Clinical, Cosmetic and Investigational Dermatology

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REVIEW

Mechanistic Insights into Flavonoids in Cosmetic Applications: Multifunctional Roles and Formulation Considerations

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Abstract: Flavonoids are plant secondary metabolites commonly found in fruits and seeds, contributing to color, aroma, and taste. They play key roles in growth regulation, pollinator attraction, and stress defense. Structurally characterized by their polyphenolic nature, flavonoids contribute to skin health through multiple mechanisms. These compounds contribute to skin health through well-characterized mechanisms, including inhibition of tyrosinase, scavenging of reactive oxygen species, and modulation of inflammatory signaling pathways such as NF-κB. As a result, flavonoids have demonstrated efficacy in skin whitening, antioxidant defense, anti-inflammatory action, and antimicrobial protection. They also promote skin hydration and elasticity by enhancing epidermal barrier function and stimulating the synthesis of collagen and hyaluronic acid. The multifunctional nature of flavonoids positions them as promising natural alternatives to synthetic cosmetic ingredients, particularly in formulations targeting acne, sensitivity, aging, and pigmentation. Although their cosmetic potential is well supported, challenges such as formulation stability, delivery efficiency, and variation in cutaneous absorption continue to limit their widespread application. This review highlights the diverse applications of flavonoids in cosmetics, underscoring their potential to address key skin concerns while advancing natural product innovation.

Keywords: flavone, function, cosmetic, skin

Introduction

The demand for natural and effective cosmetic ingredients has surged as consumers become increasingly eco-conscious and aware of the potential health risks associated with synthetic compounds.[1] The cosmetics industry, responding to this shift, is prioritizing eco-friendly, sustainable formulations to meet the growing preference for products free of synthetic additives.[2] This trend aligns with broader global efforts to reduce the environmental impact of industrial development by choosing products that support ecological balance.[3]

One important driver of this shift is the increasing prevalence of antibiotic resistance, a public health threat that has been exacerbated by the widespread use of antibiotics in food, healthcare, and animal production. Antibiotic-resistant infections currently account for approximately 700,000 deaths worldwide each year,[4] with projections indicating this number could rise dramatically without alternative antimicrobial solutions. As a result, researchers are actively pursuing plant-derived compounds that exhibit antimicrobial activity, such as flavonoids, which are known for their efficacy, low toxicity, and suitability for various applications, including cosmetics.[5–7] Although several papers have discussed the biological activities of flavonoids, few have focused on their multifunctional applications in cosmetics from a mechanistic perspective. Furthermore, the integration of formulation challenges, such as bioavailability and ingredient interactions, remains underexplored.

Synthetic preservatives, have long been used in cosmetics to prevent microbial growth and extend shelf life.[8] However, studies have raised concerns about parabens' potential to disrupt hormonal balance, cause allergic reactions, and contribute to long-term environmental damage by contaminating water systems.[9] As consumers become more informed about these risks,

https://doi.org/10.2147/CCID.S578826
Received: 3 November 2025
Accepted: 8 January 2026
Published: 7 May 2026

the demand for natural preservatives has grown, positioning flavonoids as an ideal alternative due to their antimicrobial, anti-inflammatory, and antioxidant properties.[10,11]

Contamination of cosmetics by pathogens like Staphylococcus aureus and Pseudomonas aeruginosa can occur at any stage of production or use, potentially leading to adverse health effects such as dermatitis and eye infections.[12,13] Regulations in cosmetic manufacturing emphasize microbial purity, but challenges remain in ensuring contamination-free products.[13] Flavonoids, with their inherent antimicrobial effects, provide a natural solution to enhance the safety and longevity of cosmetic formulations.[14] However, their incorporation into cosmetic formulations remains constrained by challenges such as limited aqueous solubility, instability under oxidative or pH conditions, and variable skin permeability.

The growing use of plant-based antimicrobial agents, including essential oils and plant extracts, reflects an industry-wide shift toward safer, multifunctional ingredients in cosmetics.[14] Essential oils from plants such as tea tree, rosemary, and thyme are recognized not only for their antimicrobial benefits but also for their therapeutic effects, including anti-inflammatory and soothing properties.[15] Polyphenol-rich plant extracts, including those containing flavonoids, have demonstrated notable antimicrobial and antifungal activity, further supporting their use in cosmetics as both preservatives and active skincare ingredients.[16]

Recent advancements in natural preservatives, such as silver nanoparticles and bioactive compounds like methylglyoxal from manuka honey, offer promising potential as effective antimicrobial agents in cosmetics.[17] These innovations highlight a broader trend toward natural solutions that fulfill consumer preferences for safety and environmental responsibility without compromising product efficacy.[18]

Flavonoids are increasingly studied for their therapeutic potential in skincare. However, existing research has yet to fully integrate their mechanistic pathways, formulation challenges, and the comparative activity of different subclasses. This review evaluates current evidence on the biological functions of flavonoids, including their contributions to pigmentation regulation, antioxidant defense, antimicrobial activity, and epidermal barrier support. It also addresses practical challenges such as limited bioavailability, formulation instability, and insufficient clinical data. These issues highlight important gaps in the literature and support continued research aimed at optimizing the cosmetic application of flavonoids through scientifically grounded and sustainable approaches.

Whitening Effect of Flavonoids

Human skin pigmentation is among the most variable and visually apparent traits, yet the genetic foundations and evolutionary pathways of this complex characteristic remain incompletely understood.[19] Existing research strongly indicates that natural selection has played a significant role in shaping the variation of this trait both within and between populations. A clear geographic trend shows that skin pigmentation is closely linked with latitude and the intensity of ultraviolet radiation (UVR).[20] The prevailing evolutionary theory, known as the vitamin D/folate hypothesis, suggests that this variation is a balance between the need for photoprotection and the requirement for vitamin D3 synthesis.[19]

Skin and hair color are primarily determined by the amount and distribution of melanin, while carotenoids and (de) oxyhemoglobin from dermal capillaries play a smaller role in pigmentation.[21] Melanin not only defines pigmentation but also serves as a natural barrier against UV radiation by absorbing harmful rays.[22] However, overproduction of melanin, often due to sun exposure, hormonal changes, or skin damage, can lead to hyperpigmentation.[23] This makes melanin a key target in skin-whitening treatments aimed at evening out skin tone and reducing dark spots.[24] Current research results show that melanin protects the human epidermis from ultraviolet radiation damage, but abnormal synthesis of melanin can lead to freckles, melasma, melanoma and other skin diseases.[25]

The cAMP signaling pathway regulates melanin synthesis by upregulating MITF gene expression,[26] which stimulates tyrosinase production in melanocytes.[27] MITF acts as the master regulator of pigmentation, controlling the expression of tyrosinase and other melanogenic enzymes. UV radiation triggers this pathway via oxidative stress and inflammatory signals, increasing melanin synthesis as a protective response.[28,29] This process can be triggered by various stimuli, such as UV radiation, inflammatory cytokines, and hormonal changes. In cosmetics, many skin-lightening compounds work by inhibiting the activity of the tyrosinase enzyme, which leads to reduced melanin production while exerting minimal harmful effects on melanocytes.[25] Structurally, flavonoids interact directly with tyrosinase through hydrogen bonding, altering its active conformation and obstructing substrate entry. Specific structural features, such as the C2=C3 double bond, enhance their inhibitory activity, while methoxylation and glycosylation can reduce it.[30] For example, flavonoid-rich extracts from Coptis rhizome (pazentin A)[31] and chrysanthemum petals[32] demonstrate significant tyrosinase inhibition and melanin reduction in vitro and in human trials. The magnitude of tyrosinase inhibition varies substantially across flavonoid subclasses and is strongly influenced by hydroxylation patterns, conjugation, and steric features.[30,33] Most supporting evidence is derived from enzyme assays or cell-based models, and direct translation to topical efficacy remains inconsistent because cutaneous penetration and local stability are not uniform across compounds.[33,34]

Flavonoids, as potent antioxidants, combat this process through multiple mechanisms. They neutralize reactive oxygen species (ROS) generated by UV exposure, reducing oxidative stress and inhibiting the downstream activation of the cAMP-MITF pathway. This leads to decreased tyrosinase production and reduced melanin synthesis.[35] Quercetin, one of the most extensively studied flavonoids, has been shown to significantly inhibit tyrosinase activity, leading to a marked reduction in melanin content.[36] In an in vitro study using B16 mouse melanoma cells, quercetin isolated from rose hip inhibited melanogenesis by suppressing intracellular tyrosinase activity and protein expression, without cytotoxicity.[37] In contrast, animal study reported that quercetin stimulated melanogenesis in mouse hair follicle tissues, enhancing melanin production in a concentration-dependent manner. The protein expression of tyrosinase and TRP-2 increased significantly, but their mRNA levels remained unchanged. This suggests that quercetin promotes melanogenesis by increasing the synthesis of key melanogenic proteins.[38] Similarly, inn human melanoma and normal human epidermal melanocytes, quercetin increased melanin production in a time- and dose-dependent manner. Tyrosinase activity was dramatically enhanced, with a 61.8-fold increase, while protein expression rose slightly. The effects involved both transcriptional and translational mechanisms.[39] These findings highlight the complex and dose-dependent effects of quercetin on melanogenesis, which vary between different cell types and experimental conditions.

In HMVII human melanoma cell line, several flavonoids, including kaempferol, rhamnetin, fisetin, apigenin, luteolin, chrysin, and genistein, were shown to enhance tyrosinase activity. These flavonoids stimulate melanogenesis by increasing intracellular tyrosinase activity, thereby promoting melanin production.[40] However, there are contradicting data in the literature. For example, kaempferide, a derivative of kaempferol, was found to inhibit tyrosinase activity,[41] suggesting that certain flavonoids or their derivatives may have differing effects on melanogenesis depending on their chemical structure or concentration.

Flavonoid-rich extracts from plants like Portulaca oleracea and Sanbaixia demonstrate tyrosinase inhibition while also suppressing melanoma cell proliferation, highlighting their potential as safe, natural alternatives to synthetic whitening agents, which are known to cause irritation in some users.[42] Related non-flavonoid polyphenols, including phenolic acids and stilbenes, also act as tyrosinase inhibitors in commonly used screening assays, and some display comparable inhibitory potency under identical conditions.[43–45] Head to head comparisons across compound classes remain limited,[46,47] which restricts robust ranking of flavonoids against other polyphenol families for cosmetic selection.

Beyond melanin regulation, flavonoids stabilize cell membranes by reducing lipid peroxidation, promote skin repair, and maintain collagen integrity, as shown in (Figure 1). These combined antioxidant, anti-inflammatory, and pigmentation-regulating effects underscore flavonoids' potential as safe and effective agents for protecting against UV damage, hyperpigmentation, and premature skin aging.[48,49] Their ability to address multiple skin concerns, including hyperpigmentation, inflammation, and oxidative damage, makes flavonoids invaluable as multifunctional ingredients in modern skincare formulations. These formulation factors should be considered alongside in vitro potency when identifying candidate flavonoids for depigmenting applications.

Antioxidant Effect of Flavonoids

Oxidative stress, along with the damage it causes, can intensify pigmentation and accelerate skin aging, resulting in uneven tone, wrinkles, sagging, dryness, and a rough texture.[62–64] Flavonoids, as potent antioxidants, help reduce oxidative damage by scavenging free radicals and enhancing the activity of antioxidant enzymes (Table 1).[65] In particular, their radical-scavenging ability is linked to their structure, where multiple hydroxyl groups donate electrons to neutralize ROS efficiently.[65] These hydroxyl-rich structures also allow flavonoids to interact directly with reactive oxygen species, neutralizing harmful compounds like peroxyl radicals and superoxide anions.[66] Several studies support that specific hydroxylation patterns in flavonoids contribute to higher radical-neutralizing efficiency, with notable effects against ROS generated by UV

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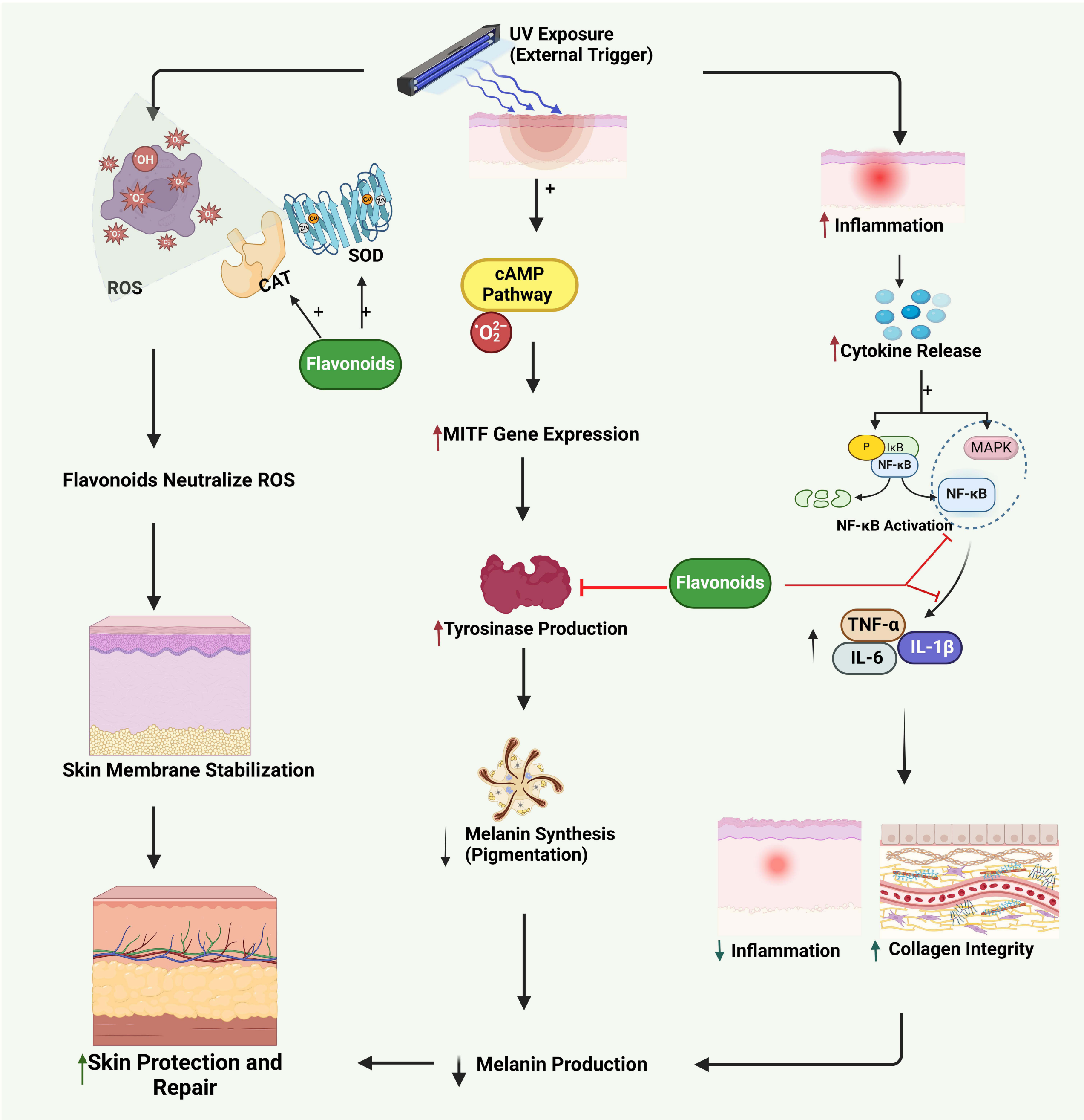

