

Review

Effects of Natural Polyphenols on Skin and Hair Health: A Review

Mang Sun¹, Ya Deng¹, Xining Cao¹, Lu Xiao¹, Qian Ding¹, Fuqing Luo¹, Peng Huang¹, Yuanyuan Gao², Mengqi Liu³ and Hengguang Zhao^{1,*} 

¹ Department of Dermatology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing 400010, China

² Department of Dermatology, Daping Hospital, The Army Medical University, Chongqing 400042, China

³ Bioengineering College, Chongqing University, Chongqing 400030, China

* Correspondence: zhao@cqmu.edu.cn

Abstract: The skin is the largest organ of the body and plays multiple essential roles, ranging from regulating temperature, preventing infections, to ultimately affecting human health. A hair follicle is a complex cutaneous appendage. Skin diseases and hair loss have a significant effect on the quality of life and psychosocial adjustment of individuals. However, the available traditional drugs for treating skin and hair diseases may have some insufficiencies; therefore, a growing number of researchers are interested in natural materials that could achieve satisfactory results and minimize adverse effects. Natural polyphenols, named for the multiple phenolic hydroxyl groups in their structures, are promising candidates and continue to be of scientific interest due to their multifunctional biological properties and safety. Polyphenols have a wide range of pharmacological effects. In addition to the most common effect, antioxidation, polyphenols have anti-inflammatory, bacteriostatic, antitumor, and other biological effects associated with reduced risk of a number of chronic diseases. Various polyphenols have also shown efficacy against different types of skin and hair diseases, both in vitro and in vivo, via different mechanisms. Thus, this paper reviews the research progress in natural polyphenols for the protection of skin and hair health, especially focusing on their potential therapeutic mechanisms against skin and hair disorders. A deep understanding of natural polyphenols provides a new perspective for the safe treatment of skin diseases and hair loss.

Keywords: polyphenols; skin; hair; human health



Citation: Sun, M.; Deng, Y.; Cao, X.; Xiao, L.; Ding, Q.; Luo, F.; Huang, P.; Gao, Y.; Liu, M.; Zhao, H. Effects of Natural Polyphenols on Skin and Hair Health: A Review. *Molecules* **2022**, *27*, 7832. <https://doi.org/10.3390/molecules27227832>

Academic Editor: Nour Eddine Es-Safi

Received: 13 October 2022

Accepted: 11 November 2022

Published: 14 November 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

The skin is the largest organ, with a complicated structure and multiple physical functions, thus providing a barrier against outside hazards. In addition, the skin is also involved in regulating the hydroelectrolytic balance and immune response of individual organisms. Due to the extensive distribution and functional diversity of the skin, skin diseases are among the most common disorders. A hair follicle is a complex cutaneous appendage. Studies have shown that hair loss has a significant effect on the quality of life and psychosocial adjustment of people. Hair loss can lead to social anxiety, symptoms of depression and anxiety, low self-confidence, and dissatisfaction with life [1]. Many factors are related to skin and hair diseases, including genetics, local infections, endocrine disorders, and mental stress. People have used various drugs and remedies to treat skin and hair diseases according to their different pathogeneses. However, the available drugs for treating skin and hair diseases still have many drawbacks. Considering the occurrence and complexity of skin and hair diseases, as well as the adverse effects of available drugs, research investigating novel remedies and less dangerous natural materials has increased in recent years.

Polyphenols, which are widely found in plants, play an increasingly important role in protecting human health. Polyphenolic compounds are chemical substances commonly

found in fruits, vegetables, and cereals. They are named for the multiple phenolic hydroxyl groups in their structures. In recent years, along with developments in science and technology that have enabled structure identification, over 1000 kinds of polyphenols have been identified, and their pharmacological activities have been extensively studied. According to their different chemical constitutions, polyphenols are mainly classified into four groups, including phenolic acids, flavonoids, stilbenes, and lignans (Figure 1). Phenolic acids can be further identified as hydroxybenzoic and hydroxycinnamic acids. Some well-known polyphenols include resveratrol, quercetin, curcumin, epigallocatechin gallate, catechin, hesperetin, cyanidin, procyanidin, caffeic acid, and genistein [2]. Polyphenols have a wide range of pharmacological effects. In addition to the most common effect, antioxidation, polyphenols have anti-inflammatory, bacteriostatic, antitumor, and other biological effects associated with reduced risk of a number of chronic diseases, including cardiovascular disease and cancer [3–6]. Various polyphenols have also shown efficacy against different types of skin and hair diseases, both in vitro and in vivo, via different mechanisms [7–9]. Herein, we primarily focused on the effects and mechanisms of polyphenols related to skin and hair health.

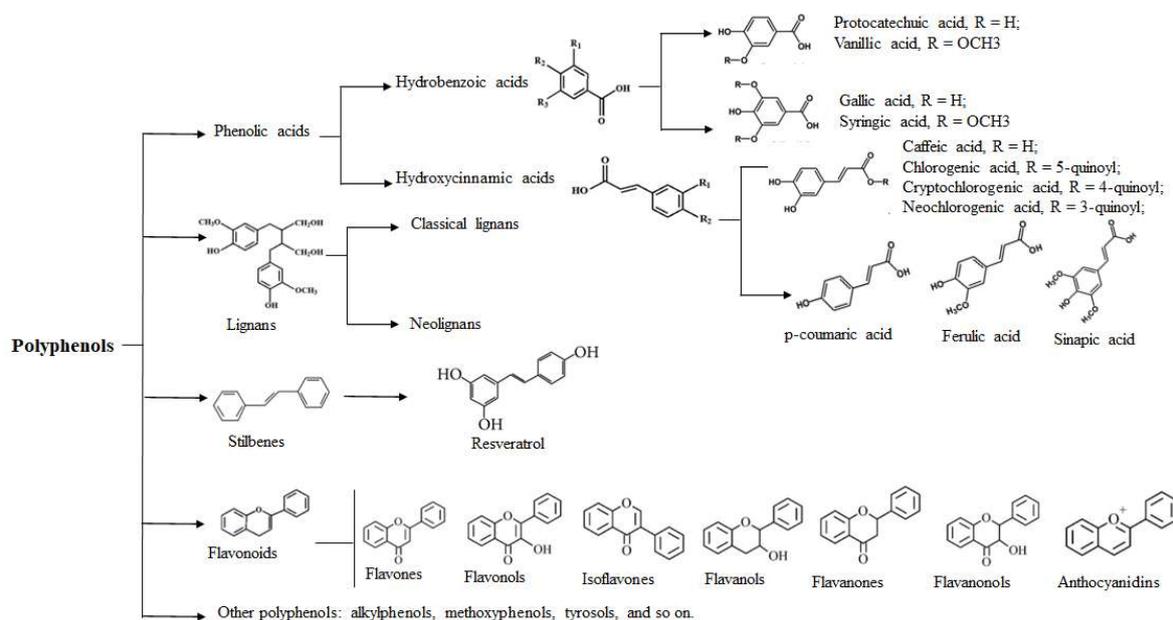


Figure 1. Main classification and basic chemical structures of polyphenols.

2. Roles of Polyphenols in Skin Health

2.1. Anti-Inflammatory Effects of Natural Polyphenols

Inflammatory skin diseases encompass a wide spectrum of skin disorders and affect people of all ages and skin types. The majority of chronic inflammatory skin diseases manifest a relapsing and remitting course throughout life, including atopic dermatitis, psoriasis vulgaris, lichen planus, and so on. These diseases are associated with complex multifactorial etiologies in which genetic and environmental factors interact both in the genesis and development of the disease. Specifically, signaling molecules released from the injured stratum corneum initiate a cytokine cascade, triggering an inflammatory response, which then contributes to the pathogenesis of a variety of dermatoses [10]. Glucocorticoids and biological agents are now commonly used to manage inflammatory skin diseases via different mechanisms, but systemic corticosteroids and immunosuppressives can only be used for short-term treatment because of their serious adverse effects, including growth inhibition, hematopoietic suppression, glaucoma, hypertension, hyperglycemia, osteoporosis, myopathy, cataracts, infection, and thin or easily bruised skin [11]. Biological therapies have revolutionized moderate-to-severe inflammatory dermatosis treatment, focusing on

inhibiting selective key pathways of inflammation, including interleukin-4 (IL-4), IL-13, IL-31, IL-12/23, IL-17, thymic stromal lymphopoietin (TSLP), and tumor necrosis factor (TNF- α) [12]. Side effects of biological agents remain unavoidable, for instance, associated serious bacterial, viral, and fungal infections, including active hepatitis B virus, reactivation of latent tuberculosis infection, and increased risk of *Candida* infections, as well as worsening of pre-existing inflammatory bowel disease and, rarely, new-onset ulcerative colitis [13–16].

