REVIEW ARTICLE

Natural Compound Apigenin Ameliorates Skin Inflammation

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Abstract

The skin functions as the primary protective barrier, mitigating oxidative stress induced by ultraviolet radiation and other components from the environment. It blocks viruses, allergens, and other harmful agents from entering the body. An excessive immune response to these substances can lead to severe skin conditions such as dermatitis, vitiligo, and cancer. The flavonoid family includes kempferol, luteolin, quercetin, and apigenin. Due to its numerous biological effects, apigenin has been used as a dietary supplement. Studies have demonstrated that it alleviates skin inflammation by suppressing key inflammatory markers and molecular pathways. In this review, we discuss the current understanding of skin inflammation and how apigenin formulation reduces skin inflammation.

Key words: Apigenin, Cytokines, Immune, Inflammation, Nanoparticles, Skin

INTRODUCTION

Apigenin is a plant-based flavonoid compound and chemically identified as 5, 7, 4'-trihydroxyflavone.[1] Chronic diseases such as cancer, stroke, diabetes, Alzheimer's, and mental health disorders are major global health burdens. Regular exercise and a healthy diet can help prevent and manage these conditions.[2] A diet rich in fruits and vegetables, which are sources of naturally occurring bioactive chemicals with pro-health qualities, has received special attention. Flavonoids, the largest recurring polyphenol, exhibit a broader range of biological actions, both *in vitro* and *in vivo*, in a variety of mammalian systems. These substances have antiviral, anti-inflammatory, and anti-mutagenic properties and function as antioxidants and free-radical scavengers. In the literature, the Artemisia family of plants has been reported as the prime source of the apigenin compound.[3-5] It has been revealed that apigenin has a wide biological applications, such as anti-inflammatory, antidiabetic, anticancer, and antiapoptotic.[6] In this review, we focus on the recited functional properties of apigenin and its biological potential in skin inflammation.[7] Figure 1 depicts the structure of apigenin.

The epidermis, dermis, and hypodermis are among the layers of the skin that can be separated based on their primary roles.[8] The skin's outermost layer, acknowledged as the epidermis, acts as a barrier to keep outside stimuli from disturbing the skin.[9,10] In addition, it serves as a defense mechanism to maintain immunological homeostasis in the face of several pathogens, including viruses, bacteria, and antigens.[11] Keratinocytes make up the mainstream of the epidermis, along with a small number of Merkel cells, melanocytes, and Langerhans cells (LCs).[12]

LCs, a type of dendritic cell (DC), present antigens for the innate immune response. Upon ultraviolet (UV) exposure, keratinocytes show reduced E-cadherin expression, activating LCs. LCs migrate to the lymph nodes, promoting the development of regulatory T cells.[13-15] Idoyaga *et al*.[16] suggest that immunomodulatory treatments can target cutaneous DCs. The skin microbiota helps maintain the epidermis' acidity, protecting against external infections.[16-18] Skin microbiota maintain immune homeostasis by forming a balanced community. Disruption of this balance can lead to disorders such as vitiligo, psoriasis, acne, pruritus, and skin cancer.[17,19,20] Traditional treatments mainly use steroidal

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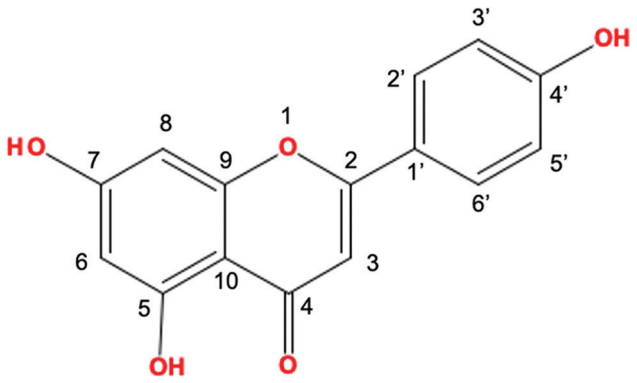

Figure 1: Structure of Apigenin

and non-steroidal drugs to reduce inflammation.[21-23] However, research into natural molecules to replace chemical medications has increased due to the negative consequences of anti-inflammatory pharmaceuticals.[24]

