cosmetics

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Review

Anti-aging Effects of Select Botanicals: Scientific Evidence and Current Trends

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Abstract: As skin ages, there is a decline in physiologic function. These changes are induced by both intrinsic (chronologic) and extrinsic (predominately UV-induced) factors. Botanicals offer potential benefits to combat some of the signs of aging. Here, we review select botanicals and the scientific evidence behind their anti-aging claims. Botanicals may offer anti-inflammatory, antioxidant, moisturizing, UV-protective, and other effects. A multitude of botanicals are listed as ingredients in popular cosmetics and cosmeceuticals, but only a select few are discussed here. These were chosen based on the availability of scientific data, personal interest of the authors, and perceived "popularity" of current cosmetic and cosmeceutical products. The botanicals reviewed here include argan oil, coconut oil, crocin, feverfew, green tea, marigold, pomegranate, and soy.

Keywords: botanical; anti-aging; argan oil; coconut oil; crocin; feverfew; green tea; marigold; pomegranate; soy

1. Introduction

Skin aging is due to the cumulative effects of both intrinsic (chronologic) aging and extrinsic (predominately ultraviolet A (UVA) and ultraviolet B (UVB) related) aging [1,2]. Aging skin demonstrates wrinkling, fragility, easy bruisability, loss of elasticity, and mottled dyspigmentation [3]. More specifically, intrinsically aged skin demonstrates cell loss, a thinned epidermis, flattening of the dermal-epidermal junction (DEJ), and fine lines and wrinkles [4,5]. Extrinsically aged skin (photoaged) demonstrates coarse wrinkling and mottled dyspigmentation [4,5]. Multiple other external factors affect or potentially affect skin aging including smoking, pollution, nutrition, sleep deprivation, stress, and extreme temperatures [2]. The cumulative effects of skin aging are alterations that decrease physiologic function [6,7].

One of the most visible signs of skin aging is skin wrinkling, which is the result of decreased levels of collagen and accelerated collagen breakdown [8]. Collagen breakdown is regulated by the transforming growth factor β (TFG-β). Collagen is synthesized from procollagen secreted by dermal fibroblasts [2]. During the aging process, collagen fibers are broken down by matrix metalloproteinases (MMPs), which can be induced by UV radiation, infrared radiation, and potentially even visible light [2,9]. Skin aging results from the formation and accumulation of reactive oxygen species (ROS) and the induction of MMPs. Eventually, this leads to the accumulation of fragmented collagen fibers that prevent normal collagen formation [1].

In addition to the decreased quantity and quality of collagen fibers, aging skin loses proper barrier function. The normal human skin barrier is composed of keratin-filled keratinocytes embedded in an extracellular matrix consisting predominately of saturated long chain lipids: cholesterol, ceramide fatty acids, and free fatty acids [10]. Together these provide a strong, flexible, water-tight barrier, which

becomes altered as the skin ages. UV radiation is associated with decomposition of sebaceous lipids, increased ROS formation, depletion of endogenous antioxidants, and results in dysregulation of the production of cytokines and alteration of the lipid barrier via lipid peroxidation [11]. Restoration of epidermal barrier function can decrease the levels of pro-inflammatory cytokines in skin and serum, which gives further evidence to the importance of a properly functioning skin barrier [12].

Although aged skin generally reflects both intrinsic and extrinsic aging, some factors can be identified that stem more specifically from chronologic aging. Intrinsic aging results in the loss of cellular reserve capacity, which in turn limits the skin's ability to respond to environmental insults [13]. Intrinsic aging also changes the protein composition of the dermal-epidermal junction (DEJ), resulting in a flattened DEJ with a decreased surface area due to the loss of rete ridges [14]. This thinning results in skin fragility and a decreased resistance to shearing forces [14]. Intrinsic aging decreases epidermal cell growth, increases caspase 14, and increases protein carbonylation, which may lead to apoptosis and inhibition of keratinocyte proliferation [6]. There is also decreased collagen XVIII, integrin β4, collagen IV, laminin-332, and collagen VII [14].