Many polyphenols, especially flavonoids, possess potent anti-inflammatory properties and can regulate immunity [17–21]. Several natural polyphenols have been well studied for their beneficial effects in autoimmune inflammatory diseases. Some polyphenols, such as resveratrol, chlorogenic acid, caffeic acid, pelargonin, and ferulic acid, modulate pro-inflammatory gene expression and cytokine production, thus impacting immune cell populations [22,23]. The non-flavonoid curcumin was shown to downregulate the expression of TNF, IL-1, adhesion molecule-like vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) in human umbilical vein endothelial cells and inflammatory mediators such as prostaglandins and leukotrienes. Topical application of green tea polyphenols (GTPs) and epigallocatechin-3-gallate (EGCG) resulted in inhibited production of prostaglandin metabolites, including prostaglandin D2 (PGD2), prostaglandin E2 (PGE2), and prostaglandin F2 α (PGF2 α) [24]. Resveratrol can induce endothelial nitric oxide synthase (eNOS), inhibit cyclooxygenase (COX), and inactivate peroxisome proliferator-activated receptor gamma (PPAR γ) in vitro and in vivo [25,26]. What's more, curcumin downregulated signal transducer and activator of transcription 3 (STAT3) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and reduced the expression of toll-like receptor-2 (TLR-2) and -4 while upregulating PPAR γ in an in vivo study [27,28]. Caffeic acid phenethyl ester suppresses LPS-mediated TLR-4 and NF- κ B activation in macrophages. Quercetin was also confirmed to inhibit leukotriene biosynthesis in human polymorphonuclear leukocytes [29].

Based on their anti-inflammatory and immunomodulatory effects, natural polyphenols are used to treat a variety of skin diseases. Vitiligo is a common skin disorder characterized by hypopigmentation. *Ginkgo biloba* is known to be a rich source of polyphenolics. *G. biloba* extract was associated with the progression of vitiligo by reducing depigmentation and promoting repigmentation [30,31]. Carnosic acid is a natural benzenediol abietane diterpene found in rosemary. Carnosol was able to reduce levels of neutrophils, inflammatory cytokines (IL-1 β and TNF- α), COX-2, and iNOS in mice blood [32,33]. Animals with atopic dermatitis topically treated with carnosol showed obvious skin lesion reductions [34]. Artichoke polyphenols, as potential anti-inflammatory agents, can improve the vasodilatation and microcirculation of endothelial cells by inhibiting nitric oxide (NO) production in both macrophages and endothelial cells. Moreover, artichoke polyphenols can improve skin elasticity and roughness by inhibiting vascular aging, thus acting as a protective ingredient for both lymphatic and endothelial cells. These effects could be the direct result of their antioxidant or anti-inflammatory properties and indirect result via modulation of molecular pathways that improve the expression of genes involved in anti-aging mechanisms [35].

2.2. Antioxidant Properties of Natural Polyphenols

Human life is dependent upon oxygen. Occasionally, oxygen becomes mutagenic and toxic. Oxidative stress plays a very important role in human dermal diseases and skin aging [36,37]. Overproduction of reactive oxygen species (ROS) can damage the membranes, lipids, proteins, RNA, and DNA of cells. The traditional view is that the antioxidant activity of a polyphenol is positively correlated with its number of phenolic hydroxyl groups. As excellent antioxidants, the phenolic hydroxyl groups of polyphenols can decrease levels of free radicals by providing electrons and can also be used as free radical scavengers or metal-chelating agents (chelating metals with redox activity, such as copper and iron) to inhibit or eliminate the formation of free radicals, thereby destroying the progress of free radical chain peroxidation [38].

The skin is directly and frequently exposed to ultraviolet (UV) rays from the sun (UVA: 320–400 nm and UVB: 280–320 nm) [39,40]. UV radiation is involved in the pathogenesis of severe skin conditions, including photoaging of the skin, immune disorders, and skin cancer [41,42]. Many plants are rich in antioxidants because they must survive continual UV radiation exposure. For example, a marine algal polyphenol isolated from the brown alga *Ecklonia cava* was confirmed to have an inhibitory effect on melanogenesis and a protective property against photo-oxidative stress induced by UVB. Intracellular ROS induced by UVB radiation was reduced by the addition of the marine algal polyphenol and cell viability was dose-dependently increased. Moreover, the marine algal polyphenol demonstrated strong protective properties against UVB radiation-induced DNA damage, including damaged tail intensity and morphological changes in fibroblasts [43]. Clove is another kind of plant that is widely used in Chinese medicine and also used in the cosmetics industry. Cloves are rich in natural polyphenols such as ferric acid. Our previous study proved that cloves can decrease UVB damage through their influence on Na⁺-K⁺-ATPase, which led to a reduction in oxidation and inflammation in mice, thereby inhibiting skin injury and protecting the skin [44]. The above studies demonstrate that many natural polyphenols contribute to the prevention of UVB skin damage and inhibit photodamage to the skin. They are very promising for future research and applications.

Estrogen deficiency is associated with deteriorating skin health as it affects internal structural balance, dermal cellular mechanisms, and other biological functions. The effects of estrogen deficiency include loss of elastin, collagen, fibroblast dysfunction, increased vascular and matrix metalloproteinase activity, and extracellular and cellular degradation, leading to wrinkles, atrophy, dryness, impaired wound healing/barrier function, and reduced antioxidant capacity. Several studies have examined polyphenolic phytochemicals, also known as phytoestrogens, which act as estrogen receptor modulators (SERMs) and possess ER β -agonist properties [45]. The resveratrol compound extracted from grapes has been known for its anti-aging effects for over a decade [22,46]. Recently, an increasing number of studies have reported the benefits of resveratrol on the skin, including its antioxidant properties, which are achieved through activation of nuclear factor erythroid 2-related factor 2 (Nrf2) by reducing the expression of nuclear factor kappa-B (NF- κ B) and activating protein 1 (AP-1), fibroblast proliferation by increasing type I, II, and III collagen expression through activation of sirtuin 1 (SIRT 1, anti-aging factor), and inhibition of melanogenesis [45–47]. In preliminary studies, human skin benefited from several types of resveratrol analogs, the most potent of which was 4'-acetoxyresveratrol (4AR) [45,48], which increased human genetic expression of the antioxidant superoxide dismutase (SOD) [45]. Equol is a relatively new phytochemical found in food sources and plants [45,49,50]. It is classified as a phytoestrogen with selective SERM properties and binds to ER β in keratinocytes [49–51]. Equol exhibits skin-protecting antioxidant properties. In a clinical investigation involving a 12-week single-center study with 59 female subjects, equol significantly improved skin characteristics, including hydration and firmness, which suggested that equol may be effective in treating estrogen-deficient skin [52].

Along with their antioxidant properties, some natural polyphenols have potential whitening effects and prominent protective effects against cell damage and skin aging, which may be used in the cosmeceutical and pharmaceutical industries (Table 1) [44,53–56].

Table 1. Several marketed formulations based on polyphenols as anti-aging cosmeceuticals.

Plant	Compounds	Bioactivity
Blackberry	Anthocyanins	↓IL-6, ↓TNF- α , ↓ERK1/2, ↓P38, ↓JNK1/2, ↓MKK4, ↓PGE2, ↓iNOS, ↓NF- κ B, ↓I κ - β
Cacao bean	Flavonoids	↓Wrinkle formation, ↑Collagen level, ↓MMP-1, ↓AP-1 expression
Strawberry	Phenolic	↓ROS, ↓NF- κ B, ↓I κ - β phosphorylation, ↓TNF- α , ↓IL-6, ↓IL-1b, ↑Nrf2, ↑CAT, ↑HO-1

Table 1. Cont.