MECHANISM OF ACTION OF APIGENIN IN THE TREATMENT OF SKIN DISEASE

Skin diseases are complex responses to various external and internal stimuli, which include contact dermatitis, atopic dermatitis (eczema), psoriasis, acne, urticaria, lichen planus, hidradenitis suppurativa, alopecia areata, and vitiligo. Apigenin, a flavonoid found in various plants, exhibits significant therapeutic potential in treating skin diseases involving a range of immune cells, cytokines, and signaling pathways through multiple mechanisms, primarily by reducing inflammation, modulating immune responses, and protecting against UV-induced damage.[25]

Several mechanisms of apigenin in skin diseases are depicted as follows:

Anti-inflammatory effect

Apigenin has potent anti-inflammatory properties. Apigenin downregulates various inflammatory markers and molecular targets, including cytokines such as interleukin (IL)-6, IL-1β, tumor necrosis factor-alpha (TNF-α), and cyclooxygenase-2 (COX-2), which are involved in skin inflammation and allergic responses. Apigenin inhibits the phosphorylation of mitogen-activated protein kinase signal molecules (extracellular signal-regulated kinase, Jun N-terminal kinase) and nuclear factor kappa B (NF-Kb), which are critical pathways in the inflammatory response. Further, it modulates IL-31, a cytokine implicated in inflammatory diseases and itch in atopic dermatitis, by inhibiting its messenger RNA and protein expression in mast cells.[26-28] Figure 2 depicts the Apigenin pathway in ameliorating skin inflammation.

Immune modulation

Apigenin can modulate both innate and adaptive immune responses, which is particularly useful in treating autoimmune or hypersensitivity-driven skin conditions. Apigenin has been shown to inhibit histamine release, which is crucial in allergic reactions. Apigenin promotes the expression of skin barrier proteins such as filaggrin, loricrin, and antimicrobial peptides (LL-37, human beta-defensin [HBD]-1, HBD-2, and HBD-3), enhancing both physical and chemical barriers of the skin.[29,30]

Antioxidant effects

Apigenin exhibits antioxidant activity by scavenging reactive oxygen species (ROS), reducing oxidative damage to skin cells, and thereby protecting against skin aging and inflammatory damage. Apigenin enhances the skin's antioxidative capacity by increasing levels of endogenous antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase. These enzymes help neutralize ROS and mitigate the cellular damage they cause, offering protection against oxidative stress that accelerates skin aging and exacerbates inflammatory conditions. Furthermore, it reduced oxidative stress markers such as malondialdehyde. Further, it activates the Nrf2 pathway, which is vital for antioxidant defense, and suppresses NF-κB, a key regulator of inflammation.[30,31]

Inhibition of skin aging

Skin aging refers to the premature aging of the skin due to prolonged UV exposure. Apigenin, with its anti-inflammatory and antioxidant properties, reduces signs of skin aging by decreasing the expression of matrix metalloproteinase-1 (MMP-1), a collagenase that degrades the skin matrix, thereby improving skin elasticity and reducing wrinkles.[32]

Anti-cancer properties

Apigenin's role as a chemopreventive agent can be beneficial in preventing or controlling the development of skin cancers, particularly in individuals with a history of chronic sun exposure. Apigenin inhibits UVB-induced skin carcinogenesis by promoting the expression of antiangiogenic proteins such as thrombospondin-1 and targeting Src kinase.[33,34]

Skin rejuvenation

Apigenin can stimulate the production of collagen, a key structural protein involved in skin repair. By increasing collagen synthesis, apigenin can support the regeneration of healthy skin tissue after injury or inflammation.[35]

Cell cycle regulation

Apigenin induces G2/M arrest in keratinocytes by inhibiting the kinase activity of p34cdc2, a cyclin-dependent kinase crucial for cell cycle progression, and reducing cyclin B1 levels, which are essential for the G2/M transition.[36] Apigenin also affects other phases of the cell cycle, such as G0/G1 arrest, by modulating cyclin D1 and E levels and inhibiting CDK1 activity, further contributing to its antiproliferative effects.[37]