Figure 1 Mechanisms of Flavonoids in Regulating Skin Pigmentation and UV Protection. Flavonoids neutralize ROS and inhibit the cAMP-MITF pathway, reducing melanin synthesis. They also suppress NF-κB activation, reducing cytokine release and preventing collagen degradation, helping to maintain skin integrity. ↑ = increase; ↓= reduce; + = activation; ⊥= Inhibition. Created with Biorender.com.

exposure and pollution.[10] The antioxidant properties of flavonoids help protect against damage from free radicals by neutralizing ROS, activating antioxidant enzymes, inhibiting oxidases like xanthine oxidase (XO), cyclooxygenase (COX), lipoxygenase, and phosphoinositide 3-kinase (PI3K), and reducing α-tocopheryl radicals.[67] Moreover, research indicates that flavonoids can stabilize cell membranes by reducing lipid peroxidation, a crucial factor in maintaining skin integrity and preventing signs of premature aging.[68] This stabilization effect is achieved by decreasing malondialdehyde levels,[69] a byproduct of lipid peroxidation commonly associated with oxidative skin damage.[64,70] Flavonoids also contribute to raising uric acid levels, enhancing metal-chelating capacity, and boosting low-molecular-weight antioxidant activity, thereby mitigating oxidative stress.[67] Antioxidant rankings are highly assay-dependent, and radical scavenging assays do not

Table 1 Comparative Summary of Flavonoids and Their Key Cosmetic Applications, Mechanisms, and Evidence Levels

Flavonoid	Key Cosmetic Function(s)	Mechanistic Target(s)	Evidence Level	References
Quercetin	Tyrosinase inhibition, Anti-inflammatory	Tyrosinase, NF-κB,	High (in vitro, animal, human)	[50, 51]
Luteolin	Anti-inflammatory, Anti-allergy	COX-2, Mast cells, MAPKs, NF-κB	High (in vitro, animal)	[52, 53]
Apigenin	Anti-aging, Anti-inflammatory	p38 MAPK, NF-κB	Moderate (in vitro, animal, human)	[54–56]
Kaempferol	Antioxidant, Anti-inflammatory	NF-κB, ROS	Moderate (in vitro)	[57, 58]
Genistein	Anti-aging, Estrogenic effects	Estrogen receptors, ROS	Moderate (animal, human)	[59]
Rutin	Anti-inflammatory, Collagen synthesis	NF-κB, ROS	Moderate (in vitro, animal, human)	[60]
Licorice Flavonoids	Tyrosinase inhibition, Anti-inflammatory	Tyrosinase, NF-κB	High (in vitro, animal, human)	[61]

Abbreviations: NF-κB, Nuclear Factor Kappa-B; COX-2, Cyclooxygenase-2; MAPK, Mitogen-Activated Protein Kinase; ROS, Reactive Oxygen Species.

necessarily predict efficacy in the stratum corneum or viable epidermis.[71] Differences in skin permeability, partitioning into lipid domains, and formulation microenvironment can substantially alter apparent antioxidant performance after topical application.[72]

Free radicals, such as ROS, are produced through normal metabolic processes but are increased by external factors like UV radiation, pollutants, and toxins.[73] Excessive ROS can lead to lipid peroxidation, protein damage, and DNA mutations, which accelerate skin aging and increase the risk of diseases such as cancer.[74,75] By protecting cell structures from oxidative stress, flavonoids support cellular resilience and integrity.[76] Flavonoids, due to their polyphenolic structure, are effective at neutralizing these harmful radicals and stabilizing cell membranes (Figure 1).[77]

Several flavonoids are used in cosmetic formulations as effective antioxidants to protect the skin against oxidative stress and photo-induced ageing. Quercetin, rutin, hesperidin, and apigenin are among the most extensively investigated flavonoids due to their ability to scavenge reactive oxygen species, inhibit lipid peroxidation, and reduce UV-induced skin damage.[78] Apigenin, a plant-derived flavonoid, exhibits strong antioxidant properties beneficial for cosmetic applications. It effectively scavenges reactive oxygen species (ROS), reduces oxidative stress, and protects skin cells from UV-induced damage. In an in vitro study using human dermal fibroblasts derived from a healthy 31-year-old male, rutin demonstrated significant photoprotective effects against UVA-induced damage. Rutin enhanced cell viability and reduced photo-oxidative stress by lowering intracellular ROS levels. These effects were mediated through activation of the Nrf2 transcriptional pathway, which led to increased reduced glutathione levels, an elevated Bcl-2/Bax ratio, and preservation of mitochondrial respiratory function (Table 1).[79] The findings suggest that rutin exerts cytoprotective and anti-apoptotic effects in UVA-exposed skin cells.

An emerging area of research emphasizes the synergy between flavonoids and other natural antioxidants, such as vitamin C and E, where they can collectively enhance antioxidative effects more effectively than when used in isolation.[80] The reported synergy is context-specific and depends on concentration ratios, pH, and the presence of transition metals or peroxides in the formulation.[81,82] In addition, certain polyphenols can exhibit pro-oxidant behavior under specific experimental conditions, which supports the need for stability testing within the final vehicle rather than reliance on chemical assays alone.[83]

Studies have shown that human diseases, cancer, and skin aging and sensitivity are strongly related to oxidative stress.[64,84] At present, the antioxidant evaluation methods of cosmetics are mainly summarized as scavenging free radical ability, enhancing antioxidant oxidase activity and reducing ROS levels.[67,68] In vitro antioxidant methods mainly include free radical scavenging ability tests, including scavenging oxygen free radicals (ORAC method), scavenging DPPH free radicals (DPPH method), total antioxidant capacity test (ABTS method).[85–87] Cellular methods mainly induce cells to produce ROS models through ultraviolet and ozone, and test cell morphology and survival rate.[88] In addition, ROS and antioxidant enzyme activities were detected to evaluate the antioxidant effect of cancer.[89] At the same time, it can also be evaluated by the relevant indicators of animal post-molding detection. Studies have shown that total polyphenols have good antioxidant activity due to the presence of several phenolic hydroxyl groups.[90] Ji et al[91] used ascorbate (Vc) as a positive control to test the scavenging ·OH and ABTS free radicals and the reducing ability of Fe^{3+} (FRAP) of brown pigment extracted from hazelnut shell.[91] Notably, several studies report that flavonoid-rich extracts achieve radical scavenging activity comparable to standard antioxidants such as vitamin C at matched concentrations, although outcomes vary with extraction method, assay type, and endpoint selection.[92–94] Vitamins C and vitamin E are widely used for their capacity to neutralize free radicals, reduce UV-induced erythema, and support collagen synthesis.[95]

Anti-Inflammatory Effects of Flavonoids

Inflammation is a protective physiological response to external stimuli, including allergens, pollutants, and pathogens, but excessive inflammation, such as in acne and allergic reactions, leads to tissue damage in the skin.[96,97] Macrophages play a central role in inflammation regulation: M1 macrophages secrete pro-inflammatory factors, initiating inflammation,[98] while M2 macrophages release anti-inflammatory factors that support tissue repair.[99]

A common method for evaluating anti-inflammatory efficacy in vitro is the LPS-induced RAW264.7 macrophage model, which measures the reduction of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6.[100,101] With increasing consumer demand, the cosmetics industry is incorporating natural anti-inflammatory compounds, such as flavonoids, into formulations aimed at reducing acne and calming irritated skin. Plant-derived flavonoids have gained attention in recent years for their safety, non-toxicity, and effectiveness in reducing inflammation.[102] Flavonoids exert these effects primarily by inhibiting the NF-κB pathway, a central regulator of inflammatory gene expression. By reducing oxidative stress and pro-inflammatory cytokine release, flavonoids promote a shift toward tissue repair and barrier recovery. For example, flavonoid glycosides from Tilia leaves, including kaempferol-3,7-O-dirhamnoside and quercetin-3,7-O-dirhamnoside, showed significant anti-inflammatory effects in a benzoquinone-induced swelling model.[102,103] Flavonoids also regulate tight junction proteins such as claudins and occludins through activation of the aryl hydrocarbon receptor (AhR) in keratinocytes, strengthening the physical barrier against irritants and preventing water loss.[104]

Beyond cytokine inhibition, flavonoids (eg. Quercetin 3-O-β-D-Glucuronide) influence lipid metabolism, natural moisturizing factor (NMF) production, and tight junction regulation, key processes in restoring skin hydration and integrity.[105] Quercetin is a key natural antioxidant widely applied in cosmetics, nutraceuticals, and pharmaceuticals for its anti-inflammatory and protective properties.[106] Despite its benefits, its low hydrophilicity and limited skin absorption hinder its use in topical formulations.

For instance, studies have shown flavonoids not only reduce inflammation but also promote tissue repair by stimulating lipid synthesis (ceramides and fatty acids) and improving transepidermal water loss (TEWL) (Figure 2).[107,108] Apigenin has demonstrated notable anti-inflammatory activity, making it a valuable compound in cosmetic formulations. It downregulates proinflammatory mediators such as COX-2 and iNOS, and inhibits NF-κB signaling pathways, thereby reducing skin inflammation.[109] These dual effects significantly enhance the skin's capacity to retain moisture, restore its protective barrier, and defend against environmental irritants (Table 1). By simultaneously reducing inflammation and promoting key processes such as barrier repair and hydration, flavonoids emerge as powerful multifunctional agents that support skin resilience, elasticity, and overall health.

Anti-Allergy Effects of Flavonoids

Flavonoids are recognized for their potential in managing skin sensitivity and reducing allergic reactions, making them valuable ingredients in sensitive skincare formulations. Allergic reactions in sensitive skin are often driven by mast cell activation and mediator release, which represents a mechanistic layer distinct from cytokine-dominant inflammatory models.[110] When activated via allergens and IgE, mast cells release histamine, proteases, and chemotactic agents, triggering acute inflammation and driving chronic allergic responses through cytokine production. Overactivation heightens cytokine and chemokine levels, intensifying inflammation and disease.[111]

Skin sensitivity is not classified as a disease but rather as a heightened response to environmental factors, leading to symptoms like dryness, tightness, redness, itching, and tingling.[112–114] These symptoms are often due to structural differences in the skin and increased responsiveness of sensory nerves.

Several factors contribute to skin sensitivity: (1) Impaired skin barrier function, often due to a thinner stratum corneum, which makes the skin more susceptible to irritants. (2) Neurological factors, as increased sensitivity in skin

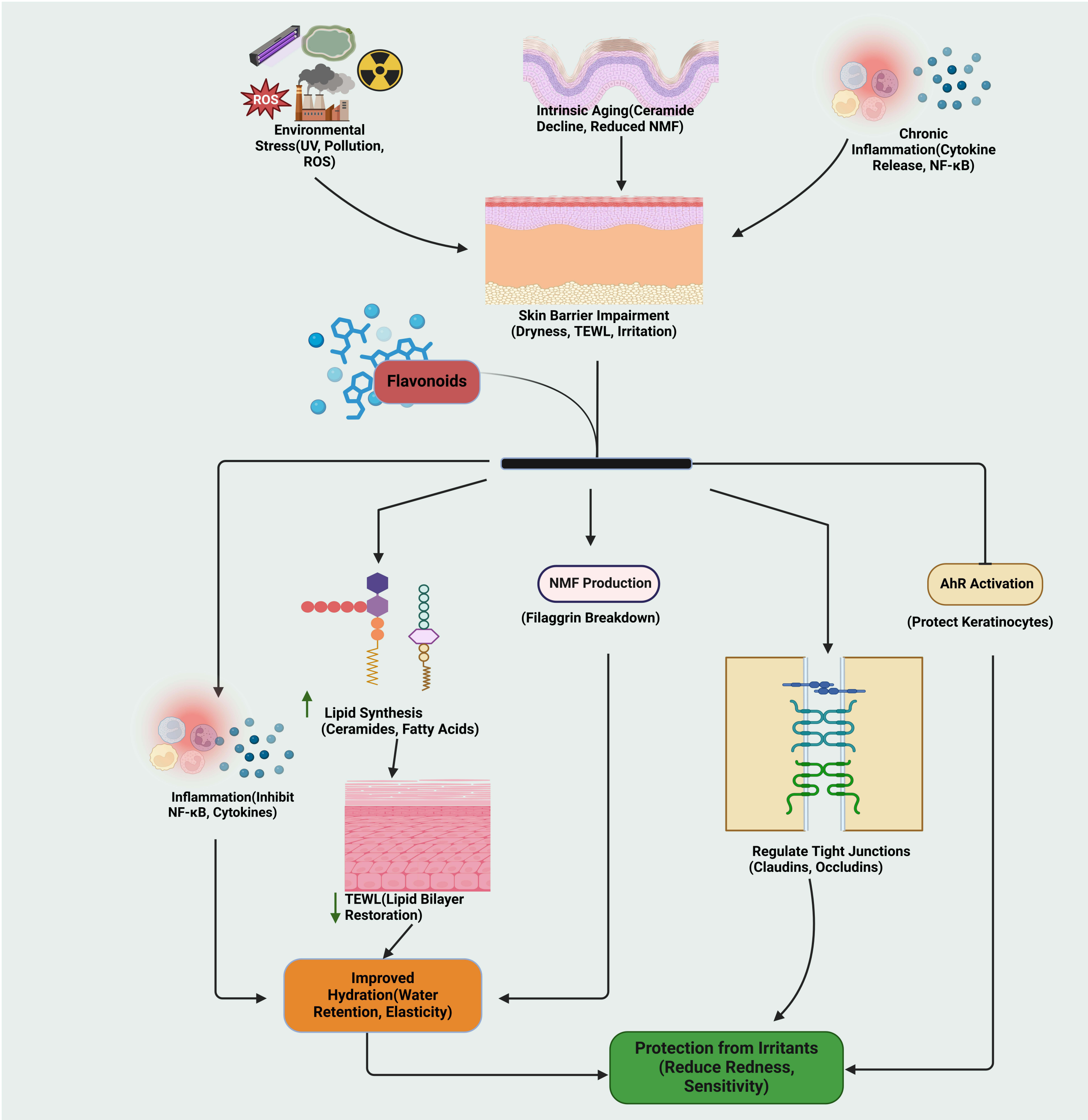

Figure 2 Anti-inflammatory and Barrier Repair Mechanisms oft Flavonoids. Flavonoids inhibit NF-κB and cytokine release, promoting lipid synthesis and restoring the skin barrier. They enhance NMF production and regulate tight junction proteins, improving hydration and reducing irritation. ↑ = increase; ↓ = reduce. Created with Biorender.com.