In addition to the effects of chronological aging, photoaging has a significant influence on the appearance of aged skin. Photoaging of human is skin is predominately due to daily exposure to low doses of UV radiation, which upregulates proliferating cell nuclear antigen and increases oxidative damage to DNA leading to long-term changes in the skin [2,6]. Both UVA and UVB exposure lead to increased ROS, and this can eventually overwhelm the body's capacity to repair oxidative damage, leading to a relative state of oxidative stress [15]. Photoaging results in the degradation of collagen and the accumulation of abnormal collagen in the superficial dermis [16]. Although the majority of photodamage is due to UV light, visible light and infrared radiation have been reported to decrease collagen production and may also contribute to skin pigmentation [2]. The extent of photoaging is influenced by intrinsic protection factors that may vary between different ethnicities, ages, and individual levels of intrinsic antioxidants, and DNA repair [2]. Histologic examination of photoaged skin demonstrates increased innate immune cells, without apparent active localized inflammation, increased abnormal elastic fibers, and loss of collagen [16]. Photoaged skin also demonstrates an increased irregular pigmentation, which may be due to increased IL-1α by keratinocytes resulting in the proliferation of melanocytes and an increase in tyrosinase activity [17].

Both intrinsic and extrinsic aging are influenced by increased oxidative stress, which occurs when the intrinsic antioxidant function of the skin is overwhelmed by ROS [1,4,5,8,13,18]. Oxidative stress occurs when the body's endogenous antioxidant system, composed of enzymes including superoxide dismutase, catalase, ceruloplasmin, and transferrin, cannot keep up with the body's antioxidant requirements [19]. ROS consists of oxygen molecules in an excited state or those with an unpaired electron. If left unchecked, ROS lead to lipid peroxidation of polyunsaturated fats, which sets off a chain reaction of damage including increased apoptosis and decreased mitochondrial function [8,20,21]. Furthermore, ROS can increase tyrosinase and tyrosinase-related protein-1, thus increasing melanogenesis and skin pigmentation. They can oxidize proteins and DNA bases, which leads to mutations and deletions [20]. The oxidation of lipids enhances the expression of MMP-1 and MMP-3, which as stated previously, lead to the breakdown of collagen [8]. Together, this multitude of effects lead to an alteration in biological skin function.

In addition to ROS and MMP, the mammalian target of rapamycin complex 2 (mTORC2) and nuclear factor-κB (NF-κB) each play a role in skin aging. The mammalian target of rapamycin complex 2, an enzymatic complex of mTOR, regulates many substrates that influence the skin aging process [22]. In both intrinsic and extrinsic aging, there is an increase in the mTORC2 pathway, which leads to the activation of NF κB; a transcription factor that plays an important role in both intrinsic and extrinsic aging [22–24]. The transcriptional activity of NF-κB is associated with multiple age-related diseases including diabetes mellitus, osteoporosis, and Alzheimer's disease [23]. It regulates numerous biological functions including the expression of genes, growth factors, and cytokines that regulate inflammation, apoptosis, and cell senescence [23]. NF-κB inhibition can enhance the expression of

extracellular matrix (ECM) genes in vitro. In one small eight week randomized clinical trial (RTC), the inhibition of NF-κB was shown to decrease the visible signs of aging [25]. This further corroborates the role of NF-κB in skin aging.

Decreased estrogen levels may play a role in skin aging in women and compounds stimulating estrogen receptors could potentially counteract some of the visible signs of aging. As people live longer, women spend a larger portion of their lives in a post-menopausal state, with a deficiency of estrogen as compared to their younger selves. Menopause may increase oxidative stress and the skin of post-menopausal women demonstrates decreased collagen types I and III [26,27]. Declining levels of serum 17β-estradiol may contribute to the intrinsic aging of the skin [28].

