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Review of Soybean Phytochemicals and Their Bioactive Properties Relevant for Skin Health

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Abstract Numerous studies have investigated the bioactive properties of compounds present in soybean (*Glycine max*) that may have beneficial effects on the health of human skin. Several such compounds have already been introduced into commercial cosmetic products to promote functional properties such as skin whitening, anti-wrinkle activity and skin hydration. However, a significantly greater understanding of the application of soybean ingredients in these types of products is needed before optimal benefits can be realized. In this review, we aim to summarize some of the biological properties of soybean constituents and the underlying mechanisms of action responsible for beneficial effects in skin. In addition, we will discuss future directions for studies that may help to expand the applications for soybean compounds.

Keywords: *anthocyanins, isoflavones, skin health, soybean, soy peptide*

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1. Introduction

The global cosmetics industry has been estimated to be approximately $426 billion (2015). Growth slowed slightly during the financial crisis in 2008, but grew by about 5% in the three years from 2012 to 2015, and is estimated to grow an additional 5% by 2020 [1]. In order to respond to the growing market, novel and evidence-backed functional materials need to be identified and investigated. All bioactive cosmetic ingredients should have their efficacy and safety claims supported scientifically. Although Europe has played a dominant role in the development of cosmetics [2], producers in Asian markets such as China, Japan, Korea and India have experienced increasing success in recent years, with products from these countries becoming popular in markets abroad [3]. With a wider global acceptance of oriental medicine and functional materials, it has become increasingly important to develop these bioactive ingredients with greater safety and efficacy [3,4,5].

The skin is the largest organ of the human body [6], and forms an environmental barrier to protect the body. As perhaps the most important feature of our appearance, the condition of our skin is directly related to perceived attractiveness and health [7]. Skin wrinkles are a direct indicator of skin aging, while white skin is often coveted as being ideal [8]. Dry skin is associated with rough personality attributes and wrinkles easily, and in severe cases represents a source of irritation. The skin should therefore be sufficiently moisturized to maintain the appearance of healthiness [9] Skin also plays a pivotal role in immune function as the primary barrier against infection from external sources. A balanced and well-functioning immune system within the skin is also an important marker for overall health [10]. Due to UV exposure, skin cancer is the most common form of cancer that arises in humans [11]. Although overall mortality is relatively low because most can be detected early, some types of skin cancers like melanoma can be extremely dangerous [12]. To improve the diverse aspects of skin health, materials that can improve skin wrinkles, whitening, moisturization, immunomodulation, and protection against cancer are needed.

Soybeans originated in the northern region of the Korean peninsula, with Samuel Bowen introducing them to the USA in 1765 [13,14]. Soy is an important source of protein in northeast Asia, where cattle farming is relatively challenging. In the United States and Europe, it has been widely used as a feed material for cattle and pigs [13,15]. Soybeans can be consumed raw or as the main constituent in diverse fermented foods such as soy sauce, soybean paste, and natto. Significant research has been conducted into the health benefits of soybeans. Studies have shown that compounds present in soybeans can prevent cancer, cardiovascular disease, chronic degenerative diseases, and improve osteoporosis symptoms. On a dry basis, soybeans contain 40% protein, 20% lipids, 35% carbohydrates, and 5% micronutrients [16]. Soy peptides are usually produced by the hydrolysis of proteins within the soybeans. The rich proteins present in soy allow for the generation of diverse peptides, and during fermentation in particular, the actions of enzymes create multiple new peptides, some of which exhibit functionality. Soybeans also contain high concentrations of functional substances including isoflavones, anthocyanins, and saponins [17]. In this review, we will summarize the results of research on various functional materials present in soybeans with a focus on improving skin health.