APIGENIN IN VARIOUS FORMULATIONS

Apigenin has been explored in various formulations for treating skin diseases due to its anti-carcinogenic, anti-inflammatory, and antioxidant properties. Here are some notable formulations and their potential benefits:

Nanoparticles

Apigenin encapsulated in poly (lactic-co-glycolide) nanoparticles showed enhanced cellular entry, DNA targeting, and induced apoptosis in melanoma cells. This formulation also preserved apigenin from UV-light-mediated photodegradation, making it a potent option for skin melanoma treatment.[38]

Nanocrystals

These nanocrystals, which were prepared using bead milling and high-pressure homogenization, exhibited enhanced antioxidant capacity and could be easily incorporated into gels for dermal application, providing efficient UV skin protection.[39]

Carbopol-based nano emulsion gel

This formulation uses tamarind gum emulsifiers and shows high drug content, good physical stability, and enhanced skin penetration. It demonstrated significant cytotoxicity against melanoma cells while being less toxic to normal skin cells, suggesting its potential for treating skin cancer.[40]

Topical cream

This cream formulation was shown to increase dermal density and elasticity, reduce fine wrinkles, and improve skin moisture and texture. It also decreased the expression of MMP-1, which is associated with skin aging.

Ointment

In this ointment, apigenin combines with the phage lysin LysGH15, showing bactericidal activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and reducing pro-inflammatory cytokines. It also accelerated wound healing in MRSA-infected skin wounds.[41]

Ethosome formulation

Apigenin-loaded ethosomes, which comprise phospholipids and short-chain alcohols, showed superior skin targeting

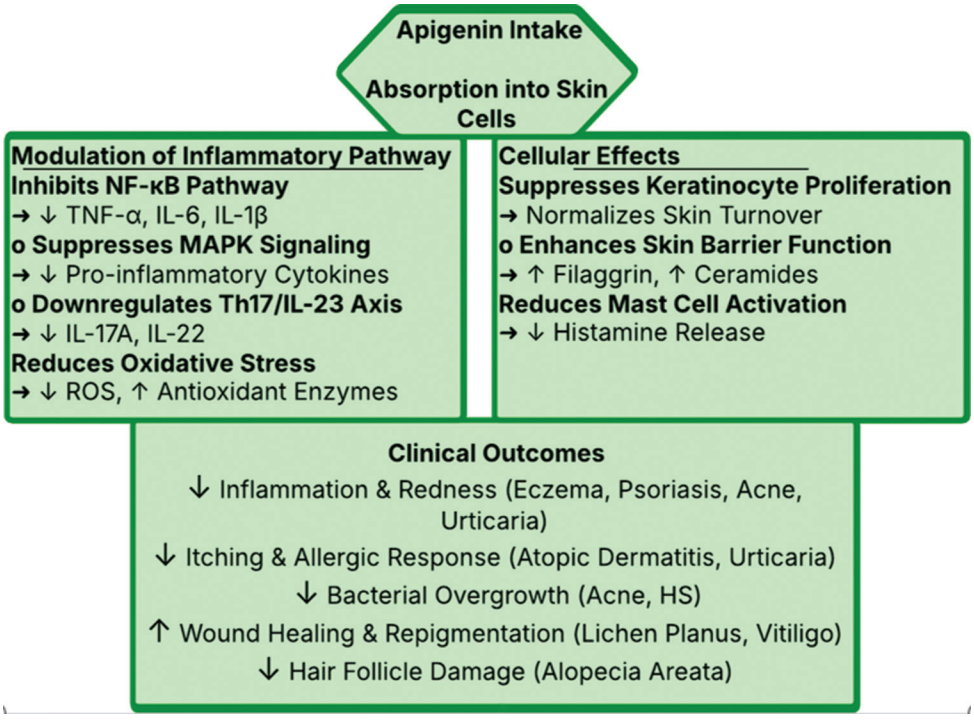

Figure 2: Apigenin pathway in ameliorating skin inflammation

and improved skin deposition both *in vitro* and *in vivo*. This formulation effectively reduced cyclooxygenase-2 levels in UVB-induced skin inflammation, indicating its promise for treating UVB-induced skin conditions.[42]