nerves, is linked to abnormal central and peripheral nerve function. (3) Heightened inflammatory responses, as a weakened barrier makes sensitive skin more vulnerable to inflammation from external allergens.[115,116] Flavonoids strengthen the skin's barrier function and reduce nerve sensitivity, providing comprehensive support for managing sensitive skin (Figure 3).[116,117]

Flavonoids are popular in cosmetics for their anti-allergic properties.[118] Flavonoids like dihydromyricetin (DHM) help mitigate mast cell-mediated allergic inflammation by inhibiting NF-κB activation, reducing cytokine release (TNF-α, IL-6), and suppressing STAT5 phosphorylation and tryptase production.[111] Studies show that flavonoids like quercetin and specific ginseng-derived flavones are effective anti-allergic agents,[118] significantly inhibiting β-hexosaminidase

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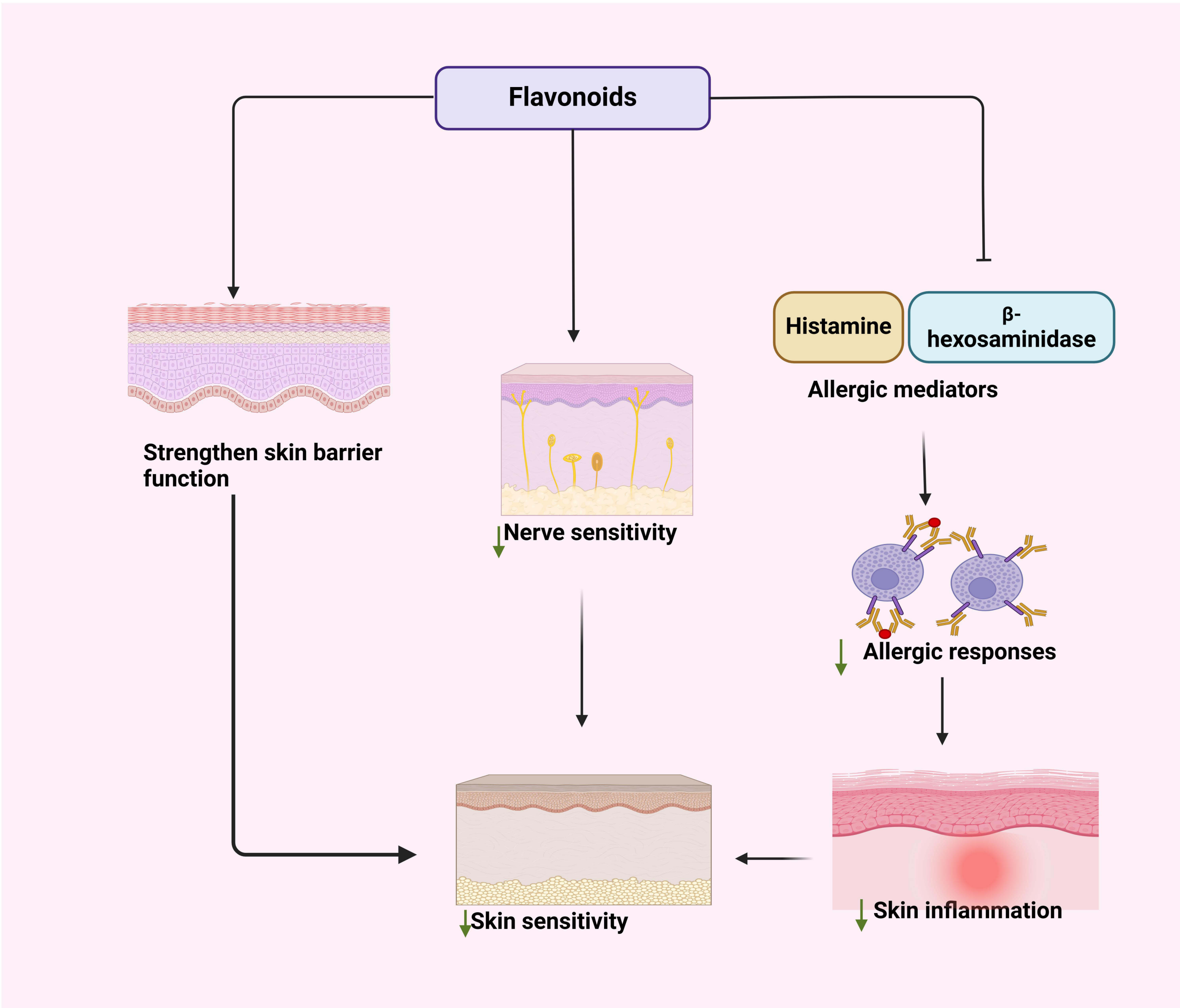

Figure 3 Flavonoid Mechanisms in Reducing Skin Sensitivity and Allergic Inflammation. Flavonoids strengthen the skin barrier, reducing permeability and attenuating sensory nerve activation. By inhibiting the release of pro-inflammatory mediators like histamine and β-hexosaminidase, flavonoids suppress allergic reactions and downstream inflammatory pathways, mitigating skin irritation and enhancing dermal resilience. ↓ = reduce. Created with Biorender.com.

release, a marker of allergic response, without causing cytotoxicity even at higher concentrations.[119] This activity highlights quercetin's suitability for products targeting sensitive and allergy-prone skin.

Commonly used evaluation methods include barrier function repair assays, inflammation suppression tests, and nerve desensitization models.[120] Specifically, assays like histamine release and β-hexosaminidase inhibition are often used to measure the effectiveness of flavonoids in reducing allergic responses.[121] Histamine, a compound often released during allergic reactions, is inhibited by flavonoids, thus reducing symptoms of redness, itching, and swelling in the skin.[122] Flavonoids also suppress key pro-inflammatory mediators, including IL-4, IL-13, and CD40 ligand, primarily by downregulating the NFAT and AP-1 signaling pathways.[123] These mechanisms contribute to their broader anti-allergic activity, positioning flavonoids as promising dietary agents for allergy prevention and symptom relief.

Antibacterial Effect

Microbial contamination in cosmetics can degrade active ingredients, producing byproducts that cause skin irritation, allergies, or infections.[124] To minimize these risks, preservatives are used; however, synthetic preservatives in excess can lead to skin sensitivity and other safety concerns.[3,125] Flavonoids, known for their natural antimicrobial properties, offer a safer alternative, enabling potential preservative-free formulations that still inhibit microbial growth—an advantage for cosmetics designed for sensitive skin.[3,126,127]

According to established cosmetic safety standards, microbial testing in cosmetics typically screens for pathogens like Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans, and Aspergillus niger.[128,129] Evidence suggests that flavonoids can inhibit these microbes, possibly reducing the need for synthetic preservatives.[126,127,130]

Acne Prevention and Treatment

Acne is a chronic inflammatory condition affecting hair follicles and sebaceous glands, often exacerbated in adolescents due to increased androgen levels.[131] Elevated androgens stimulate excess sebum production and accelerate keratinocyte proliferation, leading to blocked pores and trapped sebum, creating an ideal environment for *Propionibacterium acnes* and resulting in inflammation and acne lesions.[132] Flavonoids, with their anti-inflammatory and sebum-regulating properties, are under study for their potential in acne prevention and treatment. For example, a study demonstrated that licorice flavonoids can effectively treat acne by modulating skin microbes, thereby disrupting acne development and promoting a microecological balance similar to that of healthy skin in rats. Licorice flavonoids achieved this by reducing pro-inflammatory bacteria populations and supporting beneficial microbial growth, providing an integrative approach to acne management.[18] Furthermore, the study clarified the anti-acne action of LCF, which works by balancing metabolism and microbial communities. This discovery provides a theoretical foundation that could guide future formulation development and clinical use of this treatment.[18]

Flavonoids like genistein and daidzein exhibit mild estrogen-like properties, mimicking estrogen in reducing sebum production by inhibiting enzymes like histidine decarboxylase and catechol-O-methyltransferase.[133] This activity helps counteract androgen-induced sebum overproduction, a key contributor to acne.[134] These properties make flavonoids ideal for acne-prone formulations. The gentle, non-irritating action of these flavonoids also makes them suitable for sensitive and inflamed skin types.

Flavonoids reduce inflammation by downregulating pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6. For instance, kaempferol and quercetin are shown to inhibit the NF-κB pathway,[135] reducing inflammation and swelling associated with acne lesions (Figure 4). This anti-inflammatory effect supports skin recovery and decreases the severity of acne symptoms.[136]

Some flavonoids exhibit direct antimicrobial effects against acne-causing bacteria. Luteolin and apigenin, for example, have been shown to inhibit *P. acnes* by disrupting bacterial cell walls and generating ROS that lead to bacterial cell death.[137,138] This mechanism highlights flavonoids' suitability as natural antibacterial agents in acne treatment. Human skin studies confirm that flavonoids like genistein are non-toxic and non-irritating, making them suitable for cosmetic applications targeting acne.[48] Several flavonoids have shown promising therapeutic effects in the treatment of acne vulgaris. Licorice flavonoids such as licochalcone A, licochalcone C, licoflavone A, neobavaisoflavone, liguiritigenin, and isoliquiritigenin are known to inhibit the PI3K-Akt signaling pathways, which are involved in cell proliferation and inflammation.[48] These flavonoids also reduce mitochondrial activity, contributing to their anti-acne effect. Additionally, quercetin, a well-known flavonoid, has been shown to suppress the production of proinflammatory cytokines in *P. acnes*-stimulated cell lines. Quercetin also reduces TLR-2 expression, MMP-9 mRNA levels, and MAPK phosphorylation, thereby inhibiting the inflammatory response.[139] Furthermore, quercetin demonstrates antibacterial activity against *P. acnes*, the bacteria responsible for acne lesions.[140] These flavonoids, through their combined anti-inflammatory, antibacterial, and signaling pathway-modulating effects, present significant potential for acne vulgaris treatment.

The combination of these properties—sebum regulation, anti-inflammatory action, and antibacterial effects—positions flavonoids as highly versatile agents in acne-prevention formulations that can address multiple acne-related factors naturally and effectively.

Moisture Function of Flavonoids

Moisturizers are crucial in daily skincare routines, particularly when the epidermal barrier is compromised or skin hydration is reduced, as they help restore and maintain skin's moisture balance and integrity.[141] The multiple hydroxyl groups present in flavonoid glycosides enable the formation of hydrogen bonds with water molecules, effectively

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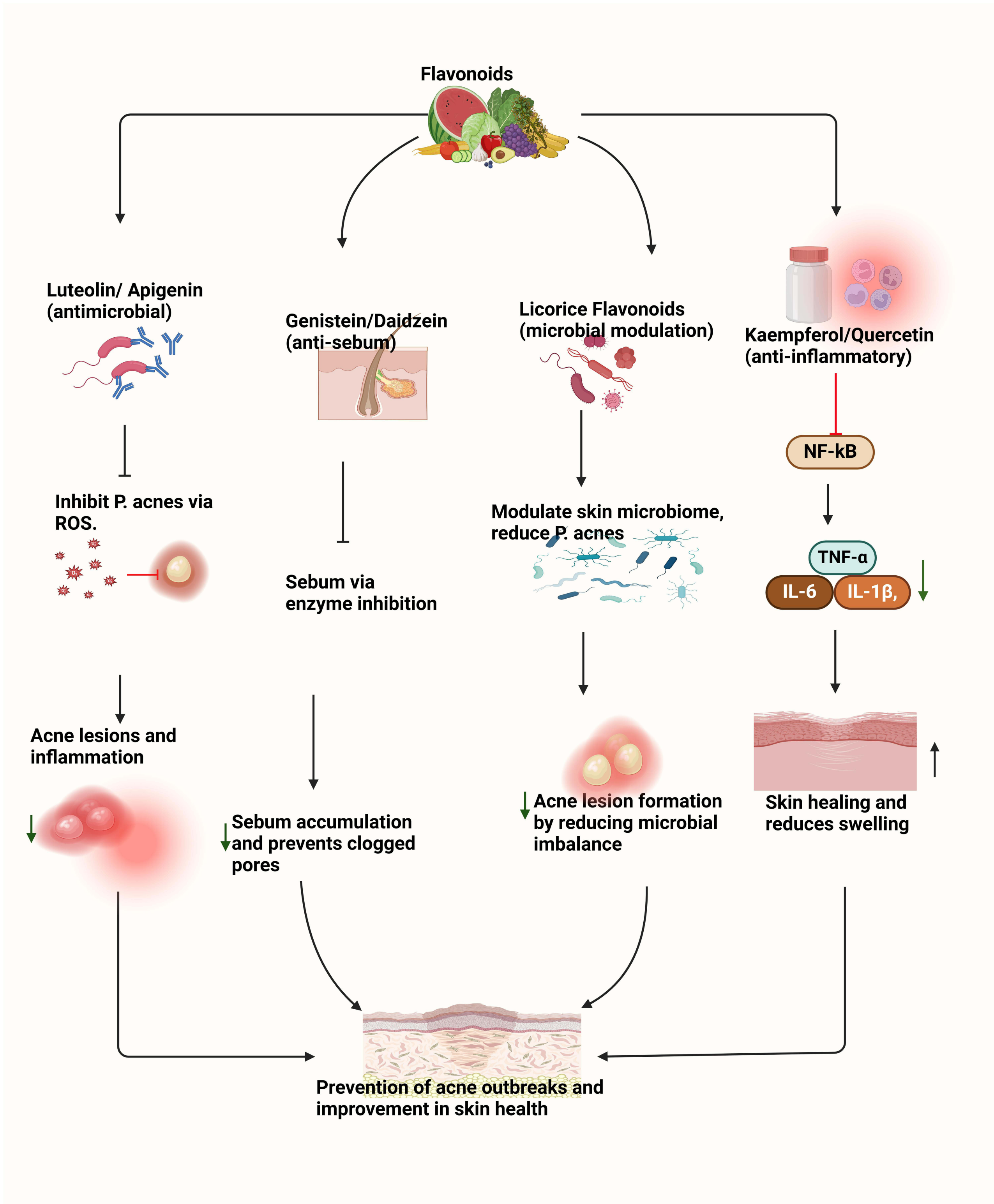