2. Functional Materials Present in Soybeans

2.1. Soybean Extracts

Studies using soybean extracts have demonstrated diverse effects on skin health (Table 1) [14]. Soybean preparations fermented by microorganisms have also been the subject of research interest. Soybean extract has been shown to reduce the expression of matrix metlloproteinase-1 (MMP-1) and decrease the MMP-1/tissue inhibitor of metalloproteinase-1 (TIMP-1) ratio by increasing the expression of TIMP-1, an MMP-1 regulatory enzyme, with a bioactive reducing effect equivalent to that of retinoids [18]. When 2.5% soybean extract is added into the diet of a mouse model, inhibitory effects on ultraviolet B (UVB)-induced skin wrinkles and skin inflammation can be observed. Furthermore, soybean extract specifically fermented by yeast elicits a wrinkle-improving effect that is greater than that observed with non-fermented extract. During the process of fermentation, the sugar moiety is removed from the compounds genistin and daidzin, converting them into their aglycon forms, genistein, and daidzein. [19]. When soybean extracts (25 g of soybean were extracted 2 times at room temperature with shaking for 48 hours using each solvent) were fed to Sprague-Dawley rats using various solvents (ethanol, n-hexane extract, ethyl acetate), all three extracts caused an increase in estrogen receptor-positive cells to emerge, but only a high-dose ethyl acetate extract group showed an increased amount of collagen in the skin. Isoflavones in soybeans act as phytoestrogens, although estrogen receptor expression is not thought to be directly associated with increased collagen [20]. Soybeans harbor a protease inhibitor as protection against enzymatic attack. The protease-activated receptor 2 signaling pathway also plays an important role in the color of the skin color. Soymilk inhibits PAR2, which has been linked to a skin whitening effect [21]. When green beans are exposed to visible light, a new oxidative product of daidzein is formed, which counteracts skin inflammation pathways associated with atopic dermatitis [22]. Further studies have shown that soybean extract has wide ranging effects on skin health.

2.2. Soybean Peptides

Soybeans are exceptional sources of plant proteins and an important staple food source for many communities [23,24]. Lunasin is a 43 amino acid-long peptide present in soybean, and consists of several arginine-glycine-aspartic acid (RGD) residues and a carboxylic acid tail of nine aspartic acid residues [25]. Lunasin exhibits various beneficial effects on human health including inhibitory effects against DMBA and TPA (12-*O*-tetradecanoylphorbol-13-acetate)-induced skin cancer and skin inflammation through the deacetylation of histones and inhibition of acetylation [26]. Yoshiki et al. [24], reported that rats fed on a diet containing soy and collagen peptides had increased Type I and III collagen levels in their skin. It was revealed that an intake of soybean containing 2% collagen peptide for 2 weeks enhanced levels of Type I and Type III tropocollagen, as well as mRNA levels of COL1A1 and COL3A1 (Table 2). Another group has reported that collagen synthesis in human dermal fibroblasts increases in the presence of soy and collagen peptides (Table 2) [27]. In the study, a mixture of soy peptides and collagen peptides increased Type I collagen gene expression after 24 h of treatment, while downregulation was seen for Smad7 and MMP-1 gene expression (two factors that are responsible for collagen degradation). Filaggrin and involucrin are two other proteins that help maintain the barrier function of human skin [28,29]. The induction of *ichthyosis vulgaris* and allergen response has been reportedly associated with loss-of-function mutations in the filaggrin gene, resulting in defective barrier functioning [28,30,31]. In 2014, Tokudone et al., reported that a low molecular weight peptide originating from soybean can modulate epidermal metabolism by enhancing the gene expression of involucrin and profilaggrinin in human epidermal keratinocytes [32]. Soybean trypsin inhibitor (STI) and Bowman-Birk protein inhibitor (BBI) were first isolated from soybean in the early 1940s. While STI is an 181-amino acid protein, BBI is a serine protease inhibitor consisting of a 71-amino acid protein (8 kDa) [33]. The depigmentation properties of STI and BBI were first reported in 2001 [21], with each inhibitor (0.1%) drastically reducing pigment deposition in keratinocyte-melanocyte co-cultures. To further support these findings, the *in vivo* depigmentation activity of STI and BBI was confirmed using a dark-skinned Yucatan microswine model. Treatment of STI (1%) and BBI (1%) elicited a 50% and 40% inhibition of pigment deposition, respectively. Although such accumulating evidence suggests that soy peptides can have a significant impact on skin health (Table 2), a deeper understanding of the underlying mechanisms involved and associated bioavailability is needed.