Plant	Compounds	Bioactivity
Black rice	Flavonoids	↓ROS, ↓MMP-1, ↓MMP-3, ↓Procollagen type 1, ↓p-cfos, ↓p-cjun, ↓p-p38, ↓p-JNK
Grape	Flavonoids Phenolics Anthocyanins Resveratrol	↑Nrf2, ↑HO-1, ↓MMP-1, ↓MMP-9
Tea	EGCG	↑Erk, ↑Akt, ↑Bcl-2/Bax
Clove	Eugenol Gallic acid	↓Skin wrinkle, ↓Skin Thickness, ↓ROS, ↓MMP-1, ↓MMP-3, ↓IL-6, ↓p-c-fos, ↓p-c-jun, ↑NF-κB, ↑Ik-βa, ↑Nrf2, ↑HO-1, ↑NQO-1, ↑Skin hydration, ↑p-Smad2/3, ↑TGF-β1

2.3. Anti-Allergic Effects of Natural Polyphenols

It is said that allergic diseases are prevalent in approximately 40% of the general population and will rapidly increase to 50% [57,58]. The skin is very often the target organ involved in allergic reactions, including urticaria, angioedema, atopic dermatitis, contact dermatitis, and vasculitis. This may be associated with many immunologically competent cells, such as mast cells, lymphocytes, eosinophils, neutrophils, and Langerhans cells, especially antigen-presenting Langerhans cells [59]. As an alternative to conventional treatments with corticosteroids and antihistamines, polyphenols also exhibit anti-allergic effects, including inhibiting the production of proinflammatory cytokines and leukocytes, as well as histamine release [60]. Polyphenols have also been shown to regulate the balance of Th1/Th2 and inhibit the formation of antigen-specific IgE antibodies. Two main mechanisms may be involved in this process. Firstly, polyphenols may affect the allergen-IgE complex formation [61]. Secondly, polyphenols may affect the binding of this complex to its receptors (FceRI) on basophils and mast cells [62]. For instance, the ingestion of tannins extracted from apples has been proven to prevent food allergies, which may be associated with the increased proportion of $\gamma\delta$ TCR T cells in intestinal intraepithelial lymphocytes [63]. EGCG has a strong suppressive effect on the migratory and adhesive abilities of peripheral blood B cells. This suppressive effect is mediated by the binding of EGCG to CD11b on B cells, and the consequent suppression of B-cell extravasation to the extravascular space. Because of the important role played by B cells in humoral immunity, EGCG is a promising drug for the prevention and/or treatment of skin allergic diseases [64]. Overall, polyphenols hold promise as anti-allergy agents capable of influencing multiple biological pathways and immune cell functions involved in the allergic immune response, and thus deserve further investigation.

2.4. Antimicrobial Activity of Polyphenols

Antibiotic therapy has been a fundamental treatment for skin diseases for many years; however, the adverse reactions caused by medications end up making the treatment unpleasant, in addition to cases of decreased sensitivity to antibiotics. Natural products are becoming increasingly common in dermatology due to the increased resistance of bacteria to synthetic antibiotics and the active principle of medicinal plants becoming new options as antiseptics and antimicrobials. It is believed that flavonoids, such as caffeic acid (CA), benzoic acid, and cinnamic acid, appear to act on the membrane or cell wall of the microorganism, causing functional and structural destruction [65]. Natural polyphenols can play dynamic roles as antimicrobials against bacteria, fungi, and viruses. Pomegranate, a kind of fruit from the Persian region, is rich in polyphenols of varying content during different stages of maturation. Due to its characteristics, pomegranate has medicinal purposes and is used to treat strep throat, hoarseness, and fever, and also has antiviral and antiseptic uses. Pomegranate polyphenols revealed antimicrobial activity when assayed against *Pseudomonas aeruginosa*, *Escherichia coli*, *Candida albicans*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Cryptococcus neoformans*, *Mycobacterium intracellulare*, and *Aspergillus*

fumigatus [66]. *Micrococcus luteus* is a kind of non-pathogenic skin commensal bacterium, although it can act as an opportunistic pathogen and cause serious infections, especially for patients with catheters and comorbidities. Pomegranate polyphenols showed antimicrobial activity against *M. luteus* via inhibition of biofilm formation. Grape seed polyphenols have shown effective antimicrobial properties and were efficiently used against Gram-positive bacteria (*Bacillus cereus*, *Staphylococcus aureus*, *Bacillus coagulans*, and *Bacillus subtilis*), but they were more effective against Gram-negative bacteria, such as *P. aeruginosa* or *E. coli* [67]. *Schinus terebinthifolius* Raddi was found to enhance microbial inhibition against the tested strains, especially against Gram-negative bacteria [68]. Its potential use as an alternative to overcome bacterial resistance can be expected. Phlorotannins, polyphenols extracted from brown seaweeds, are recognized for their antimicrobial biological capacity. Phlorotannins were more effective against Gram-positive bacteria, with *Staphylococcus epidermidis* being the most susceptible species [69]. Resveratrol has been shown to inhibit 80% of the growth of dermatophytes of *Trichophyton mentagrophytes*, in particular, and was demonstrated to be an apoptosis inducer in the human pathogenic fungus *C. albicans* by activating metacaspase and promoting cytochrome c release [70]. Pro-anthocyanidins are common natural polyphenols, which were shown to reduce the adherence properties of *C. albicans* by attenuating the inflammatory response and interfering with NF- κ B and p65 activation and the phosphorylation of specific signal intracellular kinases [71]. Although the underlying molecular mechanisms of the antimicrobial properties of polyphenols remain poorly understood, existing research results may turn many polyphenols into potent and novel pharmacological alternatives for the treatment of a wide range of microbial infections.

2.5. Polyphenols as Anticancer Agents for Skin

Chemotherapy, immunotherapy, radiotherapy, and targeted therapy are included in the current management of metastatic and/or non-metastatic skin cancer. The above methods are highly toxic, expensive, and, in some cases, ineffective due to the development of resistance, especially in metastatic cancer [72]. Thus, it is important to propose new effective therapeutic strategies or drugs which are more affordable and safer. Accumulating evidence from the last decade indicates that promising anticancer natural compounds, such as EGCG, resveratrol, and curcumin, among others, may be extracted from plants [73–76]. Polyphenols may exert these anticancer effects via a variety of mechanisms, including removal of carcinogenic agents, modulation of cancer cell signaling and cell cycle progression, promotion of apoptosis, and modulation of enzymatic activities. Tea polyphenols are abundant in green tea leaves, accounting for ca. 30% of dry leaf weight, and are also collectively referred to as catechins. The biological bioactivities of tea polyphenols, with EGCG as the primary contributor, have been well documented and include anticancer effects and reduced risk of degenerative diseases. Tea polyphenols can reduce UV-induced mouse skin carcinogenesis in terms of tumor incidence and multiplicity [77]. Tea polyphenols provided protection against 7,12-dimethyl benz(a)anthracene-induced mouse skin tumorigenesis. A population-based case-control study indicated that strong (hot) black tea had independent potentially protective effects against skin squamous cell carcinoma [78]. Pre-clinical trials have examined the anticancer properties of resveratrol in skin [79]. The underlying anticancer mechanisms of resveratrol have been shown to be due to the induction of apoptosis, antioxidant systems, amelioration of inflammation, and cell cycle suppression in mouse skin carcinogenesis models [80–82]. Curcumin extracted from *Curcuma longa* L. was also indicated to have anticancer biological activities [83].

Several signaling pathways are involved in the mechanism of polyphenols against skin cancer metastasis, including NF- κ B, epidermal growth factor receptor/mitogen activated protein kinase (EGFR/MAPK), and phosphatidylinositide 3- kinases/protein kinase B (PI3K/Akt) [83,84]. Carnosic acid has been shown to play an important protective role against melanoma. This secondary metabolite inhibited the adhesion and proliferation of B16F10 melanoma cells in a dose-dependent manner via inhibition of the expression of cell migration markers (uPA, MMP-9, VCAM-1, and TIMP-1) and phosphorylation of signaling

molecules (FAK, Sr, and Akt) [85]. A series of studies have demonstrated that various polyphenol-rich fruits and vegetables are particularly effective in protecting against colon cancer development. In general, the anticancer effects of polyphenols are a comprehensive reflection of their anti-inflammatory and antioxidant properties, as well as other effects (Figure 2).

