics such as phenolic acids, flavonoids and isoflavonoids have been identified in soybeans. Recent interest in these substances has been stimulated by the potential health benefits arising from the antioxidant activity of these phenolic compounds (85). Genistein, the major component of soybean isoflavones, has been demonstrated to inhibit ultraviolet-B (UVB)-induced skin tumorigenesis in hairless mice. The antioxidant properties of genistein may explain the mechanisms of its anti-photocarcinogenic action because through either direct quenching of reactive oxygen species or indirect anti-inflammatory effects, genistein was found to substantially inhibit a series of oxidative events elicited by UVB irradiation, including hydrogen peroxide production, lipid peroxidation, and 8-hydroxy-2-deoxyguanosine formation (83).

Undesired hair growth inhibitory effect

Unlike other mammals, humans no longer use their hair for environmental protection, but keep or remove their hair for social and cosmetic purposes. Many procedures are used to remove unwanted hair, from simple home treatments like shaving, to laser and light therapies. These methods differ in the duration of hair elimination after removal, their price range, their pain and discomfort levels and their possible undesired effects (86). Shaving, the most popular hair-removal method, requires daily treatments, may result

in nicks and cuts, may increase the risk of infection, may leave a perception of an increased rate of hair growth, and may leave undesirable stubble. An alternative to at-home hair removal is hair dying or bleaching, used to reduce hair visibility in particular body areas. However, such methods are less preferred as the emerging portions of the hair shafts are always darker than the already treated parts. An alternative to these methods is desired; particularly a method that would reduce undesired hair growth, with a safe and simple at home procedure. As the biological activities of the non denatured soybean extracts were further explored, they were found to delay hair growth, resulting in smaller and thinner hair shafts (87). The use of a skin care product containing these extracts, therefore, would reduce the visibility of undesired hair growth. Topical daily treatments with STI or BBI visually delayed hair growth and reduced the length of the hair shafts of treated mice, with reduced hair follicles size observed histologically. Non-denatured soybean extracts (containing STI, BBI and isoflavones) were superior to either STI or BBI alone in this inhibitory activity. Non-denatured soybean extracts led to delayed and reduced hair growth, and hairs were visibly thinner, more "directionally organized", and smoother to touch, relative to untreated controls (87). A statistically significant effect on hair follicle dimensions was observed, with hair shaft diameter reduced by an average of 42%, and hair bulb diameter reduced by an average of 23.8% (73). Additionally, the depigmenting effect of STI and BBI led to lighter colored hair shafts, which could potentially contribute to the reduced visibility of undesired hair growth. Heat-denatured soybean extract, or commercially available pasteurized soymilk, had no effect on hair growth or hair appearance (88, 89) further supporting the involvement of intact STI and BBI in the hair growth inhibitory effect.

CONCLUSION

In summary, *Glycine max* and its bioactve components have several dermatological and cosmeceutical effects such as anti-inflammatory, antioxidative, collagen stimulating, skin lightening, protection against UV radiation and removal of undesired hair growth. It seems that soybean seed extract and its active components such as phenolic acids, flavonoids, isoflavonoids (quercetin, genistein, and daidzein) and proteins (Bowman-Birk inhibitor and soybean trypsin inhibitor) are safe and effective in improving numerous skin care parameters. Thus, the use of soybean extracts provides multiple dermatological and cosmeceutical benefits, ranging from protection and restoration, to esthetic benefits. It is even more apparent that there is a great deal of work still left to be done.

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