2.3. Soy Isoflavones

Isoflavones are the third major class of bioactive phytochemicals present in soybean. The USDA reported in 2008 that approximately 50 mg of soy isoflavone exists in 100 g of raw soybean [34]. The two major isoflavones are genistein and daidzein, which exist in their glycoside forms. There are also a number of rare isoflavones with different frequency and positions of their OH groups. Isoflavones are considered to be phytoestrogens, as they share structural similarities with estrogen. Although isoflavones can activate the estrogen receptor, the estrogenic effect alone cannot account for their considerable overall efficacy. In a number of recent studies, it has been shown that each isoflavone elicits additional health benefits through specific molecular targets. Of particular note, genistein is regarded as a tyrosine kinase inhibitor [35], while other isoflavones have been shown to interact with molecular targets relevant to human health [36]. Studies have also shown that isoflavones are effective only if there is a specific strain of microbiota in the body, which can convert daidzein to equol.

Table 1. Clinical results of soybean constituents

Administration form	Administration amount/Total period	Trial method	Subjects	Function	Reference
Stabilized soy extract	Twice daily (cosmetic formulation/2 months	Open randomized trial	30 healthy women	- Significant lightening effect	[64]
Isoflavone-rich concentrated soy extract	100 mg/day/6 months	Not indicated	30 postmenopausal women	- Increase of the epidermal thickness - Reduce of the papillary index - Increase of the dermal collagen content - Increase of the dermal blood vessel	[60]
Active moisturized containing stabilized soy extracts	1 of the 2 test products, daily/12 weeks	Randomized, double blind, and vehicle controlled study	31 subjects received the active product 32 subjects received the vehicle	- Improvement of the mottled pigmentation - Improvement of the blotchiness and dullness - Improvement of the fine lines, overall texture and skin tone - Improvement of the overall appearance	[65]
Soy isoflavone aglycone as tablet	40 mg daily/12 weeks	Double-blind, placebo-controlled trial	13 subjects for the test food group 13 subjects for the control group	- Improvement of the fine wrinkle - Recovery of malar skin elasticity - Increase of the skin microrelief	[66]

Table 2. Pharmacological properties of soybean compounds and potential effects on skin health

Soybean compounds	Pharmacological activities relevant to skin health	Study model /Administration method	Molecular targets/Mechanisms	References
Anthocyanins	Anti-inflammation	Hairless mice/Topical application	Downregulates UVB-induced COX-2 (cyclooxygenase-2) expression	[53]
	Anti-inflammation	Sprague-Dawley rats/Rat skin flap model	Inhibits ICAM-1 and COX-2 expression	[67]
	Anti-melanogenesis	Human A375 melanocytes/Treated to the media	Inhibits melanin production via radical scavenging	[58]
	Photoprotection	Hairless mice/Topical application	Reduces UVB-induced apoptotic cell death	[54]
Soy peptides	Collagen production	Winstar rats/Oral administration	Increases type I and III tropocollagen expression	[24]
		Normal human dermal fibroblasts/ Treated to the media	Increases type I collagen and suppresses MMP-1 and Smad7 gene expression	[27]
	Regulation of epidermal metabolism	Normal human epidermal keratinocytes/ Treated to the media	Enhances expression of involucrin, transglutaminase, profillagrin	[32]
Soy isoflavones	Anti-atopic dermatitis	NC/Nga Mice/ Topical application	Reduces cytokine production (e.g. IL-6, TNF-α) Inhibits epidermal thickness and mast cell infiltration	[49]
	Anti-skin cancer	SKH-1 hairless mice/ Topical application	Inhibits UVB-induced COX-2 expression via direct inhibition of Cot and MKK4	[44]
	Anti-photoaging	ICR-Foxn/^{nu} mice/ Topical application	Suppresses UVB-induced erythema and TEWL	[68]
		Hairless mice/ Oral administration	Promotes collagen production and inhibits MMP-1 expression	[69]
		26 Japanese women/ Oral administration	Inhibits wrinkle formation and enhances skin microrelief	[66]
	Skin whitening	B16F10 cells, Human Skin Equivalents/ Treated to the media	Inhibits melanogenesis via regulation of tyrosinase activity	[39,47,70]
	Anti-oxidative stress	Hairless mice (HRS/J)/ Topical application	Reduces TPA-induced H_2O_2 production via regulation of anti-oxidative enzymes	[71]
	Anti-wrinkle formation	Normal human dermal fibroblasts/ Treated to the media	Suppresses solar UV-induced MMP-1 expression via PKCα inhibition	[41]