Botanicals are products derived from plants and numerous such products have the potential to counteract some of the signs of skin aging. Many botanical products claim to have anti-aging effects, yet only a small fraction of these claims are supported by robust scientific evidence. There are numerous bioactive compounds present in botanicals that may have anti-aging benefits, including antioxidants and polyphenols. Polyphenols function as exogenous antioxidants, due to a hydroxyl (-OH) group bound to an aromatic ring that acts as a hydrogen or electron donor to free radicals or other reactive species [19]. Additionally, topical application of antioxidants can decrease the induction of MMPs [2]. Botanical products that can prevent or reduce the signs of aging skin include products that offer photoprotection, decreased transepidermal water loss (TEWL), increased skin elasticity, increased collagen formation, decreased facial pigmentation, or offer antioxidant effects in the skin.

In this review, we will discuss multiple botanicals with potential anti-aging properties (Table 1). Although there are numerous botanicals included as ingredients in cosmetic and cosmeceutical products, we will focus only on a select few in this review. We acknowledge that there are additional botanicals with some scientific evidence that supports potential anti-aging effects that are not discussed here.

Table 1. Level of studies supporting anti-aging effect of listed botanicals.

Botanical	Level of Evidence	Potential Anti-Aging Effect	Demonstrated Anti-Aging Effects in Human Studies
Argan Oil	Animal models, human studies	Decrease hyperpigmentation due to tyrosinase inhibition, decreased TEWL, improved elasticity, antioxidant	Decreased TEWL, improved elasticity
Coconut oil	In vitro, animal models, human studies	Emollient, humectant, decreased TEWL, Anti-inflammatory, antioxidant, decrease wound healing time, increases collagen	Decreased TEWL, No UV protection
Crocin	In vitro	Antioxidant, protects squalene against UV-induced peroxidation, prevents the release of inflammatory mediators,	N/A
Feverfew	In vitro, animal models, human studies	Anti-inflammatory (inhibits NF- κB), enhance endogenous DNA-repair activity, decrease proinflammatory cytokine release, antioxidants	Antioxidant, decreased UV-induced erythema
Green tea	In vitro, animal models, human studies	Antioxidant, photoprotective, immunomodulatory, anti-angiogenic, anti-inflammatory	Decreased VEGF and HIF-1α, partial prevention of UV-induced oxidative damage, reduced depletion of Langerhans cells,
Pomegranate	In vitro, animal models, human studies	Protects fibroblast from UV-induced cell death, increased DNA repair, anti-inflammatory,	Decreased facial erythema, decreased facial pigmentation due to tyrosinase inhibition

Table 1. *Cont.*

Botanical	Level of Evidence	Potential Anti-Aging Effect	Demonstrated Anti-Aging Effects in Human Studies
Soy	In vitro, animal models, human studies	Antioxidant, increased fibroblast proliferation and increased synthesis of collagen I and III, decreased MMP-1, increased collagen and elastin,	Increased type I and III facial collagen, decreased erythema after UVB exposure, improved facial pigmentation, improved skin texture, reduced fine lines, improved skin tone
Marigold	In vitro, animal models, human studies	Antioxidant	Increased skin tightness

2. Materials and Methods

A Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/) search was performed using the following keywords: "botanicals", "skin", "inflammation", "aging" in isolation and various combinations. Specific botanicals were then chosen for further review and a keyword search was performed using "argan oil", "coconut oil", "crocin", "feverfew", "green tea", "marigold", "plant stem cells", "pomegranate", and "soy" in combination with the general keywords listed above. The studies identified were reviewed and relevant citations within these studies were also reviewed.

3. Results

Although there are numerous botanicals listed as ingredients in popular cosmetics and cosmeceuticals, we are only able to discuss a few select botanicals here. These were chosen based on the availability of scientific data, personal interest to the authors, and perceived "popularity" in cosmetics and cosmeceuticals.

3.1. Argan Oil

3.1.1. History, Usage, and Claims

Argan oil is endemic to Morocco and is produced from the seeds of *Argania sponosa* L. It has numerous traditional uses such as in cooking, treating skin infections, and skin and hair care [29].