Apigenin clinical efficacy

Most of the clinical evidence for apigenin is early-stage, with only a handful of human trials published or in progress showing good safety and low toxicity, but conclusive efficacy in large, well-controlled trials is lacking. The few available clinical trials mainly supported the potential protective effects of apigenin (or extracts rich in apigenin) on insomnia, anxiety disorders and depression, knee osteoarthritis, and Alzheimer's disease.[43,44]

In clinical studies involving an apigenin-containing cream, participants showed improvements in dermal density, elasticity, and a reduction in fine wrinkles after consistent application over 4 weeks. The cream also enhanced skin moisture levels and reduced transepidermal water loss, indicating improved barrier function.[29]

In another study, apigenin's therapeutic potential is underscored by human clinical studies using chamomile extract, which contains apigenin as an active ingredient. Collectively, chamomile extract has been reported to alleviate anxiety, improve mood, and relieve pain.[45]

Apigenin is considered safe and promising based on pre-clinical and emerging pilot clinical data, but more comprehensive human trials are needed to confirm its therapeutic efficacy and clarify optimal dosing and indications for clinical use.

Limitations of the study

The primary limitation of this review is the insufficient availability of robust human clinical research data on apigenin. This gap restricts the direct translation of the promising *in vitro* and animal-based findings to human health applications. Clinical evidence remains limited and scattered, particularly regarding apigenin's effects on cancer, inflammatory disorders, and cognitive function. Consequently, most current understanding is still derived from pre-clinical models.

In addition, apigenin's inherent physicochemical and pharmacokinetic challenges—such as low water solubility, rapid metabolism, and poor oral bioavailability—pose significant barriers to both its therapeutic utilization and an accurate assessment of its *in vivo* efficacy. These limitations further complicate the establishment of optimal dosage regimens and clarity on structure-function relationships relevant to human use.

To overcome these constraints, future research should prioritize well-designed clinical trials, improved formulation and delivery strategies, and comprehensive long-term safety evaluations.

CONCLUSION

Apigenin has demonstrated anti-inflammatory effects by reducing levels of cytokines such as IL-1β, IL-6, TNF-α, and COX-2, potentially making it a promising treatment for inflammatory skin conditions. Given the adverse effects of synthetic drugs, natural compounds such as apigenin are being actively studied. It has been applied to damaged skin or cells in previous research to alleviate inflammation. In addition, apigenin, often derived from chamomile, is available in supplements for promoting skin health and reducing stress. Overall, apigenin shows potential both as a therapeutic agent and a health supplement for skin-related conditions.

CONSENT FOR PUBLICATION

All authors agree to publish an article.

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REFERENCES

1. Tang D, Chen K, Huang L, Li J. Pharmacokinetic properties and drug interactions of apigenin, a natural flavone. Expert Opin Drug Metab Toxicol 2017;13:323-30.
2. Wang M, Firrman J, Liu L, Yam K. A review on flavonoid apigenin: Dietary intake, ADME, antimicrobial effects, and interactions with human gut microbiota. Biomed Res Int 2019;2019:7010467.
3. Ornano L, Venditti A, Donno Y, Sanna C, Ballero M, Bianco A. Phytochemical analysis of non-volatile fraction of *Artemisia caerulescens* subsp. densiflora (Viv.) (Asteraceae), an endemic species of La Maddalena Archipelago (Sardinia--Italy). Nat Prod Res 2016;30:920-5.
4. Venditti A, Maggi F, Vittori S, Papa F, Serrilli AM, Di Cecco M, *et al.* Antioxidant and α-glucosidase inhibitory activities of *Achillea tenorii*. Pharm Biol 2015;53:1505-10.
5. Sharifi-Rad M, Nazaruk J, Polito L, Morais-Braga MF, Rocha JE, Coutinho HD, *et al. Matricaria* genus as a source of antimicrobial agents: From farm to pharmacy