Oral and topical administration of genistein substantially inhibits UVB-induced skin carcinogenesis and cutaneous aging in mice, as well as photodamage in humans [37]. It has been suggested that the mechanisms involved target oxidative and photodynamically damaged DNA, the downregulation of UVB-activated signal transduction cascades, and antioxidant activities. Two-stage skin carcinogenesis models have shown that genistein suppresses skin carcinogenesis through ornithine decarboxylase activity [38]. Genistein also exhibits skin whitening effects via alteration of the Maillard reaction pathway by trapping advanced glycation end products (AGEs) both in biological and protein-lactose suspensions [39]. Daidzein is another well-known isoflavone that shows anti-aging effects. When daidzein is applied alone, skin collagen synthesis is increased and collagen degradation is inhibited *in vitro* and *in vivo* [40]. Daidzein also inhibits UVB induced MMP-1 expression in human skin fibroblasts [41]. As a metabolite of daizein, equol can prevent symptoms of skin aging by enhancing collagen, elastin and TIMP expression, while decreasing MMP gene expression [42]. Among the trace concentrations of isoflavones produced by genistein and daidzein in the metabolic process, a few have shown better efficacy than their parent compounds. It has been proposed that these observations are a direct result of the binding of equol to the estrogen receptor (ER), with its effect decreased by tamoxifen, an antagonist of ER subtypes [42]. Equol reportedly inhibits TPA-induced neoplastic transformation in skin cells and binds to MEK1 directly to inhibit the MEK/ERK/p90RSK/activator protein-1 signaling pathway. Daidzein has one more carbonyl group than equol, and this carbonyl group interacts with the hydrophobic surface formed by Phe-209, Val-211, and Leu-118. This steric collision accounts for the lower overall inhibitory effects of daidzein when compared to equol. In a clinical study, equol suppressed 'crow's feet' wrinkles in postmenopausal women without serious adverse effects [43].

Other minor isoflavones have also been investigated for the improvement of skin health [41]. These isoflavones are present in very low concentrations in soybeans, although they may increase during fermentation. Recently, through bioconversion using enzymes or microorganisms for functional food or cosmetic applications [36]. 6,7,4'-trihydroxyisoflavone (THIF), a metabolite of daidzein, exhibits anti-wrinkle formation properties via direct suppression of PKCα kinase activity [41]. 6,7,4'-THIF dose-dependently reduces *in vitro* PKCα kinase activity, and a direct interaction between 6,7,4'-THIF and PKCα was also confirmed. Furthermore, another metabolite, 7.3',4'-THIF has been proposed as an inhibitor of Cot and MKK4 in a UVB-induced skin inflammation model [44]. Cot and MKK4 are inflammatory signaling proteins that regulate MAPK phosphorylation [45,46]. The kinase activity of Cot and MKK4 were both significantly attenuated with 7,3',4'-THIF treatment, whereas p38a JNK1, ERKs, and MSK1 activities remained unaffected. Subsequently, UVB-increased COX-2 expression was reduced and, more importantly, skin tumor incidence decreased after treatment with the compound [44]. The skin whitening properties of 7,3',4'-THIF and another metabolite, 7,8,4'-THIF, have also been reported [47]. Melanogenesis levels decreased in the presence of these two compounds, concomitant with a reduction in the expression of several melanogenesis-related genes, such as microphthalmia-associated transcription factor (MITF), tyrosinase, and TRP-1 and -2. These studies confirmed the depigmentation effects using an African-American human skin equivalent, with treatment of 7,8,4'- or 7,3',4'-THIF enhancing skin tone brightness compared with DPBS treatment [47]. We have also evaluated the anti-atopic dermatitis properties of 7,3',4'-THIF in NC/Nga mice. Aberrant increases in skin cytokine production is a widely-accepted biomarker for atopic dermatitis [48]. We found that LPS-increased production of nitric oxide, and TNF-a and IL-6 was largely attenuated by 7,3',4'-THIF treatment in Raw 264.7 cells. Furthermore, using a *Dermatophagoides farinae*-induced atopic dermatitis model, the anti-atopic dermatitis effect was further defined. Whereas scratching time and ear thickness were decreased, filaggrin expression was significantly increased with topical application of the compound [49]. Although compounds such as genistein and daidzein, which are abundant in soybeans, can be easily adapted for industrial scale, the rarer isoflavones present in trace quantities represent several challenges. Recently, a technique for producing rare isoflavones using enzymes has been developed, and this may improve the economic incentive to develop soy isoflavones for wider use.