3.1.2. Composition and Mechanism of Action

Argan oil is composed of 80% monounsaturated fat and 20% saturated fatty acids and contains polyphenols, tocopherols, sterols, squalene, and triterpene alcohols [29].

3.1.3. Scientific Evidence

Argan oil has traditionally been used in Morocco to decrease facial pigmentation, but the scientific basis for this claim was not previously understood [30]. In a mouse study, argan oil inhibited tyrosinase and dopachrome tautomerase expression in B16 murine melanoma cells, resulting in a dose-dependent decrease in melanin content [30]. This suggests that argan oil may be a potential inhibitor of melanin biosynthesis, but randomized control trials (RTC) in human subjects are needed to verify this hypothesis.

A small RTC of 60 post-menopausal women suggested that daily consumption and/or topical application of argan oil decreased transepidermal water loss (TEWL), improved elasticity of skin, based on an increase in R2 (gross elasticity of skin), R5 (net elasticity of skin), and R7 (biological elasticity) parameters and a decrease in resonance running time (RRT) (a measurement inversely related to skin elasticity) [31,32]. The groups were randomized to consume either olive oil or argan oil. Both groups applied argan oil to the left volar wrist only. Measurements were taken from the right and left volar wrists. Improvements in elasticity were seen in both groups on the wrist where the argan oil was topically applied, but on the wrist where the argan oil was not applied only the group consuming

argan oil had significant increases in elasticity [31]. This was attributed to the increased antioxidant content in argan oil compared to olive oil. It is hypothesized that this could be due to its Vitamin E and ferulic acid content, which are known antioxidants.

3.2. Coconut Oil

3.2.1. History, Usage, and Claims

Coconut oil is derived from the dried fruit of *Cocos nucifera* and has many uses, both historical and modern. It has been employed as a fragrance, skin and hair conditioning agent, and in numerous cosmetic products [33,34]. While coconut oil has numerous derivatives, including coconut acid, hydrogenated coconut acid, and hydrogenated coconut oil, we will discuss research claims associated predominately with virgin coconut oil (VCO), which is prepared without heat [35].

Coconut oil has been used for moisturization of infant skin and may be beneficial in the treatment of atopic dermatitis for both its moisturizing properties and its potential effects on *Staphylococcus aureus* and other skin microbes in atopic patients [34]. Coconut oil has been shown to decrease *S. aureus* colonization on the skin of adults with atopic dermatitis in a double-blind RTC [35].

3.2.2. Composition and Mechanism of Action

Coconut oil is composed of 90–95% saturated triglycerides (lauric acid, myristic acid, caprylic acid, capric acid, and palmitic acid) [33,34]. This is in contrast to most vegetable/fruit oils, which are predominately composed of unsaturated fats [33,34]. Topically applied saturated triglycerides function to moisturize the skin as an emollient by flattening dry curled edges of corneocytes and filling the gaps between them.

3.2.3. Scientific Evidence

Coconut oil can moisturize dry aging skin [10,35]. Sixty-two percent of the fatty acids in VCO are of similar length and 92% are saturated, which allows for tighter packing that results in a greater occlusive effect than olive oil [10]. The triglycerides in coconut oil are broken down by lipases in normal skin flora to glycerin and fatty acids [10]. Glycerin is a potent humectant, which attracts water to the corneal layer of the epidermis from the outside environment and the deeper skin layers [10]. The fatty acids in VCO have a low linoleic acid content, which is relevant since linoleic acid can be irritating to the skin [10]. Coconut oil is superior to mineral oil in decreasing TEWL in patients with atopic dermatitis and is as effective and safe as mineral oil in treating xerosis [36,37].

Lauric acid, a precursor to monolaurin and an important component of VCO, may have anti-inflammatory properties, be able to modulate immune cell proliferation and be responsible for some of the antimicrobial effects of VCO [38]. VCO contains high levels of ferulic acid and *p*-coumaric acid (both phenolic acids), and high levels of these phenolic acids are associated with an increased antioxidant capacity [39]. Phenolic acids are effective against UV-induced damage [40]. However, despite claims that coconut oil can function as a sunscreen, in vitro studies suggest that it offers little-to-no UV-blocking potential [41].