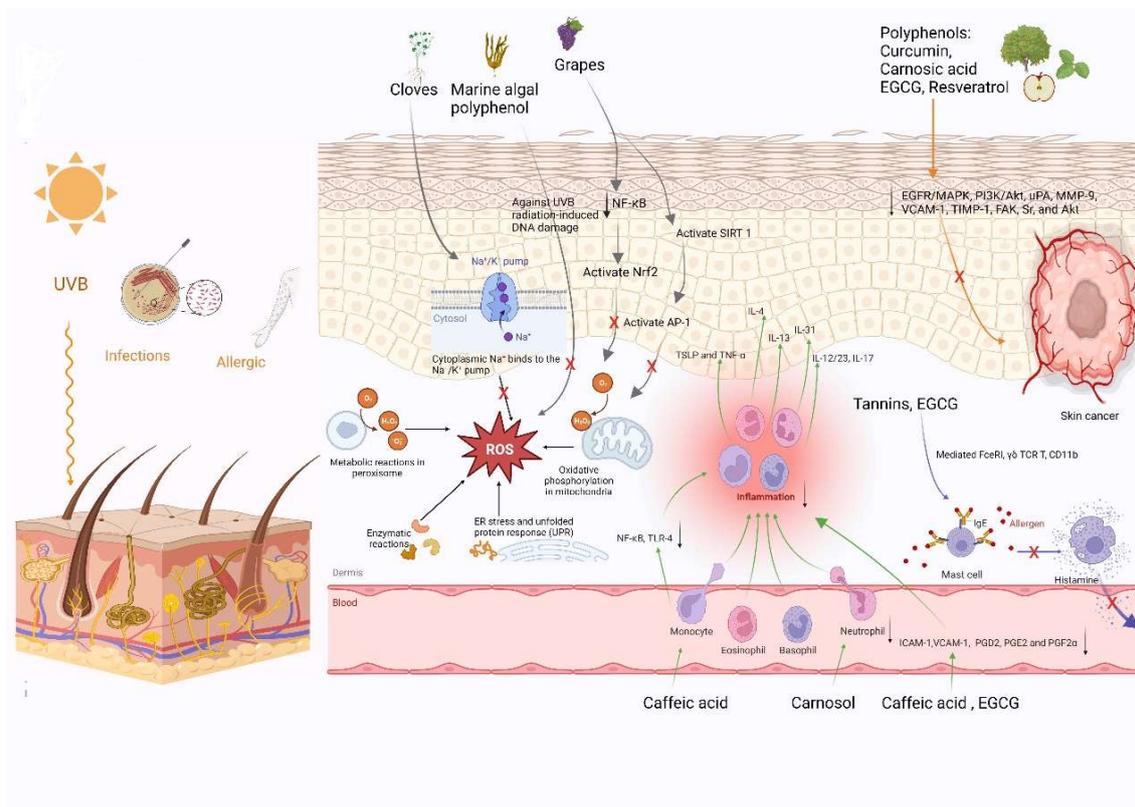


Figure 2. Overview of different mechanisms of several natural polyphenols on skin health.

3. Roles of Polyphenols in Hair Health

3.1. Effects of Polyphenols on Hair Growth

Alopecia is characterized by the loss of some or all hair. Millions of individuals have suffered due to hair loss resulting from a variety of reasons, including the primary genetic cause, social, psychological, and mental stress, local infection, and endocrine disorders. Hair disorders may considerably impact the social and psychological well-being of an individual. Androgenetic alopecia (AGA) and alopecia areata (AA) are the most common types of hair disorder. AGA affects approximately 50% of men and women. AA occurs in 2% of the population. In general, hair loss may affect up to 70% of men and 50% of women at some point in their lifetime [86]. AGA is associated with high 5- α -reductase activity, elevated 5- α -dihydrotestosterone (DHT), and dysregulated transforming growth factor- β (TGF- β) signaling [87]. Identification of lymphocytic infiltrates in AA lesions gave rise to the hypothesis that there is an autoimmune attack on hair follicles (HFs), which is likely a consequence of loss of immune privilege mediated by immune T cells [88].

It was reported that EGCG might be useful in the prevention or treatment of AGA by selectively inhibiting 5- α -reductase activity [89]. EGCG promoted hair growth in hair follicles in ex vivo culture and the proliferation of cultured dermal papilla cells (DPCs). The growth stimulation of DPCs by EGCG in vitro may be mediated through the upregulation of phosphorylated Erk and Akt and by an increase in the ratio of Bcl-2/Bax [90]. Resveratrol and fisetin regulated the genetic expression of cytokines, such as insulin-like growth factor-1 (IGF-1) and keratinocyte growth factor-2 (KGF), which activate the β -catenin pathway,

and TGF- β 1, which plays an important role in maintaining the niche of hair follicle stem cells, and were thus thought to play roles in promoting hair growth. Resveratrol and fisetin induced a shift from telogen to anagen in the hair follicle by inducing proliferation of hair follicle bulge stem cells, thus promoting hair growth [91]. Procyanidin has been found to decrease the expression of protein kinase C (PKC) in hair epithelial cells and stimulate anagen induction [92]. Additionally, it is also posited that procyanidin and flavonoids may counteract TGF- β -induced cell death by inhibiting 5- α -reductase, antioxidant-related mechanisms, and upregulating the expression of anti-apoptotic factors, such as Bcl-xL [92]. Oligomeric procyanidins have also shown remarkable hair growth stimulant effects in vitro and in vivo, being able to promote hair epithelial cell growth and anagen induction of the hair cycle [93]. In particular, procyanidins B2 and B3 show evidence of protective action against apoptosis in hair epithelial cell cultures, thereby restricting catagen induction in the hair cycle [94]. All of the above phenolics are expected to play important roles in the treatment of human AGA and AA (Figure 3).

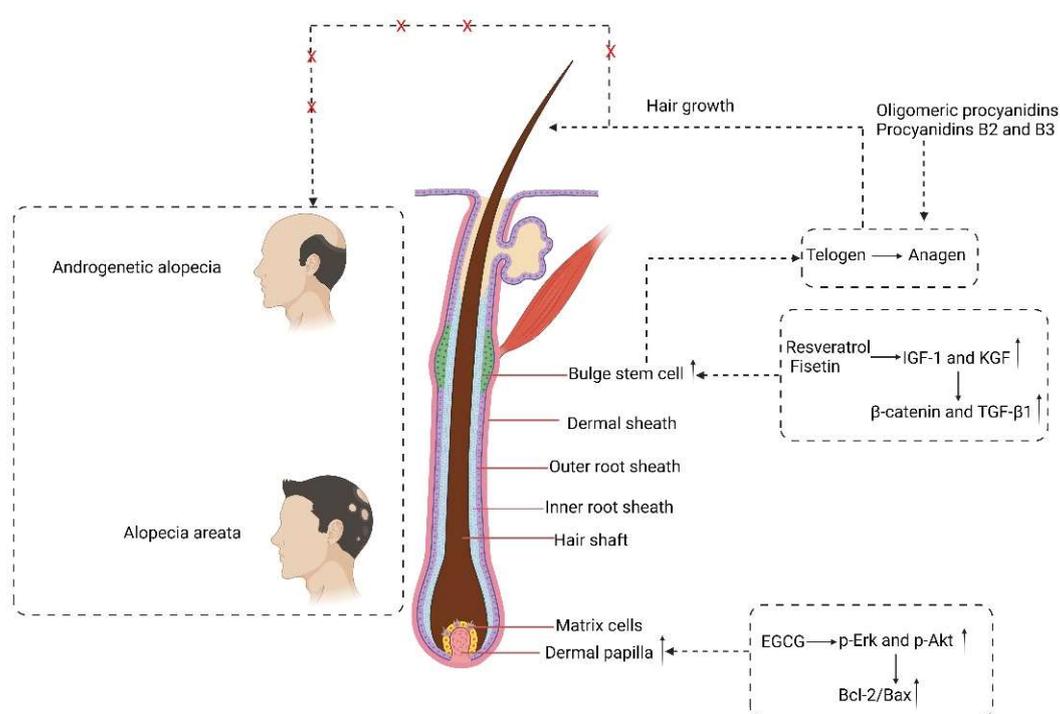


Figure 3. Mechanisms of natural polyphenols in the treatment of human AGA and AA.

3.2. Effects of Polyphenols on Hair Pigmentation

Hair pigmentation is determined by the degree and distribution of melanin in the cortex. Photodamage to hair (photobleaching) may be caused by UVA, UVB, and visible radiation, and the effects of different wavelength ranges vary. UVB and UVA radiation interact negatively with hair proteins, while visible light promotes melanin granule degradation. *Punica granatum L.* hydroalcoholic extract reduced photodamage of hair exposed to UVA radiation [95]. In addition, natural polyphenols, including tannins, present high antioxidant activity and could be used to reduce fading of natural hair color.

Hair dyeing is a common method used to recolor hair. Traditional commercial permanent hair dyeing products usually contain p-phenylenediamine (PPD) or PPD-derived compounds and hydrogen peroxide as key ingredients. These components are reportedly toxic, allergenic, mutagenic, and potentially carcinogenic to people. Recently, a method using metal—phenolic networks (MPNs), such as tannic acid (TA)-based MPNs and gallic acid (GA)-composed MPNs, reportedly dyed natural gray hair without potentially toxic chemicals and protected the dyed hair against repeated shampoo washing [96].