2.4. Anthocyanins

Although the color of the most widely-cultivated soybean is yellow, some varieties of soybean have alternative colors [50]. Anthocyanins are responsible for the naturally-occurring purple pigments of the fruits [51], and are mainly present in soybean seed coats [50]. In 2012, Djordje et al. [52], investigated the polyphenol content of colored soybean seeds from varieties in central Europe. It was determined that approximately 0.60 mg of anthocyanins in the form of cyanidin-3-glucoside dry material exists in the extracts of black soybean seeds [52]. The dominant anthocyanins present in soybean seed coats are cyanidin-3-monoglucoside and delphinidin-3-monoglucoside. Additionally, petunidin-3-glucoside and pelargonidin-3-*O*-glucoside have been identified in colored soybean seeds in trace concentrations [52].

The beneficial effects of anthocyanins present in soybean seed have been reported in previous studies [53]. Tsoyi et al., reported that anthocyanins from black soybean [Glycine max (L.) Merr] seed coats inhibit UVB-induced apoptotic cell death [54]. In this study, anthocyanins suppressed caspase-3 cleavage and Bax expression. Furthermore, UVB-induced ROS upregulation was also decreased after anthocyanin treatment (which acts as a ROS scavenger), and this was thought to be because increased ROS production can accelerate the skin aging process via oxidative stress [7,55]. In 2013, we also reported similar findings [56]. NADPH oxidase (NOX) is a major ROS-producing enzyme present in most living cells [57]. We observed that delphinidin, one of the major anthocyanins present in black soybean [52] has an inhibitory effect on NOX, and subsequently suppresses the UVB-induced skin-wrinkle promoting enzyme MMP-1 [56]. UV-induced melanin accumulation in the skin is becoming of increasing interest for anti-skin aging research. In 2013, the anti-melanogenic effects of anthocyanins were reported, showing that 50 mg/ml of liposome-encapsulated anthocyanin elicits a 60% regression in melanin synthesis [58]. The underlying mechanism responsible for this suppression was demonstrated to be a reduction in tyrosinase activity and MITF expression. Other studies have identified various anti-inflammatory properties of anthocyanins in experimental models [53]. The suppression of skin inflammation is highly significant for skin health, as chronic skin inflammation has been associated with skin carcinogenesis [12,59]. Recent studies have shown that treatment with anthocyanins can attenuate UVB-induced expression of COX-2, a well-known inflammatory molecule in the skin [53]. This inhibitory effect is at least in part due to suppression of the phosphatidylinositol 3-kinase/Akt pathway.

Although the beneficial effects of anthocyanins present in soybean are becoming more commonly accepted due to accumulating evidence, their potential for widespread application as novel cosmetic ingredients has not been extensively discussed. Thus, it is necessary for future research to focus on both the scientific and commercial aspects of soybean anthocyanins in relation to such applications.

3. Conclusions

While many reports on the beneficial effects of soybean constituents on skin health have been published [60,61], the underlying mechanisms responsible and the precise physiological outcomes require further understanding. To date, a number of soybean constituents have been incorporated in cosmetic products that imbue functional properties such as skin whitening or anti-wrinkle activity. The primary route of intake for soybean in humans is via ingestion, and orally-administered soybean compounds are converted to their metabolites via the gut and liver [62]. Interestingly, significant differences have been found in the incidence rate of prostate cancer between Asians and their European/North American counterparts [63]. At least one previous study has suggested that this may be a result of differences in diet and gut microbiota. The risk of prostate cancer is relatively higher in Caucasians compared with Asians, and this is thought to be at least partially due to lower levels of equol-producing bacteria in the gut [63]. The bioavailability and metabolic pathways potentially responsible for such an observation should be more clearly elucidated in future studies.

Although soybean metabolite research needs to be undertaken more comprehensively, it is becoming clear that oral or topical application of soybean extracts are likely to have effects on skin health with clear outcomes such as whitening and anti-wrinkle formation. For the ethical application of soybean products in the cosmetic industry, evidence-based research needs to be conducted in order to support labelling claims.

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