In addition to its moisturizing and antioxidant effects, animal models suggest that VCO may decrease wound healing time. There was an increased level of pepsin-soluble collagen (higher collagen cross-linking) in VCO treated wounds compared to controls. Histopathology showed increased fibroblast proliferation and neovascularization in these wounds [42]. More studies are necessary to see whether topical application of VCO can increase collagen levels in aging human skin.

3.3. Crocin

3.3.1. History, Usage, Claims

Crocin is a biologically active component of saffron, derived from the dried stigma of *Crocus sativus L.* Saffron is cultivated in many countries including Iran, India, and Greece and has been used in traditional medicine to alleviate a variety of ailments including depression, inflammation, liver disease, and many others [43,44].

3.3.2. Composition and Mechanism of Action

Crocin is responsible for the color of saffron [45]. Crocin is also found in the fruit of *Gardenia jasminoides Ellis* [45]. It is classified as a carotenoid glycoside [45].

3.3.3. Scientific Evidence

Crocin has antioxidant effects, protects squalene against UV-induced peroxidation, and prevents the release of inflammatory mediators [45]. The antioxidant effect has been demonstrated in in vitro assays that showed superior antioxidant activity compared to Vitamin C [45]. Additionally, crocin inhibits UVA-induced cell membrane peroxidation and inhibits the expression of numerous pro-inflammatory mediators including IL-8, PGE-2, IL-6, TNF-α, IL-1α, and LTB4 [45,46]. It also decreases the expression of multiple NF-κB dependent genes [45]. In a study using cultured human fibroblasts, crocin reduced UV-induced ROS, promoted expression of extracellular matrix protein Col-1, and decreased the number of cells with senescent phenotypes after UV radiation [47]. It decreases ROS production and limits apoptosis [46]. Crocin was shown to suppress ERK/MAPK/NF-κB/STAT signaling pathways in HaCaT cells in vitro [48]. Although crocin has the potential for an anti-aging cosmeceutical, the compound is labile. Use of nanostructured lipid dispersions for topical administration has been investigated with promising results [49]. To determine the effects of crocin in vivo, additional animal models and randomized clinical trials are needed.

3.4. Feverfew

3.4.1. History, Usage, Claims

Feverfew, *Tanacetum parthenium*, is a perennial herb that has been used for multiple purposes in folk medicine [50].

3.4.2. Composition and Mechanism of Action

Feverfew contains parthenolide, a sesquiterpene lactone, which may be responsible for some of its anti-inflammatory effects, via the inhibition of NF-κB [50,51]. This inhibition of NF-κB appears to be independent of parthenolide's antioxidant effects [52]. Parthenolide has also demonstrated anticancer effects against UVB-induced skin cancer and against melanoma cells in vitro [53–55]. Unfortunately, parthenolide can also cause allergic reactions, oral blisters, and allergic contact dermatitis. Due to these concerns, it is now generally removed before feverfew is added to cosmetic products [50,56,57].

3.4.3. Scientific Evidence

Due to the potential complications with the topical use of parthenolide, some current cosmetic products containing feverfew use parthenolide-depleted feverfew (PD-feverfew), which claims to be free of sensitization potential [56]. PD-feverfew can enhance endogenous DNA-repair activity in the skin, potentially decreasing UV-induced DNA damage [58]. In an in vitro study, PD-feverfew attenuated UV-induced hydrogen peroxide formation and decreased pro-inflammatory cytokine release [56]. It demonstrated stronger antioxidant effects than the comparator, Vitamin C, and decreased UV-induced erythema in a 12-subject RTC [56].

3.5. Green Tea

3.5.1. History, Usage, Claims

Green tea has been consumed for its health benefits in China for centuries [59]. Due to its potential antioxidant effects, there is interest in the development of a stable, bioavailable topical formulation.