Figure 4 Mechanisms of Flavonoids in Acne Prevention and Skin Health Improvement. Flavonoids exert multiple actions to prevent acne and improve skin health. Luteolin and apigenin generate reactive oxygen species (ROS), inhibiting *P. acnes* and reducing inflammation. Genistein and daidzein reduce sebum production by inhibiting sebogenic enzymes, preventing pore blockage. Licorice flavonoids modulate the skin microbiome, lowering *P. acnes* levels and restoring microbial balance. Kaempferol and quercetin suppress inflammation by inhibiting the NF-κB pathway, reducing pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and promoting skin healing. These combined mechanisms contribute to acne prevention and enhanced skin health. ↑ = increase; ↓ =reduce; ⊥= Inhibition. Created with Biorender.com.

trapping moisture within the skin and reducing transepidermal water loss. This mechanism enhances skin hydration and maintains its elasticity and smoothness.[117] The ability of flavonoids to act as both humectants and emollients further supports their function in improving skin moisture by attracting and holding water while also smoothing the skin's surface.

Maintaining optimal water content is crucial for a healthy skin barrier and provides various health and cosmetic benefits. Three key components that support skin hydration are natural moisturizing factors, the skin's lipid bilayer, and hyaluronic acid. These elements help sustain moisture within the epidermis and deeper skin layers, promoting a robust skin barrier.[142] Natural moisturizing factors (NMF) consist of powerful humectants that draw and retain water from the environment, essential for hydration in the stratum corneum. Filaggrin, a large protein in the corneocyte layer, is broken down into NMF in the upper layers of the stratum corneum.[143–145] This process, known as proteolysis, depends on water activity within corneocytes and external humidity levels, occurring only within a specific range of water activity.[146] Notably, UV radiation can disrupt the natural breakdown of filaggrin into NMF, reducing hydration.[147] Additionally, certain flavonoid aglycones, such as genistein, contribute to skin hydration through their phenolic hydroxyl groups, which improve water retention.[148]

Flavonoids inhibit hyaluronidase, an enzyme responsible for the degradation of hyaluronic acid, preserving HA levels in the dermis.[149] Intact HA interacts with CD44 receptors on dermal fibroblasts, triggering signaling pathways that promote the production of additional hyaluronic acid and collagen.[150] These processes reinforce hydration, elasticity, and skin smoothness. Collagen fibers provide a scaffold within the extracellular matrix (ECM), supporting HA and glycosaminoglycans, which retain water and contribute to skin hydration (Figure 5).[151,152]

Flavonoids also help enhance moisture retention by reinforcing the skin's barrier function and stimulating dermal fibroblasts to produce collagen and hyaluronic acid—key components for maintaining hydration, elasticity, and overall skin integrity.[153] Together, these combined properties make flavonoids an invaluable ingredient in skincare formulations, offering natural, effective support for maintaining skin hydration, elasticity, and overall health.

Delay Skin Aging Effect of Flavonoids

Skin aging is a multifactorial process primarily driven by factors such as oxidative stress, collagen breakdown, hormonal changes (eg., reduced estrogen), and prolonged UV exposure. These factors contribute to common signs of aging, including wrinkles, sagging, dryness, and a loss of elasticity. Flavonoids, with their potent antioxidant and anti-inflammatory properties, play a crucial role in combating these age-related changes.[154] By neutralizing free radicals, inhibiting collagen-degrading enzymes, and stimulating collagen production, flavonoids help preserve skin structure and prevent visible signs of aging.[117,155,156] A substantial proportion of anti-aging evidence is derived from in vitro fibroblast systems[157] and UV-induced animal models,[158] which provide important mechanistic insight and preliminary efficacy signals. However, broader validation in well-controlled human studies remains limited and often show constrained representativeness, with most trials enrolling predominantly female participants, relatively small to moderate sample sizes, and restricted age ranges. Many studies also recruit from narrow geographic populations, which limits generalizability and complicates mechanistic interpretation when participants are selected primarily on clinical features of aging.[154]

The polyphenolic structure of flavonoids allows them to scavenge free radicals, preventing oxidative damage. Flavonoids neutralize superoxide anions, chelate metal ions to block hydroxyl radicals, and inhibit lipid peroxidation, protecting skin cells and maintaining structural integrity.[65,159,160] These antioxidant effects are particularly important in mitigating the damage caused by UV-induced oxidative stress, a primary contributor to skin photoaging.[161,162] Flavonoids stimulate fibroblasts to increase collagen and hyaluronic acid production, key for maintaining skin firmness and elasticity. The mild estrogen-like activity of flavonoids like genistein further supports collagen integrity, countering age-related decline.[163] By reducing inflammation and absorbing UV rays, flavonoids help protect against photoaging.[164] Their ability to inhibit enzymes involved in collagen degradation also aids in preserving skin structure.[165] In an animal study, Naringenin, a flavonoid from citrus fruits, demonstrated potential in preventing UV-induced photoaging. When incorporated into a microemulsion and loaded into Sericin gel, NAR reduced UVB-induced wrinkles, erythema, and other signs of photoaging.[166] This formulation protected the skin from UV-induced damage, suggesting its potential for use in anti-aging cosmetic products.

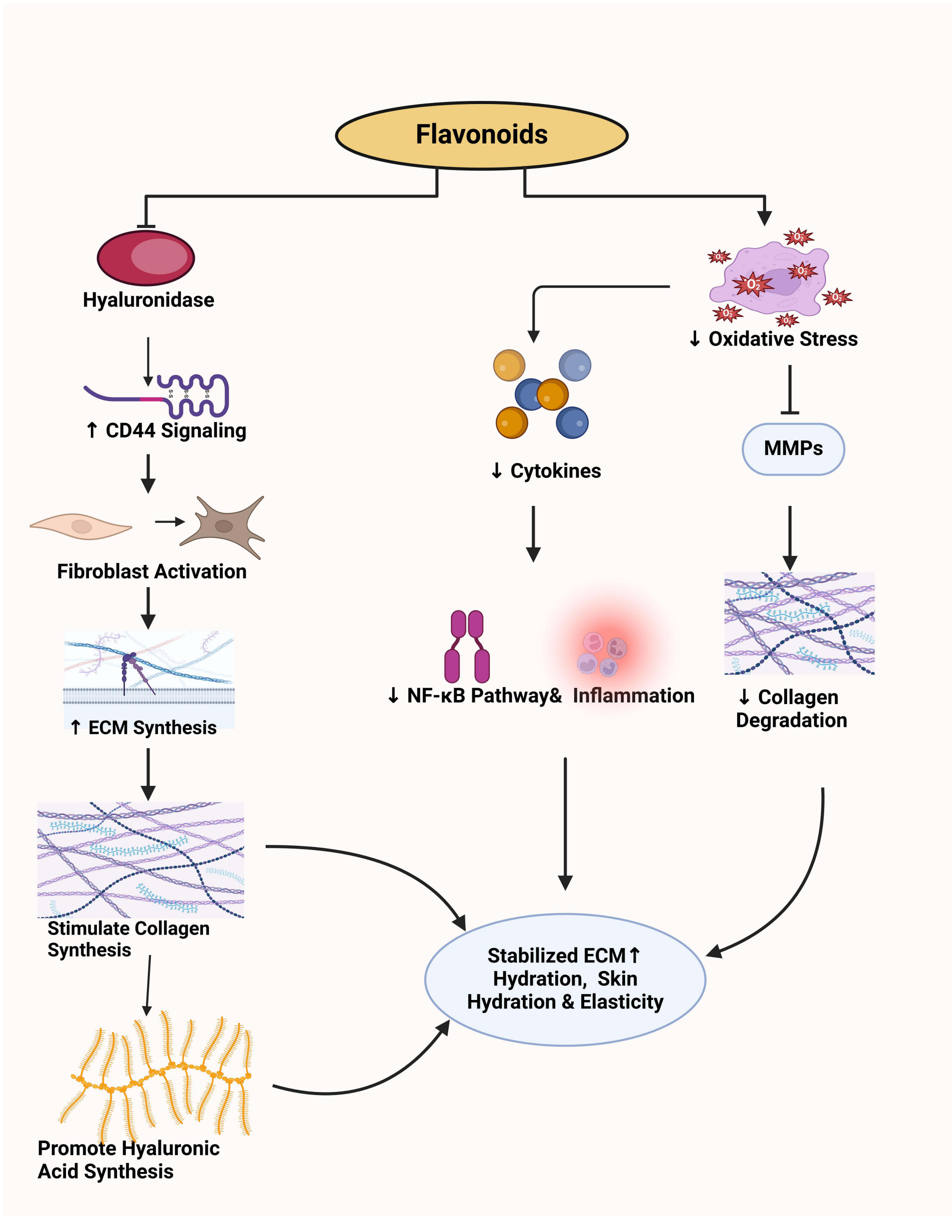

Figure 5 Mechanisms of Flavonoids in Enhancing Skin Hydration and Structural Integrity. Flavonoids promote skin hydration and elasticity through two key pathways. By inhibiting hyaluronidase, they preserve hyaluronic acid (HA), which activates CD44 on fibroblasts to stimulate HA and collagen synthesis, reinforcing the extracellular matrix (ECM). Additionally, flavonoids neutralize ROS, suppress inflammation, and inhibit matrix metalloproteinases (MMPs), preventing collagen breakdown. These combined actions support skin hydration, elasticity, and barrier function. ↑ = increase; ↓ =reduce. Created with Biorender.com.

Studies indicate that topical formulations containing flavonoid extracts can improve clinical or instrumental signs associated with photoaging, although effective concentrations and durability of benefit appear to depend on extract composition, vehicle design, and treatment duration.[167,168] Flavonoids such as quercetin, luteolin, and genistein are widely used in anti-aging formulations for their proven efficacy in reducing oxidative stress, supporting collagen production, and protecting against UV-induced damage.[169] Fr example, hesperidin (HSD) shows potential in anti-aging cosmetics by inhibiting collagenase, offering antioxidant and UV-protective effects. HSD-loaded nanoemulsions enhance skin hydration, reduce wrinkles, and protect against UV damage,[170] making it a promising ingredient for skin care. Apigenin, a flavonoid with antioxidant properties, counteracts UVA-induced skin aging by restoring fibroblast viability and inhibiting MMP-1 expression, thereby preserving collagen integrity. In a clinical trial, apigenin-containing cream improved dermal density, elasticity, hydration, and reduced fine wrinkles, supporting its potential as an effective anti-aging agent.[55]

Table 2 Molecular Mechanisms and Regulatory Pathways of Flavones in Skin Health

Mechanism	Regulatory Pathways /Molecular Targets	Cosmetic Application	References
Inhibition of Melanin Synthesis	Tyrosinase inhibition, MITF downregulation, cAMP/PKA pathway suppression	Skin whitening, melasma treatment	[171–173]
Collagen and Elastin Protection	MMP inhibition, suppression of AP-1, collagenase/elastase binding	Firming, wrinkle-reduction, anti-aging	[174–176]
Antioxidant Defense	↑ SOD, CAT, GSH-Px; activation of Nrf2, inhibition of MAPK/PI3K/AMPK	Anti-aging, UV protection, oxidative stress defense	[177–179]
Anti-inflammatory Effects	Inhibition of NF-κB, COX-2, STAT3; suppression of cytokines (TNF-α, IL-6)	Acne, sensitive skin, redness reduction	[52, 177]
Skin Barrier & Hydration	Inhibition of hyaluronidase, activation of CD44 and TGF-β/Smad pathway	Deep hydration, barrier-repair creams	[180–182]
Antibacterial and Antifungal	Cell membrane disruption, inhibition of microbial enzymes	Acne control, natural preservation	[77, 183, 184]
Estrogenic & Cell Renewal Effects	Estrogen receptor modulation (ERα/β), MAPK and PI3K/AKT activation	Menopausal skin care, dermal regeneration	[185, 186]

Abbreviations: OD, Superoxide Dismutase; CAT, Catalase; GSH-Px, Glutathione Peroxidase; MMP, Matrix Metalloproteinases; NF-κB, Nuclear Factor Kappa-B; COX-2, Cyclooxygenase-2; STAT3, Signal Transducer and Activator of Transcription 3; MAPK, Mitogen-Activated Protein Kinase; PI3K, Phosphoinositide 3-Kinase; AMPK, AMP-Activated Protein Kinase; AP-1, Activator Protein 1; MITF, Microphthalmia-Associated Transcription Factor; TGF-β, Transforming Growth Factor Beta; ERα/β, Estrogen Receptors Alpha/Beta; cAMP, Cyclic Adenosine Monophosphate; PKA, Protein Kinase A; ROS, Reactive Oxygen Species; ↑, Increase.