4. Summary and Remaining Problems

Polyphenols are ubiquitously found in plants and therefore consumed in relatively high quantities in the human diet. Polyphenolic extracts are attractive ingredients for pharmaceuticals and cosmetics due to their beneficial and multifunctional biological properties and abundant availability in various dietary sources. However, similar to conventional drugs, natural polyphenols can be toxic if they accumulate beyond acceptable levels in the human body. Moreover, some studies reported polyphenols consumed in whole foods; thus, we do not know whether the results are due to interactions between polyphenols and other ingredients, and further research is needed to focus on the isolated forms of natural polyphenols. Indeed, studies investigating the beneficial effects of polyphenols, and the magnitude of the effects, must consider interfering matrix effects, enzymatic interactions, reactions with other foods, and genetic or gender characteristics [97]. In addition, most of the clinical studies exploring isolated forms of polyphenols were short-term studies; long-term health and adverse effects should be elucidated in future studies [98–100]. The effects of polyphenols on skin and hair are primarily determined by their physicochemical properties. Therefore, it is important to assess the effectiveness of polyphenolic compounds against skin and hair diseases applied systemically and/or topically. Despite the fact that polyphenols are multi-potent compounds that can be used in the treatment of a wide spectrum of diseases, including skin and hair diseases, some properties may limit their efficient use in therapy, such as low water solubility and poor stability. Improving the percutaneous absorption of plant polyphenols is a direction of future research.

Author Contributions: M.S. created the plot of the manuscript and first draft with the help of Y.D., X.C., L.X., Q.D., F.L., P.H., Y.G., M.L. and H.Z. critically edited and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This work was funded by the National Natural Science Foundation of China to Hengguang Zhao (No. 82173440).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The authors want to dedicate this manuscript to the 130th year celebration of The Second Affiliated Hospital of Chongqing Medical University, China. The figures were created using Biorender.com (accessed on 11 October 2022).

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds are not available from the authors.

References

1. Dua, P.; Heiland, M.F.; Kracen, A.C.; Deshields, T.L. Cancer-related hair loss: A selective review of the alopecia research literature. *Psycho-Oncol.* **2017**, *26*, 438–443. [[CrossRef](#)] [[PubMed](#)]
2. Vauzour, D.; Rodriguez-Mateos, A.; Corona, G.; Oruna-Concha, M.J.; Spencer, J.P. Polyphenols and human health: Prevention of disease and mechanisms of action. *Nutrients* **2010**, *2*, 1106–1131. [[CrossRef](#)] [[PubMed](#)]
3. Brimson, J.M.; Prasanth, M.I.; Malar, D.S.; Sharika, R.; Sivamaruthi, B.S.; Kesika, P.; Chaiyasut, C.; Tencomnao, T.; Prasansuklab, A. Role of Herbal Teas in Regulating Cellular Homeostasis and Autophagy and Their Implications in Regulating Overall Health. *Nutrients* **2021**, *13*, 2162. [[CrossRef](#)]
4. Zhang, M.; Wang, R.; Tian, J.; Song, M.; Zhao, R.; Liu, K.; Zhu, F.; Shim, J.H.; Dong, Z.; Lee, M.H. Targeting LIMK1 with luteolin inhibits the growth of lung cancer in vitro and in vivo. *J. Cell. Mol. Med.* **2021**, *25*, 5560–5571. [[CrossRef](#)]
5. Yoo, H.S.; Won, S.B.; Kwon, Y.H. Luteolin Induces Apoptosis and Autophagy in HCT116 Colon Cancer Cells via p53-Dependent Pathway. *Nutr. Cancer* **2022**, *74*, 677–686. [[CrossRef](#)] [[PubMed](#)]
6. Malar, D.S.; Prasanth, M.I.; Brimson, J.M.; Sharika, R.; Sivamaruthi, B.S.; Chaiyasut, C.; Tencomnao, T. Neuroprotective Properties of Green Tea (*Camellia sinensis*) in Parkinson's Disease: A Review. *Molecules* **2020**, *25*, 3926. [[CrossRef](#)] [[PubMed](#)]
7. Piccolo, M.; Ferraro, M.G.; Maione, F.; Maisto, M.; Stornaiuolo, M.; Tenore, G.C.; Santamaria, R.; Irace, C.; Novellino, E. Induction of Hair Keratins Expression by an Annurca Apple-Based Nutraceutical Formulation in Human Follicular Cells. *Nutrients* **2019**, *11*, 3041. [[CrossRef](#)]