and food applications. Microbiol Res 2018;215:76-88.
6. Venditti A, Frezza C, Sciubba F, Serafini M, Bianco A, Cianfaglione K, *et al.* Volatile components, polar constituents and biological activity of tansy daisy (*Tanacetum macrophyllum* (Waldst. et Kit.) Schultz Bip.). Ind Crops Prod 2018;118:225-35.
7. Zhou Z, Zhang Y, Lin L, Zhou J. Apigenin suppresses the apoptosis of H9C2 rat cardiomyocytes subjected to myocardial ischemia-reperfusion injury via upregulation of the PI3K/Akt pathway. Mol Med Rep 2018;18:1560-70.
8. Wang J, Liu YT, Xiao L, Zhu L, Wang Q, Yan T. Anti-inflammatory effects of apigenin in lipopolysaccharide-induced inflammatory in acute lung injury by suppressing COX-2 and NF-kB pathway. Inflammation 2014;37:2085-90.
9. Hsu YC, Li L, Fuchs E. Emerging interactions between skin stem cells and their niches. Nat Med 2014;20:847-56.
10. Belkaid Y, Tamoutounour S. The influence of skin microorganisms on cutaneous immunity. Nat Rev Immunol 2016;16:353-66.
11. Byrd AL, Belkaid Y, Segre JA. The human skin microbiome. Nat Rev Microbiol 2018;16:143-55.
12. Nestle FO, Di Meglio P, Qin JZ, Nickoloff BJ. Skin immune sentinels in health and disease. Nat Rev Immunol 2009;9:679-91.
13. Abdo JM, Sopko NA, Milner SM. The applied anatomy of human skin: A model for regeneration. Wound Med 2020;28:100179.
14. Tang A, Amagai M, Granger LG, Stanley JR, Udey MC. Adhesion of epidermal Langerhans cells to keratinocytes mediated by E-cadherin. Nature 1993;361:82-5.
15. Schwarz A, Noordegraaf M, Maeda A, Torii K, Clausen BE, Schwarz T. Langerhans cells are required for UVR-induced immunosuppression. J Invest Dermatol 2010;130:1419-27.
16. Idoyaga J, Fiorese C, Zbytnuik L, Lubkin A, Miller J, Malissen B, *et al.* Specialized role of migratory dendritic cells in peripheral tolerance induction. J Clin Invest 2013;123:844-54.
17. Scharschmidt TC, Fischbach MA. What lives on our skin: Ecology, genomics and therapeutic opportunities of the skin microbiome. Drug Discov Today Dis Mech 2013;10:e83-9.
18. Belkaid Y, Segre JA. Dialogue between skin microbiota and immunity. Science 2014;346:954-59.
19. McLoughlin IJ, Wright EM, Tagg JR, Jain R, Hale JD. Skin microbiome-the next frontier for probiotic intervention. Probiotics Antimicrob Proteins 2022;14:630-47.
20. Iebba V, Totino V, Gagliardi A, Santangelo F, Cacciotti F, Trancassini M, *et al.* Eubiosis and dysbiosis: The two sides of the microbiota. New Microbiol 2016;39:1-12.
21. Di Meglio P, Perera GK, Nestle FO. The multitasking organ: Recent insights into skin immune function. Immunity 2011;35:857-69.
22. Abdulla A, Adams N, Bone M, Elliott AM, Gaffin J, Jones D, Knaggs R, *et al.* Guidance on the management of pain in older people. Age Ageing 2013;42:i1-57.
23. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. Eur J Pain 2006;10:287-333.
24. Conaghan PG. A turbulent decade for NSAIDs: Update on current concepts of classification, epidemiology, comparative efficacy, and toxicity. Rheumatol Int 2012;32:1491-502.
25. Borquaye LS, Darko G, Laryea MK, Roberts V, Boateng R, Gasu EN. Anti-inflammatory activities of extracts from *Oliva* sp., *Patella rustica*, and *Littorina littorea* collected from Ghana's coastal shorelines. Cogent Biol 2017;3:1364063.
26. Byun S, Park J, Lee E, Lim S, Yu JG, Lee SJ, *et al.* Src kinase is a direct target of apigenin against UVB-induced skin inflammation. Carcinogenesis 2013;34:397-405.
27. Che DN, Cho BO, Shin JY, Kang HJ, Kim JS, Oh H, *et al.* Apigenin inhibits IL-31 cytokine in human mast cell and mouse skin tissues. Molecules 2019;24:1290.
28. Cheng M, Zhang L, Zhang H, Li X, Wang Y, Xia F, *et al.* An ointment consisting of the phage lysin LysGH15 and apigenin for decolonization of methicillin-resistant *Staphylococcus aureus* from skin wounds. Viruses 2018;10:244.
29. Choi S, Youn J, Kim K, Joo DH, Shin S, Lee J, *et al.*, Apigenin inhibits UVA-induced cytotoxicity *in vitro* and prevents signs of skin aging *in vivo*. Int J Mol Med 2016;38:627-34.
30. Das S, Das J, Samadder A, Paul A, Khuda-Bukhsh AR. Strategic formulation of apigenin-loaded PLGA nanoparticles for intracellular trafficking, DNA targeting and improved therapeutic effects in skin melanoma *in vitro*. Toxicol Lett 2013;223:124-38.
31. Jangdey MS, Gupta A, Saraf S. Fabrication, *in-vitro* characterization, and enhanced *in-vivo* evaluation of carbopol-based nanoemulsion gel of apigenin for UV-induced skin carcinoma. Drug Deliv 2017;24:1026-36.
32. Lepley DM, Li B, Birt DF, Pelling JC. The chemopreventive flavonoid apigenin induces G2/M arrest in keratinocytes. Carcinogenesis 1996;17:2367-75.
33. Li J, Mao B, Tang X, Zhang Q, Zhao J, Zhang H, *et al*. Protective effects of naringenin and apigenin in ameliorating skin damage via mediating the Nrf2 and NF-κB pathways in mice. Foods 2023;12:2120.
34. Maggioni D, Garavello W, Rigolio R, Pignataro L, Gaini R, Nicolini G. Apigenin impairs oral squamous cell carcinoma growth *in vitro* inducing cell cycle arrest and apoptosis. Int J Oncol 2013;43:1675-82.
35. Mirzoeva S, Tong X, Bridgeman BB, Plebanek MP, Volpert OV. Apigenin inhibits UVB-induced skin carcinogenesis: The role of thrombospondin-1 as an anti-inflammatory factor. Neoplasia 2018;20:930-42.
36. Oo AM, Mat Nor MN, Lwin OM, Simbak N, Adnan LH, Mahadeva Rao US. Immunomodulatory effects of apigenin, luteolin, and quercetin through natural killer