3.5.2. Composition and Mechanism of Action

Green tea, from *Cammelia sinensis*, contains multiple bioactive compounds with possible anti-aging effects, including caffeine, vitamins, and polyphenols [21]. The major polyphenols in green tea are catechins, specifically gallocatechin, epiglallocatechin (ECG), and epigallocatechin-3-gallate (EGCG) [15,19,60]. Epigallocatechin-3-gallate has antioxidant, photoprotective, immunomodulatory, anti-angiogenic, and anti-inflammatory properties [60,61]. Green tea also contains high amounts of the flavonol glycoside kaempferol, which is well-absorbed in the skin after topical application [62,63].

3.5.3. Scientific Evidence

Green tea extract reduces intracellular ROS production in vitro and has decreased ROS-induced necrosis [64]. Epigallocatechin-3-gallate (a green tea polyphenol) inhibits the UV-induced release of hydrogen peroxide, suppresses phosphorylation of MAPK, and decreases inflammation through the activation of NF-κB [15]. Using ex vivo skin from a healthy 31-year-old woman, skin pretreated with white or green tea extract demonstrated retention of Langerhans cells (antigen presenting cells responsible for the induction of immunity in the skin) after UV light exposure [65].

In a mouse model, topical application of green tea extract before UV exposure lead to decreased erythema, decreased skin infiltration of leukocytes, and decreased myeloperoxidase activity [21,64]. It can also inhibit 5-α-reductase [59,66].

Several studies involving human subjects have evaluated the potential benefits of topical application of green tea. Topical application of a green tea emulsion inhibited 5-α-reductase and led to a decrease in microcomedone size in microcomedonal acne [66]. In a small six week human split-face study, a cream containing EGCG decreased hypoxia-inducible factor 1 α (HIF-1α) and vascular endothelial growth factor (VEGF) expression, exhibiting the potential to prevent telangiectasias [61]. In a double-blind study, either green tea, white tea, or vehicle only were applied to the buttocks of 10 healthy volunteers. The skin was then irradiated with 2× minimal erythema dose (MED) of solar-simulated UVR. Skin biopsies from these sites demonstrated that the application of green or white tea extract could significantly reduce the depletion of Langerhans cells, based on CD1a positivity. There was also a partial prevention of UV-induced oxidative DNA damage, as evidenced by decreased levels of 8-OHdG [65]. In a different study, 90 adult volunteers were randomized into three groups: No treatment, topical green tea, or topical white tea. Each group was further subdivided into different levels of UV radiation. The in vivo sun protection factor was found to be approximately SPF 1 [65].

3.6. Marigold

3.6.1. History, Usage, Claims

Marigold, *Calendula officinalis*, is an aromatic flowering plant with potential therapeutic possibilities [67]. It has been used in folk medicine in both Europe and the United States as a topical medicament for burns, bruises, cuts, and rashes [67]. Marigold has also shown anticancer effects in murine models of non-melanoma skin cancer [68].

3.6.2. Composition and Mechanism of Action

The main chemical components of marigolds are steroids, terpenoids, free and esterified triterpenic alcohols, phenolic acids, flavonoids, and other compounds [67]. Although one study demonstrated that topical application of marigold extract may decrease the severity and pain of radiation dermatitis

in patients receiving radiation for breast cancer, other clinical trials have demonstrated no superiority when compared to the application of aqueous cream alone [69,70].

3.6.3. Scientific Evidence

Marigold has a demonstrated antioxidant potential and cytotoxic effects on human cancer cells in an in vitro human skin cell model [71]. In a separate in vitro study, a cream containing calendula oil was evaluated via UV spectrophotometrics and found to have an absorbance spectrum in the range of 290-320 nm; this was taken to mean that the application of this cream offered good sun protection [72]. It is important to note, however, that this was not an in vivo test that calculated the minimum erythema dose in human volunteers and it remains unclear how this would translate in clinical trials [72].