Flavonoids' broad range of biological activities is driven by several interrelated molecular mechanisms that regulate key skin functions such as pigmentation, elasticity, hydration, and protection from environmental stressors. These effects, discussed in detail throughout this paper, are mediated through the inhibition of key enzymes, modulation of inflammatory and oxidative pathways, and the enhancement of structural proteins in the skin. The following table provides a summary of these primary mechanisms, their regulatory pathways, and their corresponding cosmetic applications, highlighting the versatility of flavonoids in skincare formulations (Table 2).

Flavonoids, including quercetin, rutin, and catechins, are widely utilized in cosmetic formulations due to their wide range properties. However, their application is limited by several factors. These compounds often exhibit poor solubility in lipophilic media, which can impair their effectiveness in skin care products.[187,188] Flavonoids face challenges with skin penetration, as their molecular structure hinders efficient absorption through the skin barrier.[34,189] Their stability can also be compromised under exposure to light, heat, and air, reducing their long-term efficacy in formulations.[34] Despite these limitations, ongoing research into enhancing their bioavailability and stability offers promising solutions for their improved use in cosmetics.

Safety and Toxicity Considerations

Under cosmetic use conditions, flavonoids are generally considered safe when appropriately formulated and used at cosmetic-relevant concentrations,[48] with safety evaluation focusing primarily on local skin tolerance and photo-safety rather than systemic toxicity. Commonly used cosmetic flavonoids include quercetin and rutin, apigenin, luteolin, and the isoflavone genistein.[190] Topical quercetin formulations are well tolerated in both in vitro skin models and in vivo animal dermatitis models when adequately solubilized, minimizing irritation risk.[191,192] Apigenin and luteolin show low irritation potential in in vitro and in vivo skin models, with anti-inflammatory and anti-photoaging activity,[52] while genistein, despite documented topical safety in controlled human studies, requires particular attention due to its estrogenic activity, emphasizing the importance of limiting systemic absorption (Table 1).[59] A study assessed the safety of luteolin, apigenin, quercetin, and genistein using multiple in vitro, in vivo, and computational models. The authors tested developmental toxicity in the chicken embryo model, where luteolin and genistein exhibited significant developmental toxicity, with mortality rates reaching 43.75% and 50% at higher doses, respectively. Quercetin and apigenin demonstrated lower mortality, but still affected developmental indices and liver weight. The Ames mutagenicity test indicated that all compounds showed signs of mutagenicity, with quercetin and luteolin exhibiting the highest mutagenic indices (up to 1.4–1.9). In silico toxicity predictions using the T.E.S.T. model classified all compounds as developmental toxicants, with genistein and luteolin also flagged for mutagenicity risks.[193] Genistein has been associated with endocrine and hypersensitivity effects. A human study reported a 19% decrease in serum testosterone in healthy men after four weeks of high soy protein intake, although results across studies are inconsistent.[194] Additionally, genistein-containing soy products can cause allergic reactions, typically mild and often beginning in childhood, with symptoms such as eczema, pruritus, gastrointestinal discomfort, and skin erythema, while severe reactions are rare.[195] These results highlight the potential risks associated with the use of flavonoids, with varying degrees of toxicity observed across different models. Although several studies show favorable outcomes, careful formulation and dose control are essential to minimize risks, particularly regarding endocrine disruption and allergic reactions. Therefore, the use of flavonoids in cosmetics requires rigorous safety evaluation to prevent adverse effects.

Conclusion and Future Perspectives

Flavonoids have emerged as a highly promising group of ingredients in cosmetics, showcasing a wide range of bioactive properties that address various skin concerns. Their effectiveness in skin whitening, antioxidant defense, anti-inflammatory modulation, antimicrobial protection, and anti-aging is well documented, positioning them as versatile compounds in skincare and other cosmetic applications. By modulating key molecular pathways such as tyrosinase inhibition, ROS scavenging, NF-κB suppression, and collagen production, flavonoids offer multifunctional benefits that align with the increasing consumer demand for natural, sustainable cosmetic products. However, challenges related to poor bioavailability, skin penetration, and formulation stability remain, limiting their practical application. Ongoing research aimed at enhancing the stability and delivery of flavonoids, particularly through emerging technologies like nanocarriers and other advanced delivery systems, holds promise for overcoming these barriers and expanding their role in cosmetics.

The future of flavonoid-based cosmetic formulations lies in overcoming critical formulation challenges and leveraging emerging delivery technologies. There is a significant need for innovative delivery systems, such as nanocarriers, liposomes, and other targeted vehicles, which can improve flavonoid stability, solubility, and skin penetration, thereby enhancing their bioavailability and therapeutic potential. In addition, research into ingredient interactions should be prioritized to better understand how flavonoids work synergistically with other natural compounds, further amplifying their effectiveness. Currently, the majority of research on flavonoids focuses heavily on cell-based studies, but there is a pressing need for animal studies and clinical trials to validate their in vivo efficacy and long-term safety. These studies are crucial to translate laboratory findings into safe, effective cosmetic products for broader consumer use. Furthermore, addressing regulatory considerations and establishing standardized safety protocols will be pivotal to gaining consumer trust and ensuring the widespread adoption of flavonoid-rich formulations. As these research gaps are addressed, flavonoids have the potential to revolutionize the cosmetic industry, offering a safe, eco-friendly, and multifunctional alternative to synthetic ingredients.

Data Sharing Statement

All datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study didn't involve in any ethic event.

Funding

Initiation Funds for High-level Talents Program of Xi'an International University (Grant No. XAIU202610).

Disclosure

The authors declare that they have no competing interests in this work.

References

1. Alnuqaydan AM. The dark side of beauty: an in-depth analysis of the health hazards and toxicological impact of synthetic cosmetics and personal care products. *Front Public Health*. 2024;12:1439027. doi:10.3389/fpubh.2024.1439027
2. Sasounian R, Martinez RM, Lopes AM, et al. Innovative approaches to an eco-friendly cosmetic industry: a review of sustainable ingredients. *Clean Technologies*. 2024;6(1):176–198. doi:10.3390/cleantechnol6010011

3. Nowak-Lange M, Niedziałkowska K, Lisowska K. Cosmetic Preservatives: hazardous Micropollutants in Need of Greater Attention? *Int J Mol Sci*. 2022;23(22):14495. doi:10.3390/ijms232214495
4. Rybczyńska-Tkaczyk K, Grenda A, Jakubczyk A, Kiersnowska K, Bik-Małodzińska M. Natural Compounds with Antimicrobial Properties in Cosmetics. *Pathogens*. 2023;12(2):320. doi:10.3390/pathogens12020320
5. Yan Y, Xia X, Fatima A, et al. Antibacterial Activity and Mechanisms of Plant Flavonoids against Gram-Negative Bacteria Based on the Antibacterial Statistical Model. *Pharmaceuticals*. 2024;17(3):292. doi:10.3390/ph17030292
6. Ahmed IA, Zamakshshari NH, Mikail MA, Bello I, Hossain MS. Garcinia flavonoids for healthy aging: anti-senescence mechanisms and cosmeceutical applications in skin care. *Fitoterapia*. 2024;180:106282. doi:10.1016/j.fitote.2024.106282
7. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. *J Nutr Sci*. 2016;5:e47. doi:10.1017/jns.2016.41
8. Rathee P, Sehrawat R, Rathee P, et al. Polyphenols: natural Preservatives with Promising Applications in Food, Cosmetics and Pharma Industries; Problems and Toxicity Associated with Synthetic Preservatives; Impact of Misleading Advertisements; Recent Trends in Preservation and Legislation. *Materials*. 2023;16(13):4793. doi:10.3390/ma16134793
9. Nowak K, Jabłońska E, Ratajczak-Wrona W. Controversy around parabens: alternative strategies for preservative use in cosmetics and personal care products. *Environ Res*. 2021;198:110488. doi:10.1016/j.envres.2020.110488
10. Chagas M, Behrens MD, Moragas-Tellis CJ, Penedo GXM, Silva AR, Gonçalves-de-Albuquerque CF. Flavonols and Flavones as Potential anti-Inflammatory, Antioxidant, and Antibacterial Compounds. *Oxid Med Cell Longev*. 2022;2022(1):9966750. doi:10.1155/2022/9966750
11. Mahmud AR, Ema TI, Siddiquee MF, et al. Natural flavonols: actions, mechanisms, and potential therapeutic utility for various diseases. *Beni Suef Univ J Basic Appl Sci*. 2023;12(1):47. doi:10.1186/s43088-023-00387-4
12. Alshehrei FM. Isolation and Identification of Microorganisms associated with high-quality and low-quality cosmetics from different brands in Mecca region -Saudi Arabia. *Saudi J Biol Sci*. 2023;30(12):103852. doi:10.1016/j.sjbs.2023.103852
13. Skowron K, Jakubicz A, Budzyńska A, et al. Microbiological purity assessment of cosmetics used by one and several persons and cosmetics after their expiry date. *Rocz Panstw Zakl Hig*. 2017;68(2):191–197.
14. Fan X, Fan Z, Yang Z, et al. Flavonoids-Natural Gifts to Promote Health and Longevity. *Int J Mol Sci*. 2022;23(4):2176. doi:10.3390/ijms23042176
15. Olivero-Verbel J, Quintero-Rincón P, Caballero-Gallardo K. Aromatic plants as cosmeceuticals: benefits and applications for skin health. *Planta*. 2024;260(6):132. doi:10.1007/s00425-024-04550-8
16. Mueed A, Shibli S, Al-Quwaie DA, et al. Extraction, characterization of polyphenols from certain medicinal plants and evaluation of their antioxidant, antitumor, antidiabetic, antimicrobial properties, and potential use in human nutrition. *Front Nutr*. 2023;10:1125106. doi:10.3389/fnut.2023.1125106
17. Juliano C, Magrini GA. Methylglyoxal, the major antibacterial factor in manuka honey: an alternative to preserve natural cosmetics? *Cosmetics*. 2018;6(1):1. doi:10.3390/cosmetics6010001
18. Ruan SF, Hu Y, Wu WF, et al. Explore the Anti-Acne Mechanism of Licorice Flavonoids Based on Metabonomics and Microbiome. *Front Pharmacol*. 2022;13:832088. doi:10.3389/fphar.2022.832088
19. Del Bino S, Duval C, Bernerd F. Clinical and Biological Characterization of Skin Pigmentation Diversity and Its Consequences on UV Impact. *Int J Mol Sci*. 2018;19(9):2668. doi:10.3390/ijms19092668
20. Jablonski NG, Chaplin G. Colloquium paper: human skin pigmentation as an adaptation to UV radiation. *Proc Natl Acad Sci U S A*. 2010;107 (Suppl 2):8962–8968. doi:10.1073/pnas.0914628107
21. Fajuyigbe D, Young AR. The impact of skin colour on human photobiological responses. *Pigm Cell Melanoma Res*. 2016;29(6):607–618. doi:10.1111/pcmr.12511
22. Maddodi N, Jayanthy A, Setaluri V. Shining light on skin pigmentation: the darker and the brighter side of effects of UV radiation. *Photochem Photobiol*. 2012;88(5):1075–1082. doi:10.1111/j.1751-1097.2012.01138.x
23. Thawabteh AM, Jibreen A, Karaman D, Thawabteh A, Karaman R. Skin Pigmentation Types, Causes and Treatment-A Review. *Molecules*. 2023;28(12):4839. doi:10.3390/molecules28124839
24. Pillaiyar T, Manickam M, Namasivayam V. Skin whitening agents: medicinal chemistry perspective of tyrosinase inhibitors. *J Enzyme Inhib Med Chem*. 2017;32(1):403–425. doi:10.1080/14756366.2016.1256882
25. Karkoszka M, Rok J, Wrześniok D. Melanin Biopolymers in Pharmacology and Medicine-Skin Pigmentation Disorders, Implications for Drug Action, Adverse Effects and Therapy. *Pharmaceuticals*. 2024;17(4):521. doi:10.3390/ph17040521
26. Nguyen NT, Fisher DE. MITF and UV responses in skin: from pigmentation to addiction. *Pigm Cell Melanoma Res*. 2019;32(2):224–236. doi:10.1111/pcmr.12726
27. Qu Y, Zhan Q, Du S, et al. Catalysis-based specific detection and inhibition of tyrosinase and their application. *J Pharm Anal*. 2020;10 (5):414–425. doi:10.1016/j.jpha.2020.07.004
28. Carradori S, Melfi F, Rešetar J, Şimşek R. Tyrosinase enzyme and its inhibitors: an update of the literature. *Metalloenzymes*. 2024;2024:533–546.
29. Niu C, Aisa HA. Upregulation of Melanogenesis and Tyrosinase Activity: potential Agents for Vitiligo. *Molecules*. 2017;22(8):1303. doi:10.3390/molecules22081303
30. Jakimiuk K, Sari S, Milewski R, Supuran CT, Şöhretoğlu D, Tomczyk M. Flavonoids as tyrosinase inhibitors in in silico and in vitro models: basic framework of SAR using a statistical modelling approach. *J Enzyme Inhib Med Chem*. 2022;37(1):421–430. doi:10.1080/14756366.2021.2014832
31. Santi MD, Peralta MA, Mendoza CS, Cabrera JL, Ortega MG. Chemical and bioactivity of flavanones obtained from roots of Dalea pazensis Rusby. *Bioorg Med Chem Lett*. 2017;27(8):1789–1794. doi:10.1016/j.bmcl.2017.02.058
32. Lv Q, Wu X, Guan Y, et al. Integration of network pharmacology, transcriptomics and molecular docking reveals two novel hypoglycemic components in snow chrysanthemum. *Biomed Pharmacother*. 2023;163:114818. doi:10.1016/j.biopha.2023.114818
33. El-Nashar HAS, El-Din MIG, Hritcu L, Eldahshan OA. Insights on the Inhibitory Power of Flavonoids on Tyrosinase Activity: a Survey from 2016 to 2021. *Molecules*. 2021;26(24):7546. doi:10.3390/molecules26247546
34. Costa R, Costa Lima SA, Gameiro P, Reis S. On the Development of a Cutaneous Flavonoid Delivery System: advances and Limitations. *Antioxidants*. 2021;10(9):1376. doi:10.3390/antiox10091376