8. Sajadimajd, S.; Bahramsoltani, R.; Iranpanah, A.; Kumar Patra, J.; Das, G.; Gouda, S.; Rahimi, R.; Rezaei-amiri, E.; Cao, H.; Giampieri, F.; et al. Advances on Natural Polyphenols as Anticancer Agents for Skin Cancer. *Pharmacol. Res.* **2020**, *151*, 104584. [[CrossRef](#)]
9. Ratz-Łyko, A.; Arct, J.; Majewski, S.; Pytkowska, K. Influence of polyphenols on the physiological processes in the skin. *Phytother. Res.* **2015**, *29*, 509–517. [[CrossRef](#)]
10. Elias, P.M.; Wood, L.C.; Feingold, K.R. Epidermal pathogenesis of inflammatory dermatoses. *Am. J. Contact Dermat.* **1999**, *10*, 119–126.
11. Passali, D.; Spinosi, M.C.; Crisanti, A.; Bellussi, L.M. Mometasone furoate nasal spray: A systematic review. *Multidiscip. Respir. Med.* **2016**, *11*, 18. [[CrossRef](#)] [[PubMed](#)]
12. Michalak-Stoma, A.; Pietrzak, A.; Szepietowski, J.C.; Zalewska-Janowska, A.; Paszkowski, T.; Chodorowska, G. Cytokine network in psoriasis revisited. *Eur. Cytokine Netw.* **2011**, *22*, 160–168. [[CrossRef](#)] [[PubMed](#)]
13. van de Kerkhof, P.C.; Griffiths, C.E.; Reich, K.; Leonardi, C.L.; Blauvelt, A.; Tsai, T.F.; Gong, Y.; Huang, J.; Papavassilis, C.; Fox, T. Secukinumab long-term safety experience: A pooled analysis of 10 phase II and III clinical studies in patients with moderate to severe plaque psoriasis. *J. Am. Acad. Dermatol.* **2016**, *75*, 83–98.e84. [[CrossRef](#)] [[PubMed](#)]
14. Strober, B.; Leonardi, C.; Papp, K.A.; Mrowietz, U.; Ohtsuki, M.; Bissonnette, R.; Ferris, L.K.; Paul, C.; Lebwohl, M.; Braun, D.K.; et al. Short- and long-term safety outcomes with ixekizumab from 7 clinical trials in psoriasis: Etanercept comparisons and integrated data. *J. Am. Acad. Dermatol.* **2017**, *76*, 432–440.e417. [[CrossRef](#)] [[PubMed](#)]
15. Farahnik, B.; Beroukhi, K.; Abrouk, M.; Nakamura, M.; Zhu, T.H.; Singh, R.; Lee, K.; Bhutani, T.; Koo, J. Brodalumab for the Treatment of Psoriasis: A Review of Phase III Trials. *Dermatol. Ther.* **2016**, *6*, 111–124. [[CrossRef](#)]
16. Targan, S.R.; Feagan, B.; Vermeire, S.; Panaccione, R.; Melmed, G.Y.; Landers, C.; Li, D.; Russell, C.; Newmark, R.; Zhang, N.; et al. A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of Brodalumab in Patients with Moderate-to-Severe Crohn's Disease. *Am. J. Gastroenterol.* **2016**, *111*, 1599–1607. [[CrossRef](#)]
17. Bucio-Noble, D.; Kautto, L.; Krisp, C.; Ball, M.S.; Molloy, M.P. Polyphenol extracts from dried sugarcane inhibit inflammatory mediators in an in vitro colon cancer model. *J. Proteom.* **2018**, *177*, 1–10. [[CrossRef](#)]
18. Jantan, I.; Ahmad, W.; Bukhari, S.N. Plant-derived immunomodulators: An insight on their preclinical evaluation and clinical trials. *Front. Plant Sci.* **2015**, *6*, 655. [[CrossRef](#)]
19. Middleton, E., Jr. Effect of plant flavonoids on immune and inflammatory cell function. *Adv. Exp. Med. Biol.* **1998**, *439*, 175–182. [[CrossRef](#)]
20. Wei, B.L.; Weng, J.R.; Chiu, P.H.; Hung, C.F.; Wang, J.P.; Lin, C.N. Antiinflammatory flavonoids from *Artocarpus heterophyllus* and *Artocarpus communis*. *J. Agric. Food Chem.* **2005**, *53*, 3867–3871. [[CrossRef](#)]
21. Rengasamy, K.R.R.; Khan, H.; Gowrishankar, S.; Lagoa, R.J.L.; Mahomoodally, F.M.; Khan, Z.; Suroowan, S.; Tewari, D.; Zengin, G.; Hassan, S.T.S.; et al. The role of flavonoids in autoimmune diseases: Therapeutic updates. *Pharmacol. Ther.* **2019**, *194*, 107–131. [[CrossRef](#)] [[PubMed](#)]
22. Wen, S.; Zhang, J.; Yang, B.; Elias, P.M.; Man, M.Q. Role of Resveratrol in Regulating Cutaneous Functions. *Evid.-Based Complement. Altern. Med.* **2020**, *2020*, 2416837. [[CrossRef](#)] [[PubMed](#)]
23. Karasawa, K.; Uzuhashi, Y.; Hirota, M.; Otani, H. A matured fruit extract of date palm tree (*Phoenix dactylifera* L.) stimulates the cellular immune system in mice. *J. Agric. Food Chem.* **2011**, *59*, 11287–11293. [[CrossRef](#)] [[PubMed](#)]
24. Katiyar, S.K.; Matsui, M.S.; Elmets, C.A.; Mukhtar, H. Polyphenolic antioxidant (-)-epigallocatechin-3-gallate from green tea reduces UVB-induced inflammatory responses and infiltration of leukocytes in human skin. *Photochem. Photobiol.* **1999**, *69*, 148–153. [[CrossRef](#)]
25. Speciale, A.; Chirafisi, J.; Saija, A.; Cimino, F. Nutritional antioxidants and adaptive cell responses: An update. *Curr. Mol. Med.* **2011**, *11*, 770–789. [[CrossRef](#)]
26. Biasutto, L.; Mattarei, A.; Zoratti, M. Resveratrol and health: The starting point. *ChemBiochem* **2012**, *13*, 1256–1259. [[CrossRef](#)]
27. Marchiani, A.; Rozzo, C.; Fadda, A.; Delogu, G.; Ruzza, P. Curcumin and curcumin-like molecules: From spice to drugs. *Curr. Med. Chem.* **2014**, *21*, 204–222. [[CrossRef](#)]
28. Noorafshan, A.; Ashkani-Esfahani, S. A review of therapeutic effects of curcumin. *Curr. Pharm. Des.* **2013**, *19*, 2032–2046.
29. Akyol, S.; Ozturk, G.; Ginis, Z.; Armutcu, F.; Yigitoglu, M.R.; Akyol, O. In vivo and in vitro antineoplastic actions of caffeic acid phenethyl ester (CAPE): Therapeutic perspectives. *Nutr. Cancer* **2013**, *65*, 515–526. [[CrossRef](#)]
30. Szczurko, O.; Shear, N.; Taddio, A.; Boon, H. Ginkgo biloba for the treatment of vitiligo vulgaris: An open label pilot clinical trial. *BMC Complement. Altern. Med.* **2011**, *11*, 21. [[CrossRef](#)]
31. Qaadan, F.; Nahrstedt, A.; Schmidt, M.; Mansoor, K. Polyphenols from Ginkgo biloba. *Sci. Pharm.* **2010**, *78*, 897–907. [[CrossRef](#)] [[PubMed](#)]
32. Lim, S.J.; Kim, M.; Randy, A.; Nam, E.J.; Nho, C.W. Effects of *Hovenia dulcis* Thunb. extract and methyl vanillate on atopic dermatitis-like skin lesions and TNF- α /IFN- γ -induced chemokines production in HaCaT cells. *J. Pharm. Pharmacol.* **2016**, *68*, 1465–1479. [[CrossRef](#)]
33. Boos, A.C.; Hagl, B.; Schlesinger, A.; Halm, B.E.; Ballenberger, N.; Pinarci, M.; Heinz, V.; Kreilinger, D.; Spielberger, B.D.; Schimke-Marques, L.F.; et al. Atopic dermatitis, STAT3- and DOCK8-hyper-IgE syndromes differ in IgE-based sensitization pattern. *Allergy* **2014**, *69*, 943–953. [[CrossRef](#)]