cell cytokine secretion. J Appl Pharm Sci 2022;12:121-6.
37. Park CH, Min SY, Yu HW, Kim K, Kim S, Lee HJ, *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;21:4620.
38. Majma Sanaye P, Mojaveri MR, Ahmadian R, Sabet Jahromi M, Bahramsoltani R. Apigenin and its dermatological applications: A comprehensive review. Phytochemistry 2022;203:113390.
39. Al Shaal L, Shegokar R, Müller RH. Production and characterization of antioxidant apigenin nanocrystals as a novel UV skin protective formulation. Int J Pharm 2011;420:133-40.
40. Shen LN, Zhang YT, Wang Q, Xu L, Feng NP. Enhanced *in vitro* and *in vivo* skin deposition of apigenin delivered using ethosomes. Int J Pharm 2014;460:280-8.
41. Yoon JH, Kim MY, Cho JY. Apigenin: A therapeutic agent for treatment of skin inflammatory diseases and cancer. Int J Mol Med Sci 2023;24:1498.
42. Zhang Y, Wang J, Cheng X, Yi B, Zhang X, Li Q. Apigenin induces dermal collagen synthesis via smad2/3 signaling pathway. Eur J Histochem 2015;59:2467.
43. Nabavi SF, Khan H, D'onofrio G, Šamec D, Shirooie S, Dehpour AR, *et al.* Apigenin as neuroprotective agent: Of mice and men. Pharmacol Res 2018;128:359-65.
44. Jiang X, Huang H. The therapeutic potential of apigenin against atherosclerosis. Heliyon 2025;11:e41272.
45. Kramer DJ, Johnson AA. Apigenin: A natural molecule at the intersection of sleep and aging. Front Nutr 2024;11:1359176.

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