35. Liu-Smith F, Meyskens FL. Molecular mechanisms of flavonoids in melanin synthesis and the potential for the prevention and treatment of melanoma. *Mol Nutr Food Res*. 2016;60(6):1264–1274. doi:10.1002/mnfr.201500822
36. Okselni T, Septama AW, Juliadmi D, et al. Quercetin as a therapeutic agent for skin problems: a systematic review and meta-analysis on antioxidant effects, oxidative stress, inflammation, wound healing, hyperpigmentation, aging, and skin cancer. *Naunyn Schmiedebergs Arch Pharmacol*. 2025;398(5):5011–5055. doi:10.1007/s00210-024-03722-3
37. Fujii T, Saito M. Inhibitory effect of quercetin isolated from rose Hip (Rosa canina L.) against melanogenesis by mouse melanoma cells. *Biosci Biotechnol Biochem*. 2009;73(9):1989–1993. doi:10.1271/bbb.90181
38. Takekoshi S, Matsuzaki K, Kitatani K. Quercetin stimulates melanogenesis in hair follicle melanocyte of the mouse. *Tokai J Exp Clin Med*. 2013;38(4):129–134.
39. Nagata H, Takekoshi S, Takeyama R, Homma T, Yoshiyuki Osamura R. Quercetin enhances melanogenesis by increasing the activity and synthesis of tyrosinase in human melanoma cells and in normal human melanocytes. *Pigment Cell Res*. 2004;17(1):66–73. doi:10.1046/j.1600-0749.2003.00113.x
40. Takekoshi S, Nagata H, Kitatani K. Flavonoids enhance melanogenesis in human melanoma cells. *Tokai J Exp Clin Med*. 2014;39(3):116–121.
41. Matsuda H, Nakashima S, Oda Y, Nakamura S, Yoshikawa M. Melanogenesis inhibitors from the rhizomes of Alpinia officinarum in B16 melanoma cells. *Bioorg Med Chem*. 2009;17(16):6048–6053. doi:10.1016/j.bmc.2009.06.057
42. Chen WC, Wang SW, Li CW, et al. Comparison of Various Solvent Extracts and Major Bioactive Components from Portulaca oleracea for Antioxidant, Anti-Tyrosinase, and Anti-α-Glucosidase Activities. *Antioxidants*. 2022;11(2):398. doi:10.3390/antiox11020398
43. Panzella L, Napolitano A. Natural and bioinspired phenolic compounds as tyrosinase inhibitors for the treatment of skin hyperpigmentation: recent advances. *Cosmetics*. 2019;6(4):57.
44. Zhang L, Martinelli E, Senizza B, et al. The Combination of Mild Salinity Conditions and Exogenously Applied Phenolics Modulates Functional Traits in Lettuce. *Plants*. 2021;10(7):1457. doi:10.3390/plants10071457
45. Sadeer NB, Rocchetti G, Senizza B, et al. Untargeted Metabolomic Profiling, Multivariate Analysis and Biological Evaluation of the True Mangrove (Rhizophora mucronata Lam.). *Antioxidants*. 2019;8(10):489. doi:10.3390/antiox8100489
46. Angelis A, Hubert J, Aligiannis N, et al. Bio-Guided Isolation of Methanol-Soluble Metabolites of Common Spruce (Picea abies) Bark by-Products and Investigation of Their Dermo-Cosmetic Properties. *Molecules*. 2016;21(11):1586. doi:10.3390/molecules21111586
47. Quinty V, Colas C, Nasreddine R, et al. Screening and Evaluation of Dermo-Cosmetic Activities of the Invasive Plant Species Polygonum cuspidatum. *Plants*. 2022;12(1):83. doi:10.3390/plants12010083
48. Čižmárová B, Hubková B, Tomečková V, Birková A. Flavonoids as Promising Natural Compounds in the Prevention and Treatment of Selected Skin Diseases. *Int J Mol Sci*. 2023;24(7):6324. doi:10.3390/ijms24076324
49. Hasnat H, Shompa SA, Islam MM, et al. Flavonoids: a treasure house of prospective pharmacological potentials. *Heliyon*. 2024;10(6):e27533. doi:10.1016/j.heliyon.2024.e27533
50. Kurek-Górecka A, Górecki M, Rzepecka-Stojko A, Balwierz R, Stojko J. Bee Products in Dermatology and Skin Care. *Molecules*. 2020;25(3):556. doi:10.3390/molecules25030556
51. Bastin A, Teimouri M, Faramarz S, Shabani M, Doustimotlagh AH, Sadeghi A. In vitro and Molecular Docking Analysis of Quercetin as an Anti-inflammatory and Antioxidant. *Curr Pharm Des*. 2023;29(11):883–891. doi:10.2174/1381612829666230330084043
52. Gendrisch F, Esser PR, Schempp CM, Wölfle U. Luteolin as a modulator of skin aging and inflammation. *Biofactors*. 2021;47(2):170–180. doi:10.1002/biof.1699
53. Kang OH, Choi JG, Lee JH, Kwon DY. Luteolin isolated from the flowers of Lonicera japonica suppresses inflammatory mediator release by blocking NF-kappaB and MAPKs activation pathways in HMC-1 cells. *Molecules*. 2010;15(1):385–398. doi:10.3390/molecules15010385
54. Zhang H, Xu Q, Jiang Z, et al. Targeting Senescence with Apigenin Improves Chemotherapeutic Efficacy and Ameliorates Age-Related Conditions in Mice. *Adv Sci*. 2025;12(20):e2412950. doi:10.1002/advs.202412950
55. Choi S, Youn J, Kim K, et al. Apigenin inhibits UVA-induced cytotoxicity in vitro and prevents signs of skin aging in vivo. *Int J Mol Med*. 2016;38(2):627–634. doi:10.3892/ijmm.2016.2626
56. Park CH, Min SY, Yu HW, et al. Effects of Apigenin on RBL-2H3, RAW264.7, and HaCaT Cells: anti-Allergic, Anti-Inflammatory, and Skin-Protective Activities. *Int J Mol Sci*. 2020;21(13):4620. doi:10.3390/ijms21134620
57. Siridechakorn I, Pimpa J, Choodej S, Ngamrojanavanich N, Pudhom K. Synergistic impact of arbutin and kaempferol-7-O-α-L-rhamnopyranoside from Nephelium lappaceum L. on whitening efficacy and stability of cosmetic formulations. *Sci Rep*. 2023;13(1):22004. doi:10.1038/s41598-023-49351-3
58. Ko J, Rho T, Yoon KD. Kaempferol tri- and tetrasaccharides from Camellia japonica seed cake and their inhibitory activities against matrix metalloproteinase-1 secretion using human dermal fibroblasts. *Carbohydr Res*. 2020;495:108101. doi:10.1016/j.carres.2020.108101
59. Sharifi-Rad J, Quispe C, Imran M, et al. Genistein: an Integrative Overview of Its Mode of Action, Pharmacological Properties, and Health Benefits. *Oxid Med Cell Longev*. 2021;2021(1):3268136. doi:10.1155/2021/3268136
60. Choi SJ, Lee SN, Kim K, et al. Biological effects of rutin on skin aging. *Int J Mol Med*. 2016;38(1):357–363. doi:10.3892/ijmm.2016.2604
61. Fu B, Li H, Wang X, Lee FS, Cui S. Isolation and identification of flavonoids in licorice and a study of their inhibitory effects on tyrosinase. *J Agric Food Chem*. 2005;53(19):7408–7414. doi:10.1021/jf051258h
62. Baldea I, Mocan T, Cosgarea R. The role of ultraviolet radiation and tyrosine stimulated melanogenesis in the induction of oxidative stress alterations in fair skin melanocytes. *Exp Oncol*. 2009;31(4):200–208.
63. Pizzino G, Irrera N, Cucinotta M, et al. Oxidative Stress: harms and Benefits for Human Health. *Oxid Med Cell Longev*. 2017;2017(1):8416763. doi:10.1155/2017/8416763
64. Chen J, Liu Y, Zhao Z, Qiu J. Oxidative stress in the skin: impact and related protection. *Int J Cosmet Sci*. 2021;43(5):495–509. doi:10.1111/ics.12728
65. Hassanpour SH, Doroudi A. Review of the antioxidant potential of flavonoids as a subgroup of polyphenols and partial substitute for synthetic antioxidants. *Avicenna J Phytomed*. 2023;13(4):354–376. doi:10.22038/ajp.2023.21774
66. Andrés CMC, Pérez de la Lastra JM, Andrés Juan C, Plou FJ, Pérez-Lebeña E. Superoxide Anion Chemistry-Its Role at the Core of the Innate Immunity. *Int J Mol Sci*. 2023;24(3):1841. doi:10.3390/ijms24031841

67. Shen N, Wang T, Gan Q, Liu S, Wang L, Jin B. Plant flavonoids: classification, distribution, biosynthesis, and antioxidant activity. *Food Chem*. 2022;383:132531. doi:10.1016/j.foodchem.2022.132531
68. Michalak M. Plant-Derived Antioxidants: significance in Skin Health and the Ageing Process. *Int J Mol Sci*. 2022;23(2):585. doi:10.3390/ijms23020585
69. Tsikas D. Assessment of lipid peroxidation by measuring malondialdehyde (MDA) and relatives in biological samples: analytical and biological challenges. *Anal Biochem*. 2017;524:13–30. doi:10.1016/j.ab.2016.10.021
70. Rinnerthaler M, Bischof J, Streubel MK, Trost A, Richter K. Oxidative stress in aging human skin. *Biomolecules*. 2015;5(2):545–589. doi:10.3390/biom5020545
71. Bibi Sadeer N, Montesano D, Albrizio S, Zengin G, Mahomoodally MF. The Versatility of Antioxidant Assays in Food Science and Safety-Chemistry, Applications, Strengths, and Limitations. *Antioxidants*. 2020;9(8):709. doi:10.3390/antiox9080709
72. Sagrafena I, Morin M, Paraskevopoulos G, et al. Structure and function of skin barrier lipids: effects of hydration and natural moisturizers in vitro. *Biophys J*. 2024;123(22):3951–3963. doi:10.1016/j.bpj.2024.10.006
73. Phaniendra A, Jestadi DB, Periyasamy L. Free radicals: properties, sources, targets, and their implication in various diseases. *Indian J Clin Biochem*. 2015;30(1):11–26. doi:10.1007/s12291-014-0446-0
74. Juan CA, Pérez de la Lastra JM, Plou FJ, Pérez-Lebeña E. The Chemistry of Reactive Oxygen Species (ROS) Revisited: outlining Their Role in Biological Macromolecules (DNA, Lipids and Proteins) and Induced Pathologies. *Int J Mol Sci*. 2021;22(9):4642. doi:10.3390/ijms22094642
75. Jomova K, Raptova R, Alomar SY, et al. Reactive oxygen species, toxicity, oxidative stress, and antioxidants: chronic diseases and aging. *Arch Toxicol*. 2023;97(10):2499–2574. doi:10.1007/s00204-023-03562-9
76. Muscolo A, Mariateresa O, Giulio T, Mariateresa R. Oxidative Stress: the Role of Antioxidant Phytochemicals in the Prevention and Treatment of Diseases. *Int J Mol Sci*. 2024;25(6):3264. doi:10.3390/ijms25063264
77. Zahra M, Abrahamse H, George BP. Flavonoids: antioxidant Powerhouses and Their Role in Nanomedicine. *Antioxidants*. 2024;13(8):922. doi:10.3390/antiox13080922
78. Jain MS. Role of Topical Flavonoids as Antioxidants to Preserve Healthy Skin–A Review. *Asian J Pharm*. 2022;16(1):1.
79. Tabolacci E, Tringali G, Nobile V, et al. Rutin Protects Fibroblasts from UVA Radiation through Stimulation of Nrf2 Pathway. *Antioxidants*. 2023;12(4):820. doi:10.3390/antiox12040820
80. Andrés CMC, Pérez de la Lastra JM, Juan CA, Plou FJ, Pérez-Lebeña E. Antioxidant Metabolism Pathways in Vitamins, Polyphenols, and Selenium: parallels and Divergences. *Int J Mol Sci*. 2024;25(5):2600. doi:10.3390/ijms25052600
81. Qin X, Lu Y, Peng Z, Fan S, Yao Y. Systematic Chemical Analysis Approach Reveals Superior Antioxidant Capacity via the Synergistic Effect of Flavonoid Compounds in Red Vegetative Tissues. *Front Chem*. 2018;6:9. doi:10.3389/fchem.2018.00009
82. Robichon C, Villeneuve P, Bohuon P, et al. Unveiling synergistic antioxidant combinations for α-tocopherol in emulsions: a spectrophotometric-mathematical approach. *Curr Res Food Sci*. 2025;11:101134. doi:10.1016/j.crfs.2025.101134
83. Jomová K, Hudecova L, Lauro P, et al. A Switch between Antioxidant and Prooxidant Properties of the Phenolic Compounds Myricetin, Morin, 3',4'-Dihydroxyflavone, Taxifolin and 4-Hydroxy-Coumarin in the Presence of Copper(II) Ions: a Spectroscopic, Absorption Titration and DNA Damage Study. *Molecules*. 2019;24(23):4335. doi:10.3390/molecules24234335
84. Di Carlo E, Sorrentino C. Oxidative Stress and Age-Related Tumors. *Antioxidants*. 2024;13(9):1109. doi:10.3390/antiox13091109
85. Baliyan S, Mukherjee R, Priyadarshini A, et al. Determination of Antioxidants by DPPH Radical Scavenging Activity and Quantitative Phytochemical Analysis of *Ficus religiosa*. *Molecules*. 2022;27(4):1326. doi:10.3390/molecules27041326
86. Munteanu IG, Apetrei C. Analytical Methods Used in Determining Antioxidant Activity: a Review. *Int J Mol Sci*. 2021;22(7):3380. doi:10.3390/ijms22073380
87. Hussen EM, Endalew SA. In vitro antioxidant and free-radical scavenging activities of polar leaf extracts of Vernonia amygdalina. *BMC Complement Med Ther*. 2023;23(1):146. doi:10.1186/s12906-023-03923-y
88. Wei M, He X, Liu N, Deng H. Role of reactive oxygen species in ultraviolet-induced photodamage of the skin. *Cell Div*. 2024;19(1):1. doi:10.1186/s13008-024-00107-z
89. Vilchis-Landeros MM, Vázquez-Meza H, Vázquez-Carrada M, Uribe-Ramírez D, Matuz-Mares D. Antioxidant Enzymes and Their Potential Use in Breast Cancer Treatment. *Int J Mol Sci*. 2024;25(11):5675. doi:10.3390/ijms25115675
90. Dibacto REK, Tchuente BRT, Nguedjo MW, et al. Total Polyphenol and Flavonoid Content and Antioxidant Capacity of Some Varieties of Persea americana Peels Consumed in Cameroon. *Sci World J*. 2021;2021:8882594. doi:10.1155/2021/8882594
91. Youn JS, Kim YJ, Na HJ, et al. Antioxidant activity and contents of leaf extracts obtained from Dendropanax morbifera LEV are dependent on the collecting season and extraction conditions. *Food Sci Biotechnol*. 2019;28(1):201–207. doi:10.1007/s10068-018-0352-y
92. Effiong ME, Umeokwochi CP, Afolabi IS, Chinedu SN. Comparative antioxidant activity and phytochemical content of five extracts of Pleurotus ostreatus (oyster mushroom). *Sci Rep*. 2024;14(1):3794. doi:10.1038/s41598-024-54201-x
93. Gulcin İ. Antioxidants: a comprehensive review. *Arch Toxicol*. 2025;99(5):1893–1997. doi:10.1007/s00204-025-03997-2
94. Tan C, Wang Z, Feng X, Irfan M, Changjiang L. Identification of bioactive compounds in leaves and fruits of Actinidia arguta accessions from northeastern China and assessment of their antioxidant activity with a radical-scavenging effect. *Biotechnol Biotechnol Equip*. 2021;35(1):593–607. doi:10.1080/13102818.2021.1908166
95. Pullar JM, Carr AC, Vissers MCM. The Roles of Vitamin C in Skin Health. *Nutrients*. 2017;9(8):866. doi:10.3390/nu9080866
96. Sawada Y, Saito-Sasaki N, Mashima E, Nakamura M. Daily Lifestyle and Inflammatory Skin Diseases. *Int J Mol Sci*. 2021;22(10):5204. doi:10.3390/ijms22105204
97. Dréno B, Dagnelie MA, Khammari A, Corvec S. The Skin Microbiome: a New Actor in Inflammatory Acne. *Am J Clin Dermatol*. 2020;21(Suppl 1):18–24. doi:10.1007/s40257-020-00531-1
98. Xia T, Fu S, Yang R, et al. Advances in the study of macrophage polarization in inflammatory immune skin diseases. *J Inflamm*. 2023;20(1):33. doi:10.1186/s12950-023-00360-z
99. Yu Y, Yue Z, Xu M, et al. Macrophages play a key role in tissue repair and regeneration. *PeerJ*. 2022;10:e14053. doi:10.7717/peerj.14053
100. Kim M, An J, Shin S-A, et al. Anti-inflammatory effects of TP1 in LPS-induced Raw264. 7 macrophages. *Appl Biol Chem*. 2024;67(1):16. doi:10.1186/s13765-024-00873-y