34. Lee, D.Y.; Hwang, C.J.; Choi, J.Y.; Park, M.H.; Song, M.J.; Oh, K.W.; Son, D.J.; Lee, S.H.; Han, S.B.; Hong, J.T. Inhibitory Effect of Carnosol on Phthalic Anhydride-Induced Atopic Dermatitis via Inhibition of STAT3. *Biomol. Ther.* **2017**, *25*, 535–544. [[CrossRef](#)]
35. D'Antuono, I.; Carola, A.; Sena, L.M.; Linsalata, V.; Cardinali, A.; Logrieco, A.F.; Colucci, M.G.; Apone, F. Artichoke Polyphenols Produce Skin Anti-Age Effects by Improving Endothelial Cell Integrity and Functionality. *Molecules* **2018**, *23*, 2729. [[CrossRef](#)] [[PubMed](#)]
36. Natarajan, V.T.; Ganju, P.; Ramkumar, A.; Grover, R.; Gokhale, R.S. Multifaceted pathways protect human skin from UV radiation. *Nat. Chem. Biol.* **2014**, *10*, 542–551. [[CrossRef](#)] [[PubMed](#)]
37. Makrantonaki, E.; Zouboulis, C.C. Androgens and ageing of the skin. *Curr. Opin. Endocrinol. Diabetes Obes.* **2009**, *16*, 240–245. [[CrossRef](#)]
38. Fraga, C.G.; Galleano, M.; Verstraeten, S.V.; Oteiza, P.I. Basic biochemical mechanisms behind the health benefits of polyphenols. *Mol. Asp. Med.* **2010**, *31*, 435–445. [[CrossRef](#)]
39. Matsumura, Y.; Ananthaswamy, H.N. Toxic effects of ultraviolet radiation on the skin. *Toxicol. Appl. Pharmacol.* **2004**, *195*, 298–308. [[CrossRef](#)] [[PubMed](#)]
40. Yin, L.; Morita, A.; Tsuji, T. Alterations of extracellular matrix induced by tobacco smoke extract. *Arch. Dermatol. Res.* **2000**, *292*, 188–194. [[CrossRef](#)]
41. Kondo, S. The roles of cytokines in photoaging. *J. Dermatol. Sci.* **2000**, *23* (Suppl. 1), S30–S36. [[CrossRef](#)]
42. Pallela, R.; Na-Young, Y.; Kim, S.K. Anti-photoaging and photoprotective compounds derived from marine organisms. *Mar. Drugs* **2010**, *8*, 1189–1202. [[CrossRef](#)] [[PubMed](#)]
43. Heo, S.J.; Ko, S.C.; Cha, S.H.; Kang, D.H.; Park, H.S.; Choi, Y.U.; Kim, D.; Jung, W.K.; Jeon, Y.J. Effect of phlorotannins isolated from *Ecklonia cava* on melanogenesis and their protective effect against photo-oxidative stress induced by UV-B radiation. *Toxicol. In Vitro* **2009**, *23*, 1123–1130. [[CrossRef](#)] [[PubMed](#)]
44. Gao, X.; Luo, F.; Zhao, H. Cloves Regulate Na(+)-K(+)-ATPase to Exert Antioxidant Effect and Inhibit UVB Light-Induced Skin Damage in Mice. *Oxidative Med. Cell. Longev.* **2021**, *2021*, 5197919. [[CrossRef](#)]
45. Lephart, E.D. Resveratrol, 4' Acetoxy Resveratrol, R-equol, Racemic Equol or S-equol as Cosmeceuticals to Improve Dermal Health. *Int. J. Mol. Sci.* **2017**, *18*, 1193. [[CrossRef](#)]
46. Ratz-Łyko, A.; Arct, J. Resveratrol as an active ingredient for cosmetic and dermatological applications: A review. *J. Cosmet. Laser Ther.* **2019**, *21*, 84–90. [[CrossRef](#)]
47. Liu, T.; Li, N.; Yan, Y.Q.; Liu, Y.; Xiong, K.; Liu, Y.; Xia, Q.M.; Zhang, H.; Liu, Z.D. Recent advances in the anti-aging effects of phytoestrogens on collagen, water content, and oxidative stress. *Phytother. Res.* **2020**, *34*, 435–447. [[CrossRef](#)]
48. Lephart, E.D.; Acerson, M.J.; Andrus, M.B. Synthesis and skin gene analysis of 4'-acetoxy-resveratrol (4AR), therapeutic potential for dermal applications. *Bioorganic Med. Chem. Lett.* **2016**, *26*, 3258–3262. [[CrossRef](#)]
49. Gopaul, R.; Knaggs, H.E.; Lephart, E.D. Biochemical investigation and gene analysis of equol: A plant and soy-derived isoflavonoid with antiaging and antioxidant properties with potential human skin applications. *BioFactors* **2012**, *38*, 44–52. [[CrossRef](#)]
50. Lephart, E.D. Skin aging and oxidative stress: Equol's anti-aging effects via biochemical and molecular mechanisms. *Ageing Res. Rev.* **2016**, *31*, 36–54. [[CrossRef](#)]
51. Lephart, E.D. Protective effects of equol and their polyphenolic isomers against dermal aging: Microarray/protein evidence with clinical implications and unique delivery into human skin. *Pharm. Biol.* **2013**, *51*, 1393–1400. [[CrossRef](#)] [[PubMed](#)]
52. Yoshikata, R.; Myint, K.Z.Y.; Ohta, H.; Ishigaki, Y. Effects of an equol-containing supplement on advanced glycation end products, visceral fat and climacteric symptoms in postmenopausal women: A randomized controlled trial. *PLoS ONE* **2021**, *16*, e0257332. [[CrossRef](#)] [[PubMed](#)]
53. Divya, S.P.; Wang, X.; Pratheeshkumar, P.; Son, Y.O.; Roy, R.V.; Kim, D.; Dai, J.; Hitron, J.A.; Wang, L.; Asha, P.; et al. Blackberry extract inhibits UVB-induced oxidative damage and inflammation through MAP kinases and NF-κB signaling pathways in SKH-1 mice skin. *Toxicol. Appl. Pharmacol.* **2015**, *284*, 92–99. [[CrossRef](#)]
54. Hwang, E.; Lin, P.; Ngo, H.T.T.; Yi, T.H. Clove attenuates UVB-induced photodamage and repairs skin barrier function in hairless mice. *Food Funct.* **2018**, *9*, 4936–4947. [[CrossRef](#)]
55. Verma, A.; Kushwaha, H.N.; Srivastava, A.K.; Srivastava, S.; Jamal, N.; Srivastava, K.; Ray, R.S. Piperine attenuates UV-R induced cell damage in human keratinocytes via NF-κB, Bax/Bcl-2 pathway: An application for photoprotection. *J. Photochem. Photobiology. B Biol.* **2017**, *172*, 139–148. [[CrossRef](#)]
56. Hernandez, D.F.; Cervantes, E.L.; Luna-Vital, D.A.; Mojica, L. Food-derived bioactive compounds with anti-aging potential for nutricosmetic and cosmeceutical products. *Crit. Rev. Food Sci. Nutr.* **2021**, *61*, 3740–3755. [[CrossRef](#)]
57. Strózek, J.; Samoliński, B.K.; Kłak, A.; Gawińska-Drużba, E.; Izdebski, R.; Krzych-Fałta, E.; Raciborski, F. The indirect costs of allergic diseases. *Int. J. Occup. Med. Environ. Health* **2019**, *32*, 281–290. [[CrossRef](#)]
58. Canonica, G.W.; Cox, L.; Pawankar, R.; Baena-Cagnani, C.E.; Blaiss, M.; Bonini, S.; Bousquet, J.; Calderón, M.; Compalati, E.; Durham, S.R.; et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ. J.* **2014**, *7*, 6. [[CrossRef](#)] [[PubMed](#)]
59. Ding, S.; Jiang, H.; Fang, J. Regulation of Immune Function by Polyphenols. *J. Immunol. Res.* **2018**, *2018*, 1264074. [[CrossRef](#)]
60. Di Meo, F.; Lemaury, V.; Cornil, J.; Lazzaroni, R.; Duroux, J.L.; Olivier, Y.; Trouillas, P. Free radical scavenging by natural polyphenols: Atom versus electron transfer. *J. Phys. Chem. A* **2013**, *117*, 2082–2092. [[CrossRef](#)]

61. Persia, F.A.; Mariani, M.L.; Fogal, T.H.; Penissi, A.B. Hydroxytyrosol and oleuropein of olive oil inhibit mast cell degranulation induced by immune and non-immune pathways. *Phytomedicine* **2014**, *21*, 1400–1405. [[CrossRef](#)]
62. Choi, Y.H.; Yan, G.H. Silibinin attenuates mast cell-mediated anaphylaxis-like reactions. *Biol. Pharm. Bull.* **2009**, *32*, 868–875. [[CrossRef](#)]
63. Sato, Y.; Akiyama, H.; Matsuoka, H.; Sakata, K.; Nakamura, R.; Ishikawa, S.; Inakuma, T.; Totsuka, M.; Sugita-Konishi, Y.; Ebisawa, M.; et al. Dietary carotenoids inhibit oral sensitization and the development of food allergy. *J. Agric. Food Chem.* **2010**, *58*, 7180–7186. [[CrossRef](#)] [[PubMed](#)]
64. Kawai, K.; Tsuno, N.H.; Kitayama, J.; Sunami, E.; Takahashi, K.; Nagawa, H. Catechin inhibits adhesion and migration of peripheral blood B cells by blocking CD11b. *Immunopharmacol. Immunotoxicol.* **2011**, *33*, 391–397. [[CrossRef](#)] [[PubMed](#)]
65. Carolina Oliveira Dos Santos, L.; Spagnol, C.M.; Guillot, A.J.; Melero, A.; Corrêa, M.A. Caffeic acid skin absorption: Delivery of microparticles to hair follicles. *Saudi Pharm. J.* **2019**, *27*, 791–797. [[CrossRef](#)] [[PubMed](#)]
66. Reddy, M.K.; Gupta, S.K.; Jacob, M.R.; Khan, S.I.; Ferreira, D. Antioxidant, antimalarial and antimicrobial activities of tannin-rich fractions, ellagitannins and phenolic acids from *Punica granatum* L. *Planta Med.* **2007**, *73*, 461–467. [[CrossRef](#)]
67. Mayer, R.; Stecher, G.; Wuerzner, R.; Silva, R.C.; Sultana, T.; Trojer, L.; Feuerstein, I.; Krieg, C.; Abel, G.; Popp, M.; et al. Proanthocyanidins: Target compounds as antibacterial agents. *J. Agric. Food Chem.* **2008**, *56*, 6959–6966. [[CrossRef](#)]
68. Celiksoy, V.; Moses, R.L.; Sloan, A.J.; Moseley, R.; Heard, C.M. Synergistic In Vitro Antimicrobial Activity of Pomegranate Rind Extract and Zinc (II) against *Micrococcus luteus* under Planktonic and Biofilm Conditions. *Pharmaceutics* **2021**, *13*, 851. [[CrossRef](#)]
69. Lopes, G.; Sousa, C.; Silva, L.R.; Pinto, E.; Andrade, P.B.; Bernardo, J.; Mouga, T.; Valentão, P. Can phlorotannins purified extracts constitute a novel pharmacological alternative for microbial infections with associated inflammatory conditions? *PLoS ONE* **2012**, *7*, e31145. [[CrossRef](#)]
70. Jung, H.J.; Hwang, I.A.; Sung, W.S.; Kang, H.; Kang, B.S.; Seu, Y.B.; Lee, D.G. Fungicidal effect of resveratrol on human infectious fungi. *Arch. Pharmacol. Res.* **2005**, *28*, 557–560. [[CrossRef](#)]
71. Simonetti, G.; Brasili, E.; Pasqua, G. Antifungal Activity of Phenolic and Polyphenolic Compounds from Different Matrices of *Vitis vinifera* L. against Human Pathogens. *Molecules* **2020**, *25*, 3748. [[CrossRef](#)] [[PubMed](#)]
72. Simões, M.C.F.; Sousa, J.J.S.; Pais, A. Skin cancer and new treatment perspectives: A review. *Cancer Lett.* **2015**, *357*, 8–42. [[CrossRef](#)] [[PubMed](#)]
73. Curti, V.; Di Lorenzo, A.; Dacrema, M.; Xiao, J.; Nabavi, S.M.; Daglia, M. In vitro polyphenol effects on apoptosis: An update of literature data. *Semin. Cancer Biol.* **2017**, *46*, 119–131. [[CrossRef](#)] [[PubMed](#)]
74. Shi, J.; Liu, F.; Zhang, W.; Liu, X.; Lin, B.; Tang, X. Epigallocatechin-3-gallate inhibits nicotine-induced migration and invasion by the suppression of angiogenesis and epithelial-mesenchymal transition in non-small cell lung cancer cells. *Oncol. Rep.* **2015**, *33*, 2972–2980. [[CrossRef](#)] [[PubMed](#)]
75. Xiao, J. Dietary flavonoid aglycones and their glycosides: Which show better biological significance? *Crit. Rev. Food Sci. Nutr.* **2017**, *57*, 1874–1905. [[CrossRef](#)]
76. Khan, H.; Reale, M.; Ullah, H.; Sureda, A.; Tejada, S.; Wang, Y.; Zhang, Z.J.; Xiao, J. Anti-cancer effects of polyphenols via targeting p53 signaling pathway: Updates and future directions. *Biotechnol. Adv.* **2020**, *38*, 107385. [[CrossRef](#)]
77. Kalra, N.; Prasad, S.; Shukla, Y. Antioxidant potential of black tea against 7,12-dimethylbenz(a)anthracene- induced oxidative stress in Swiss albino mice. *J. Environ. Pathol. Toxicol. Oncol.* **2005**, *24*, 105–114. [[CrossRef](#)]
78. Hakim, I.A.; Harris, R.B. Joint effects of citrus peel use and black tea intake on the risk of squamous cell carcinoma of the skin. *BMC Dermatol.* **2001**, *1*, 3. [[CrossRef](#)]
79. Bishayee, A. Cancer prevention and treatment with resveratrol: From rodent studies to clinical trials. *Cancer Prev. Res.* **2009**, *2*, 409–418. [[CrossRef](#)]
80. Afaq, F.; Adhami, V.M.; Ahmad, N. Prevention of short-term ultraviolet B radiation-mediated damages by resveratrol in SKH-1 hairless mice. *Toxicol. Appl. Pharmacol.* **2003**, *186*, 28–37. [[CrossRef](#)]
81. Reagan-Shaw, S.; Afaq, F.; Aziz, M.H.; Ahmad, N. Modulations of critical cell cycle regulatory events during chemoprevention of ultraviolet B-mediated responses by resveratrol in SKH-1 hairless mouse skin. *Oncogene* **2004**, *23*, 5151–5160. [[CrossRef](#)] [[PubMed](#)]
82. Aziz, M.H.; Reagan-Shaw, S.; Wu, J.; Longley, B.J.; Ahmad, N. Chemoprevention of skin cancer by grape constituent resveratrol: Relevance to human disease? *FASEB J.* **2005**, *19*, 1193–1195. [[CrossRef](#)] [[PubMed](#)]
83. Kunnumakkara, A.B.; Anand, P.; Aggarwal, B.B. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. *Cancer Lett.* **2008**, *269*, 199–225. [[CrossRef](#)]
84. Balasubramanian, S.; Efimova, T.; Eckert, R.L. Green tea polyphenol stimulates a Ras, MEKK1, MEK3, and p38 cascade to increase activator protein 1 factor-dependent involucrin gene expression in normal human keratinocytes. *J. Biol. Chem.* **2002**, *277*, 1828–1836. [[CrossRef](#)]
85. Park, S.Y.; Song, H.; Sung, M.K.; Kang, Y.H.; Lee, K.W.; Park, J.H. Carnosic acid inhibits the epithelial-mesenchymal transition in B16F10 melanoma cells: A possible mechanism for the inhibition of cell migration. *Int. J. Mol. Sci.* **2014**, *15*, 12698–12713. [[CrossRef](#)] [[PubMed](#)]
86. Aljuffali, I.A.; Sung, C.T.; Shen, F.M.; Huang, C.T.; Fang, J.Y. Squarticles as a lipid nanocarrier for delivering diphencyprone and minoxidil to hair follicles and human dermal papilla cells. *AAPS J.* **2014**, *16*, 140–150. [[CrossRef](#)] [[PubMed](#)]