In an in vivo murine model, marigold extract demonstrated a strong antioxidant effect after UV-exposure [67]. In a different study, involving albino rats, the topical application of calendula essential oil decreased malonyldialdehyde (a marker of oxidative stress) while increasing the levels of catalase, glutathione, superoxide dismutase, and ascorbic acid in the skin [73].

In an eight week single-blinded study with 21 human subjects, application of calendula cream to the cheeks increased skin tightness but did not have any significant effects on skin elasticity [74].

A potential limitation to the use of marigold in cosmetics is that marigold is a known cause of allergic contact dermatitis, like several other members of the Compositae family [75].

3.7. Pomegranate

3.7.1. History, Usage, Claims

Pomegranate, *Punica granatum*, has potent antioxidant potential and has been used in multiple products as a topical antioxidant. Its high antioxidant content makes it an interesting potential ingredient in cosmetic formulations.

3.7.2. Composition and Mechanism of Action

The biologically active components of pomegranate are tannins, anthocyanins, ascorbic acid, niacin, potassium, and piperidine alkaloids [76]. These biologically active components can be extracted from the juice, seeds, peel, bark, root, or stem of the pomegranate [76]. Some of these components are thought to have antitumor, anti-inflammatory, anti-microbial, antioxidant, and photoprotective effects. Additionally, pomegranate is a potent source of polyphenols. Ellegic acid, a component of the pomegranate extract, may decrease skin pigmentation [77,78]. Due to being a promising anti-aging ingredient, multiple studies have investigated methods to increase skin penetration of this compound for topical use [77,78].

3.7.3. Scientific Evidence

Pomegranate fruit extract protects human fibroblasts, in vitro, from UV-induced cell death; likely due to the decreased activation of NF-κB, downregulation of proapoptotic caspace-3, and increased DNA repair [79]. It demonstrates anti-skin-tumor promoting effects in vitro and inhibits UVB-induced modulation of NF-κB and MAPK pathways [80,81]. Topical application of pomegranate rind extract downregulates COX-2 in freshly extracted porcine skin, resulting in significant anti-inflammatory effects [82]. Although ellegic acid is often thought to be the most active component of pomegranate extract, a murine model demonstrated higher anti-inflammatory activity with standardized pomegranate rind extract compared to ellegic acid alone [83]. The topical application of a microemulsion of pomegranate extract using a polysorbate surfactant (Tween 80®) in a 12-week split-face comparison with 11 subjects, demonstrated decreased melanin (due to tyrosinase inhibition) and decreased erythema compared to the vehicle control [77,78].

3.8. Soy

3.8.1. History, Usage, Claims

Soybeans are a high protein food with bioactive components that may have anti-aging effects. In particular, soybeans are high in isoflavones, which may have anticarcinogenic effects and have estrogen-like effects due to the diphenolic structure [84]. These estrogen-like effects could potentially combat some of the effects of menopause on skin aging.

3.8.2. Composition and Mechanism of Action

Soy, from *Glycine maxi*, is high in protein and contains isoflavones, including glycitein, equol, daidzein, and genistein [19,85–87]. These isoflavones, also called phytoestrogens, may have estrogenic effects in humans.

3.8.3. Scientific Evidence

Soybeans contain multiple isoflavones with potential anti-aging benefits. Among other biologic effects, glycitein demonstrates antioxidant effects [85]. Dermal fibroblasts treated with glycitein showed an increased cell proliferation and migration, increased synthesis of collagen types I and III, and decreased MMP-1 [85]. In a separate study, soy extract was combined with *haematococcus* extract (a freshwater algae also high in antioxidants), which downregulated MMP-1 mRNA and protein expression [84]. Daidzein, a soy isoflavone, has demonstrated anti-wrinkle, skin-lightening, and skin hydrating effects [86]. Diadzein may function by activating the estrogen-receptor-β in skin, resulting in an enhanced expression of endogenous antioxidants and decreased expression of the transcription factors that lead to keratinocyte proliferation and migration [88]. The soy-derived isoflavonoid equol increased collagen and elastin and decreased MMPs in cell culture [87].