101. Hankittichai P, Buacheen P, Pitchakarn P, et al. Artocarpus lakoocha Extract Inhibits LPS-Induced Inflammatory Response in RAW 264.7 Macrophage Cells. *Int J Mol Sci*. 2020;21(4):1355. doi:10.3390/ijms21041355
102. Ferraz CR, Carvalho TT, Manchope MF, et al. Therapeutic Potential of Flavonoids in Pain and Inflammation: mechanisms of Action, Pre-Clinical and Clinical Data, and Pharmaceutical Development. *Molecules*. 2020;25(3):762. doi:10.3390/molecules25030762
103. Toker G, Küpeli E, Memisoğlu M, Yesilada E. Flavonoids with antinociceptive and anti-inflammatory activities from the leaves of Tilia argentea (silver linden). *J Ethnopharmacol*. 2004;95(2–3):393–397. doi:10.1016/j.jep.2004.08.008
104. Zhang S, Qin C, Safe SH. Flavonoids as aryl hydrocarbon receptor agonists/antagonists: effects of structure and cell context. *Environ Health Perspect*. 2003;111(16):1877–1882. doi:10.1289/ehp.6322
105. Ha AT, Rahmawati L, You L, Hossain MA, Kim JH, Cho JY. Anti-Inflammatory, Antioxidant, Moisturizing, and Antimelanogenesis Effects of Quercetin 3-O-β-D-Glucuronide in Human Keratinocytes and Melanoma Cells via Activation of NF-κB and AP-1 Pathways. *Int J Mol Sci*. 2021;23(1):433. doi:10.3390/ijms23010433
106. Wadhwa K, Kadian V, Puri V, et al. New insights into quercetin nanoformulations for topical delivery. *Phytomedicine Plus*. 2022;2(2):100257. doi:10.1016/j.phyplu.2022.100257
107. Al-Khayri JM, Sahana GR, Nagella P, Joseph BV, Alessa FM, Al-Mssallem MQ. Flavonoids as Potential Anti-Inflammatory Molecules: a Review. *Molecules*. 2022;27(9):2901. doi:10.3390/molecules27092901
108. Alalaiwe A, Lin CF, Hsiao CY, et al. Development of flavanone and its derivatives as topical agents against psoriasis: the prediction of therapeutic efficiency through skin permeation evaluation and cell-based assay. *Int J Pharm*. 2020;581:119256. doi:10.1016/j.ijpharm.2020.119256
109. Yoon JH, Kim MY, Cho JY. Apigenin: a Therapeutic Agent for Treatment of Skin Inflammatory Diseases and Cancer. *Int J Mol Sci*. 2023;24(2):1498. doi:10.3390/ijms24021498
110. Hsu CL, Chhiba KD, Krier-Burris R, et al. Allergic inflammation is initiated by IL-33-dependent crosstalk between mast cells and basophils. *PLoS One*. 2020;15(1):e0226701. doi:10.1371/journal.pone.0226701
111. Chang TM, Hsiao TC, Yang TY, Huang HC. IgE-Induced Mast Cell Activation Is Suppressed by Dihydromyricetin through the Inhibition of NF-κB Signaling Pathway. *Molecules*. 2021;26(13):3877. doi:10.3390/molecules26133877
112. M-m G, W-t X, L-y L, et al. Anti-allergic activity of natural plant products for the treatment of sensitive skin: a review. *Pharmacological Research-Modern Chinese Medicine*. 2022;3:100117. doi:10.1016/j.prmcm.2022.100117
113. Dias MC, Pinto D, Silva AMS. Plant Flavonoids: chemical Characteristics and Biological Activity. *Molecules*. 2021;26(17):5377. doi:10.3390/molecules26175377
114. Koch W, Zagórska J, Marzec Z, Kukula-Koch W. Applications of Tea (Camellia sinensis) and its Active Constituents in Cosmetics. *Molecules*. 2019;24(23):4277. doi:10.3390/molecules24234277
115. Legeas C, Misery L, Fluhr JW, Roudot AC, Ficheux AS, Brenaut E. Proposal for Cut-off Scores for Sensitive Skin on Sensitive Scale-10 in a Group of Adult Women. *Acta Derm Venereol*. 2021;101(1):adv00373. doi:10.2340/00015555-3741
116. Baker P, Huang C, Radi R, Moll SB, Jules E, Arbiser JL. Skin Barrier Function: the Interplay of Physical, Chemical, and Immunologic Properties. *Cells*. 2023;12(23):2745. doi:10.3390/cells12232745
117. Domaszewska-Szostek A, Puzianowska-Kuźnicka M, Kuryłowicz A. Flavonoids in Skin Senescence Prevention and Treatment. *Int J Mol Sci*. 2021;22(13):6814. doi:10.3390/ijms22136814
118. Mlcek J, Jurikova T, Skrovankova S, Sochor J. Quercetin and Its Anti-Allergic Immune Response. *Molecules*. 2016;21(5):623. doi:10.3390/molecules21050623
119. Jo B-G, Bong S-K, Jegal J, Kim S-N, Yang MH. Antiallergic effects of phenolic compounds isolated from Stellera chamaejasme on RBL-2H3 cells. *Nat Prod Commun*. 2020;15(7):1934578X20942352. doi:10.1177/1934578X20942352
120. Chen B, Tang H, Liu Z, et al. Mechanisms of Sensitive Skin and the Soothing Effects of Active Compounds: a Review. *Cosmetics*. 2024;11(6):190. doi:10.3390/cosmetics11060190
121. Wu T, Li Z, Wu Y, et al. Exploring plant polyphenols as anti-allergic functional products to manage the growing incidence of food allergy. *Front Nutr*. 2023;10:1102225. doi:10.3389/fnut.2023.1102225
122. Oršolić N. Allergic Inflammation: effect of Propolis and Its Flavonoids. *Molecules*. 2022;27(19):6694. doi:10.3390/molecules27196694
123. Kawai M, Hirano T, Higa S, et al. Flavonoids and related compounds as anti-allergic substances. *Allergol Int*. 2007;56(2):113–123. doi:10.2332/allergolint.R-06-135
124. Adu SA, Naughton PJ, Marchant R, Banat IM. Microbial Biosurfactants in Cosmetic and Personal Skincare Pharmaceutical Formulations. *Pharmaceutics*. 2020;12(11):1099. doi:10.3390/pharmaceutics12111099
125. Halla N, Fernandes IP, Heleno SA, et al. Cosmetics Preservation: a Review on Present Strategies. *Molecules*. 2018;23(7):1571. doi:10.3390/molecules23071571
126. Salatin S, Bazmani A, Shahi S, Naghili B, Memar MY, Dizaj SM. Antimicrobial Benefits of Flavonoids and their Nanoformulations. *Curr Pharm Des*. 2022;28(17):1419–1432. doi:10.2174/1381612828666220509151407
127. Biharee A, Sharma A, Kumar A, Jaitak V. Antimicrobial flavonoids as a potential substitute for overcoming antimicrobial resistance. *Fitoterapia*. 2020;146:104720. doi:10.1016/j.fitote.2020.104720
128. Alshehrei FM. Microbiological Quality Assessment of Skin and Body care Cosmetics by using Challenge test. *Saudi J Biol Sci*. 2024;31(4):103965. doi:10.1016/j.sjbs.2024.103965
129. Barthe M, Bavoux C, Finot F, et al. Safety testing of cosmetic products: overview of established methods and new approach methodologies (NAMs). *Cosmetics*. 2021;8(2):50. doi:10.3390/cosmetics8020050
130. Singh G, Kumar P. Evaluation of antimicrobial efficacy of flavonoids of withania somnifera L. *Indian J Pharm Sci*. 2011;73(4):473–478. doi:10.4103/0250-474x.95656
131. Kutlu Ö, Karadağ AS, Wollina U. Adult acne versus adolescent acne: a narrative review with a focus on epidemiology to treatment. *An Bras Dermatol*. 2023;98(1):75–83. doi:10.1016/j.abd.2022.01.006
132. Fox L, Csongradi C, Aucamp M, du Plessis J, Gerber M. Treatment Modalities for Acne. *Molecules*. 2016;21(8):1063. doi:10.3390/molecules21081063