87. Inui, S.; Fukuzato, Y.; Nakajima, T.; Yoshikawa, K.; Itami, S. Androgen-inducible TGF-beta1 from balding dermal papilla cells inhibits epithelial cell growth: A clue to understand paradoxical effects of androgen on human hair growth. *FASEB J.* **2002**, *16*, 1967–1969. [[CrossRef](#)] [[PubMed](#)]
88. Paus, R.; Bulfone-Paus, S.; Bertolini, M. Hair Follicle Immune Privilege Revisited: The Key to Alopecia Areata Management. *J. Investig. Dermatol. Symp. Proc.* **2018**, *19*, S12–S17. [[CrossRef](#)] [[PubMed](#)]
89. Shen, Y.L.; Li, X.Q.; Pan, R.R.; Yue, W.; Zhang, L.J.; Zhang, H. Medicinal Plants for the Treatment of Hair Loss and the Suggested Mechanisms. *Curr. Pharm. Des.* **2018**, *24*, 3090–3100. [[CrossRef](#)]
90. Kwon, O.S.; Han, J.H.; Yoo, H.G.; Chung, J.H.; Cho, K.H.; Eun, H.C.; Kim, K.H. Human hair growth enhancement in vitro by green tea epigallocatechin-3-gallate (EGCG). *Phytomedicine* **2007**, *14*, 551–555. [[CrossRef](#)]
91. Kubo, C.; Ogawa, M.; Uehara, N.; Katakura, Y. Fisetin Promotes Hair Growth by Augmenting TERT Expression. *Front. Cell Dev. Biol.* **2020**, *8*, 566617. [[CrossRef](#)] [[PubMed](#)]
92. Loing, E.; Lachance, R.; Ollier, V.; Hocquaux, M. A new strategy to modulate alopecia using a combination of two specific and unique ingredients. *J. Cosmet. Sci.* **2013**, *64*, 45–58. [[PubMed](#)]
93. Kamimura, A.; Takahashi, T. Procyanidin B-2, extracted from apples, promotes hair growth: A laboratory study. *Br. J. Dermatol.* **2002**, *146*, 41–51. [[CrossRef](#)] [[PubMed](#)]
94. Kamimura, A.; Takahashi, T.; Morohashi, M.; Takano, Y. Procyanidin oligomers counteract TGF-beta1- and TGF-beta2-induced apoptosis in hair epithelial cells: An insight into their mechanisms. *Ski. Pharmacol. Physiol.* **2006**, *19*, 259–265. [[CrossRef](#)]
95. Dario, M.F.; Pahl, R.; de Castro, J.R.; de Lima, F.S.; Kaneko, T.M.; Pinto, C.A.; Baby, A.R.; Velasco, M.V. Efficacy of *Punica granatum* L. hydroalcoholic extract on properties of dyed hair exposed to UVA radiation. *J. Photochem. Photobiol. B Biol.* **2013**, *120*, 142–147. [[CrossRef](#)] [[PubMed](#)]
96. Geng, H.; Zhuang, L.; Li, M.; Liu, H.; Caruso, F.; Hao, J.; Cui, J. Interfacial Assembly of Metal-Phenolic Networks for Hair Dyeing. *ACS Appl. Mater. Interfaces* **2020**, *12*, 29826–29834. [[CrossRef](#)] [[PubMed](#)]
97. Bertelli, A.; Biagi, M.; Corsini, M.; Baini, G.; Cappellucci, G.; Miraldi, E. Polyphenols: From Theory to Practice. *Foods* **2021**, *10*, 2595. [[CrossRef](#)]
98. Vittala Murthy, N.T.; Paul, S.K.; Chauhan, H.; Singh, S. Polymeric Nanoparticles for Transdermal Delivery of Polyphenols. *Curr. Drug Deliv.* **2022**, *19*, 182–191. [[CrossRef](#)]
99. Cristiano, M.C.; Barone, A.; Mancuso, A.; Torella, D.; Paolino, D. Rutin-Loaded Nanovesicles for Improved Stability and Enhanced Topical Efficacy of Natural Compound. *J. Funct. Biomater.* **2021**, *12*, 74. [[CrossRef](#)]
100. Li, Q.; Duan, M.; Liu, L.; Chen, X.; Fu, Y.; Li, J.; Zhao, T.; McClements, D.J. Impact of Polyphenol Interactions with Titanium Dioxide Nanoparticles on Their Bioavailability and Antioxidant Activity. *J. Agric. Food Chem.* **2021**, *69*, 9661–9670. [[CrossRef](#)]