Additional in vivo murine studies demonstrate decreased UVB-induced cell death and a decreased epidermal thickness in cells after topical application of isoflavone extracts [89]. In a pilot study of 30 postmenopausal women, oral administration of isoflavone extract for six months resulted in an increased epidermal thickness and increased dermal collagen as measured by skin biopsies in sun-protected areas [90]. In a separate study, purified soy isoflavones inhibited UV-induced keratinocyte death and decreased TEWL, epidermal thickness, and erythema in UV-exposed mouse skin [91].

A prospective double-blind RCT of 30 women aged 45–55 compared the topical application of estrogen and genistein (soy isoflavone) to the skin for 24 weeks. Although the group applying estrogen to the skin had superior results, both groups demonstrated an increased type I and III facial collagen based on skin biopsies of preauricular skin [92]. Soy oligopeptides can decrease the erythema index in UVB exposed skin (forearm) and decrease sunburnt cells and cyclobutene pyrimidine dimers in UVB irradiated foreskin cells ex vivo [90,93]. A randomized double-blind vehicle-controlled 12 week clinical trial involving 65 female subjects with moderate facial photodamage demonstrated an improvement in mottled pigmentation, blotchiness, dullness, fine lines, skin texture, and skin tone when compared to the vehicle [94]. Together, these factors could offer potential anti-aging effects, but more robust randomized clinical trials are needed to adequately demonstrate its benefit.

3.9. Plant Stem Cells

Although plant stem cells are not a specific botanical, as are the other entities reviewed here, we wanted to briefly discuss them as they pertain to other botanical products. There are many products on the market that advertise plant stem cells as an anti-aging product. The underlying question surrounding these products is whether products derived from plant stem cells can have an effect on human skin stem cells. Any plant stem cells in cosmetic products are dead cells, but secondary metabolites from plant stem cells may offer benefits to aging skin. Companies using "plant stem cells" in their products are generally using the extracts from these cells, rather than the cells

themselves [95]. These plant-derived metabolites a have high binding affinity in humans and can compete with endogenous ligands, which results in inhibition or induction of metabolic or signal transduction pathways [96]. This use of terminology may be confusing to consumers, who may believe that their cosmetic product is a source of actual renewable stem cells. Plant cell culture technologies have been used as a valuable source of plant-based ingredients, specifically for the cultivation of meristem plant cells [96]. This could potentially be a more sustainable method for producing desired metabolites, in particular those occurring in rare plants [96].

4. Discussion

Botanical products, including those discussed here, have potential anti-aging effects. Mechanisms of anti-aging botanicals include the free radical scavenging potential of topically applied antioxidants, increased sun protection, increased skin moisturization, and multiple effects leading to increased collagen formation or decreased collagen breakdown. Some of these effects are modest when compared to pharmaceuticals, but this does not discount their potential benefit when used in conjunction with other measures such as sun avoidance, the use of sunscreens, daily moisturization and appropriate medical professional treatment of existing skin conditions.

Additionally, botanicals offer alternative biologically active ingredients for patients who prefer to use only "natural" ingredients on their skin. Although these ingredients are found in nature, it is important to stress to patients that this does not mean that these ingredients have zero adverse effects, in fact, many botanical products are known to be a potential cause of allergic contact dermatitis.

As cosmetic products do not require the same level of evidence to prove efficacy, it is often difficult to determine whether claims of anti-aging effects are true. Several of the botanicals listed here, however, have potential anti-aging effects, but more robust clinical trials are needed. Although it is difficult to predict how these botanical agents will directly benefit patients and consumers in the future, it is very likely that for the majority of these botanicals, formulations that incorporate them as ingredients will continue to be introduced as skin care products and if they maintain a wide safety margin, high consumer acceptability, and optimal affordability, they will remain part of regular skin care routines, providing minimal benefits to skin health. For a limited number of these botanical agents, however, a greater impact to the general population may be obtained by strengthening the evidence of their biological action, through standard high throughput biomarker assays and thereafter subjecting the most promising targets to clinical trial testing.

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