133. Kiyama R. Estrogenic flavonoids and their molecular mechanisms of action. *J Nutr Biochem*. 2023;114:109250. doi:10.1016/j.jnutbio.2022.109250
134. Del Rosso JQ, Kircik L. The primary role of sebum in the pathophysiology of acne vulgaris and its therapeutic relevance in acne management. *J DermatolTreat*. 2024;35(1):2296855. doi:10.1080/09546634.2023.2296855
135. Leyva-López N, Gutierrez-Grijalva EP, Ambriz-Perez DL, Heredia JB. Flavonoids as Cytokine Modulators: a Possible Therapy for Inflammation-Related Diseases. *Int J Mol Sci*. 2016;17(6):921. doi:10.3390/ijms17060921
136. Vasam M, Korutla S, Bohara RA. Acne vulgaris: a review of the pathophysiology, treatment, and recent nanotechnology based advances. *Biochem Biophys Rep*. 2023;36:101578. doi:10.1016/j.bbrep.2023.101578
137. Lee YJ, Park KS, Nam HS, Cho MK, Lee SH. Apigenin causes necroptosis by inducing ROS accumulation, mitochondrial dysfunction, and ATP depletion in malignant mesothelioma cells. *Korean J Physiol Pharmacol*. 2020;24(6):493–502. doi:10.4196/kjpp.2020.24.6.493
138. Koch W, Zagórska J, Michalak-Tomczyk M, Karav S, Wawruszak A. Plant Phenolics in the Prevention and Therapy of Acne: a Comprehensive Review. *Molecules*. 2024;29(17):4234. doi:10.3390/molecules29174234
139. Lim HJ, Kang SH, Song YJ, Jeon YD, Jin JS. Inhibitory Effect of Quercetin on *Propionibacterium acnes*-induced Skin Inflammation. *Int Immunopharmacol*. 2021;96:107557. doi:10.1016/j.intimp.2021.107557
140. Amer SS, Nasr M, Abdel-Aziz RTA, et al. Cosm-nutraceutical nanovesicles for acne treatment: physicochemical characterization and exploratory clinical experimentation. *Int J Pharm*. 2020;577:119092. doi:10.1016/j.ijpharm.2020.119092
141. Purnamawati S, Indrastuti N, Danarti R, Saefudin T. The Role of Moisturizers in Addressing Various Kinds of Dermatitis: a Review. *Clin Med Res*. 2017;15(3–4):75–87. doi:10.3121/cmr.2017.1363
142. McDaniel DH, Dover JS, Wortzman M, Nelson DB. In vitro and in vivo evaluation of a moisture treatment cream containing three critical elements of natural skin moisturization. *J Cosmet Dermatol*. 2020;19(5):1121–1128. doi:10.1111/jocd.13359
143. Spada F, Barnes TM, Greive KA. Skin hydration is significantly increased by a cream formulated to mimic the skin's own natural moisturizing systems. *Clin Cosmet Invest Dermatol*. 2018;11:491–497. doi:10.2147/ccid.S177697
144. Levin J, Friedlander SF, Del Rosso JQ. Atopic dermatitis and the stratum corneum: part 1: the role of filaggrin in the stratum corneum barrier and atopic skin. *J Clin Aesthet Dermatol*. 2013;6(10):16–22.
145. Hoober JK, Eggink LL. The Discovery and Function of Filaggrin. *Int J Mol Sci*. 2022;23(3):1455. doi:10.3390/ijms23031455
146. Baldwin H, Del Rosso J. Going Beyond Ceramides in Moisturizers: the Role of Natural Moisturizing Factors. *J Drugs Dermatol*. 2024;23(6):466–471. doi:10.36849/jdd.8358
147. Simonsen S, Thyssen JP, Heegaard S, Kezic S, Skov L. Expression of Filaggrin and its Degradation Products in Human Skin Following Erythemal Doses of Ultraviolet B Irradiation. *Acta Derm Venereol*. 2017;97(7):797–801. doi:10.2340/00015555-2662
148. Kotik M, Kulik N, Valentová K. Flavonoids as Aglycones in Retaining Glycosidase-Catalyzed Reactions: prospects for Green Chemistry. *J Agric Food Chem*. 2023;71(41):14890–14910. doi:10.1021/acs.jafc.3c04389
149. Li X, Liu H, Yang Z, et al. Study on the interaction of hyaluronidase with certain flavonoids. *J Mol Struct*. 2021;1241:130686. doi:10.1016/j.molstruc.2021.130686
150. Misra S, Hascall VC, Markwald RR, Ghatak S. Interactions between Hyaluronan and Its Receptors (CD44, RHAMM) Regulate the Activities of Inflammation and Cancer. *Front Immunol*. 2015;6:201. doi:10.3389/fimmu.2015.00201
151. Diller RB, Tabor AJ. The Role of the Extracellular Matrix (ECM) in Wound Healing: a Review. *Biomimetics*. 2022;7(3):87. doi:10.3390/biomimetics7030087
152. Mamun AA, Shao C, Geng P, Wang S, Xiao J. Recent advances in molecular mechanisms of skin wound healing and its treatments. *Front Immunol*. 2024;15:1395479. doi:10.3389/fimmu.2024.1395479
153. Polito F, Marini H, Bitto A, et al. Genistein aglycone, a soy-derived isoflavone, improves skin changes induced by ovariectomy in rats. *Br J Pharmacol*. 2012;165(4):994–1005. doi:10.1111/j.1476-5381.2011.01619.x
154. He X, Wan F, Su W, Xie W. Research Progress on Skin Aging and Active Ingredients. *Molecules*. 2023;28(14):5556. doi:10.3390/molecules28145556
155. Widgerow AD, Ziegler ME, Garruto JA, Shafiq F. Antioxidants with proven efficacy and elastin-conserving vitamin C-A new approach to free radical defense. *J Cosmet Dermatol*. 2023;22(12):3320–3328. doi:10.1111/jocd.15999
156. Silva S, Michniak-Kohn B, Leonardi GR. An overview about oxidation in clinical practice of skin aging. *An Bras Dermatol*. 2017;92(3):367–374. doi:10.1590/abd1806-4841.20175481
157. Cruz AM, Gonçalves MC, Marques MS, Veiga F, Paiva-Santos AC, Pires PC. In vitro models for anti-aging efficacy assessment: a critical update in dermocosmetic research. *Cosmetics*. 2023;10(2):66. doi:10.3390/cosmetics10020066
158. Bellavite P, Imbriano A. Skin Photoaging and the Biological Mechanism of the Protective Effects of Hesperidin and Derived Molecules. *Antioxidants*. 2025;14(7):788. doi:10.3390/antiox14070788
159. Zouboulis CC, Ganceviciene R, Liakou AI, Theodoridis A, Elewa R, Makrantonaki E. Aesthetic aspects of skin aging, prevention, and local treatment. *Clin Dermatol*. 2019;37(4):365–372. doi:10.1016/j.clindermatol.2019.04.002
160. Ferreira MS, Magalhães MC, Oliveira R, Sousa-Lobo JM, Almeida IF. Trends in the Use of Botanicals in Anti-Aging Cosmetics. *Molecules*. 2021;26(12):3584. doi:10.3390/molecules26123584
161. Cao L, Qian X, Min J, Zhang Z, Yu M, Yuan D. Cutting-edge developments in the application of hydrogels for treating skin photoaging. *Front Mater*. 2024;11:1443514. doi:10.3389/fmats.2024.1443514
162. Abdallah HM, Koshak AE, Farag MA, et al. Taif Rose Oil Ameliorates UVB-Induced Oxidative Damage and Skin Photoaging in Rats via Modulation of MAPK and MMP Signaling Pathways. *ACS Omega*. 2023;8(37):33943–33954. doi:10.1021/acsomega.3c04756
163. Lee JJ, Ng SC, Hsu JY, et al. Galangin Reverses H(2)O(2)-Induced Dermal Fibroblast Senescence via SIRT1-PGC-1α/Nrf2 Signaling. *Int J Mol Sci*. 2022;23(3):1387. doi:10.3390/ijms23031387
164. Anbualakan K, Tajul Urus NQ, Makpol S, et al. A Scoping Review on the Effects of Carotenoids and Flavonoids on Skin Damage Due to Ultraviolet Radiation. *Nutrients*. 2022;15(1):92. doi:10.3390/nu15010092
165. Petruk G, Del Giudice R, Rigano MM, Monti DM. Antioxidants from Plants Protect against Skin Photoaging. *Oxid Med Cell Longev*. 2018;2018:1454936. doi:10.1155/2018/1454936

166. Parashar P, Pal S, Dwivedi M, Saraf SA. Augmented Therapeutic Efficacy of Naringenin Through Microemulsion-Loaded Sericin Gel Against UVB-Induced Photoaging. *AAPS Pharm Sci Tech*. 2020;21(6):215. doi:10.1208/s12249-020-01766-1
167. Goda C, Kulkarni R, Rudich A, et al. Cellular taxonomy of the preleukemic bone marrow niche of acute myeloid leukemia. *bioRxiv*. 2023;39:51.
168. Păcularu-Burada B, Cîrîc AI, Begea M. Anti-Aging Effects of Flavonoids from Plant Extracts. *Foods*. 2024;13(15):2441. doi:10.3390/foods13152441
169. Werner R, Carnazza M, Li XM, Yang N. Effect of Small-Molecule Natural Compounds on Pathologic Mast Cell/Basophil Activation in Allergic Diseases. *Cells*. 2024;13(23):1994. doi:10.3390/cells13231994
170. Stanisic D, Liu LHB, Dos Santos RV, Costa AF, Durán N, Tasic L. New Sustainable Process for Hesperidin Isolation and Anti-Ageing Effects of Hesperidin Nanocrystals. *Molecules*. 2020;25(19):4534. doi:10.3390/molecules25194534
171. Chang TS. Natural Melanogenesis Inhibitors Acting Through the Down-Regulation of Tyrosinase Activity. *Materials*. 2012;5(9):1661–1685. doi:10.3390/ma5091661
172. Chen YP, Li M, Liu Z, Wu J, Chen F, Zhang S. Inhibition of Tyrosinase and Melanogenesis by Carboxylic Acids: mechanistic Insights and Safety Evaluation. *Molecules*. 2025;30(7):1642. doi:10.3390/molecules30071642
173. Qian W, Liu W, Zhu D, et al. Natural skin-whitening compounds for the treatment of melanogenesis (Review). *Exp Ther Med*. 2020;20(1):173–185. doi:10.3892/etm.2020.8687
174. Feng C, Chen X, Yin X, Jiang Y, Zhao C. Matrix Metalloproteinases on Skin Photoaging. *J Cosmet Dermatol*. 2024;23(12):3847–3862. doi:10.1111/jocd.16558
175. Lim H, Kim HP. Inhibition of mammalian collagenase, matrix metalloproteinase-1, by naturally-occurring flavonoids. *Planta Med*. 2007;73(12):1267–1274. doi:10.1055/s-2007-990220
176. Novalia Rahmawati Sianipar R, Suryanegara L, Fatriasari W, et al. The role of selected flavonoids from bajakah tampala (Spatholobus littoralis Hassk.) stem on cosmetic properties: a review. *Saudi Pharm J*. 2023;31(3):382–400. doi:10.1016/j.jsps.2023.01.006
177. Wójciak M, Drozdowski P, Skalska-Kamińska A, et al. Protective, Anti-Inflammatory, and Anti-Aging Effects of Soy Isoflavones on Skin Cells: an Overview of In Vitro and In Vivo Studies. *Molecules*. 2024;29(23):5790. doi:10.3390/molecules29235790
178. Jomova K, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, Valko M. Several lines of antioxidant defense against oxidative stress: antioxidant enzymes, nanomaterials with multiple enzyme-mimicking activities, and low-molecular-weight antioxidants. *Arch Toxicol*. 2024;98(5):1323–1367. doi:10.1007/s00204-024-03696-4
179. Chiu TM, Huang CC, Lin TJ, Fang JY, Wu NL, Hung CF. In vitro and in vivo anti-photoaging effects of an isoflavone extract from soybean cake. *J Ethnopharmacol*. 2009;126(1):108–113. doi:10.1016/j.jep.2009.07.039
180. Thonthula S, Sousa S, Dubuis A, et al. Improved Skin Barrier Function Along with Hydration Benefits of Viola yedoensis Extract, Aesculin, and Schaftoside and LC-HRMS/MS Dereplication of Its Bio-Active Components. *Int J Mol Sci*. 2024;25(23):12770. doi:10.3390/ijms252312770
181. Su W, Matsumoto S, Banine F, et al. A modified flavonoid accelerates oligodendrocyte maturation and functional remyelination. *Glia*. 2020;68(2):263–279. doi:10.1002/glia.23715
182. Wang Y, Mack JA, Maytin EV. CD44 inhibits α-SMA gene expression via a novel G-actin/MRTF-mediated pathway that intersects with TGFβR/p38MAPK signaling in murine skin fibroblasts. *J Biol Chem*. 2019;294(34):12779–12794. doi:10.1074/jbc.RA119.007834
183. Yan W, Cheng J, Xu B. Dietary Flavonoids Vitexin and Isovitexin: new Insights into Their Functional Roles in Human Health and Disease Prevention. *Int J Mol Sci*. 2025;26(14):6997. doi:10.3390/ijms26146997
184. Aboody MSA, Mickymaray S. Anti-Fungal Efficacy and Mechanisms of Flavonoids. *Antibiotics*. 2020;9(2):45. doi:10.3390/antibiotics9020045
185. Mbachu OC, Howell C, Simmler C, et al. SAR Study on Estrogen Receptor α/β Activity of (Iso)flavonoids: importance of Prenylation, C-Ring (Un)Saturation, and Hydroxyl Substituents. *J Agric Food Chem*. 2020;68(39):10651–10663. doi:10.1021/acs.jafc.0c03526
186. Lephart ED. Phytoestrogens (Resveratrol and Equol) for Estrogen-Deficient Skin-Controversies/Misinformation versus Anti-Aging In Vitro and Clinical Evidence via Nutraceutical-Cosmetics. *Int J Mol Sci*. 2021;22(20):11218. doi:10.3390/ijms222011218
187. Pápay ZE, Sebestyén Z, Ludányi K, et al. Comparative evaluation of the effect of cyclodextrins and pH on aqueous solubility of apigenin. *J Pharm Biomed Anal*. 2016;117:210–216. doi:10.1016/j.jpba.2015.08.019
188. Fenyvesi F, Klusóczki Á, Rusznyák Á, Zsebik B, Bácskay I, Váradi J. Cyclodextrin-Based Delivery Systems for Flavonoids: mechanisms, Advances, Formulation, and Application Opportunities. *Antioxidants*. 2025;14(8):998. doi:10.3390/antiox14080998
189. Palafox-Carlos H, Ayala-Zavala JF, González-Aguilar GA. The role of dietary fiber in the bioaccessibility and bioavailability of fruit and vegetable antioxidants. *J Food Sci*. 2011;76(1):R6–R15. doi:10.1111/j.1750-3841.2010.01957.x
190. Ullah A, Munir S, Badshah SL, et al. Important Flavonoids and Their Role as a Therapeutic Agent. *Molecules*. 2020;25(22):5243. doi:10.3390/molecules25225243
191. Sainakham M, Arunlakvilart P, Samran N, Vivattanaseth P, Preedalikit W. Formulation and Stability of Quercetin-Loaded Pickering Emulsions Using Chitosan/Gum Arabic Nanoparticles for Topical Skincare Applications. *Polymers*. 2025;17(13):1871. doi:10.3390/polym17131871
192. Tang Z, Zhang Q. The potential toxic side effects of flavonoids. *Biocell*. 2022;46(2):357. doi:10.32604/biocell.2022.015958
193. Zhang X, Wu C. *In Silico*, *In Vitro*, and *In Vivo* Evaluation of the Developmental Toxicity, Estrogenic Activity, and Mutagenicity of Four Natural Phenolic Flavonoids at Low Exposure Levels. *ACS Omega*. 2022;7(6):4757–4768. doi:10.1021/acsomega.1c04239
194. Haun CT, Mobley CB, Vann CG, et al. Soy protein supplementation is not androgenic or estrogenic in college-aged men when combined with resistance exercise training. *Sci Rep*. 2018;8(1):11151. doi:10.1038/s41598-018-29591-4
195. Messina M, Venter C. Recent surveys on food allergy prevalence. *Nutr Today.* 2020;55(1):22–29. doi:10.1097/NT.0000000000000389