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Understanding the Therapeutic Versatility of Apigenin and Quercetin: Broad Applications in Health and Wellness

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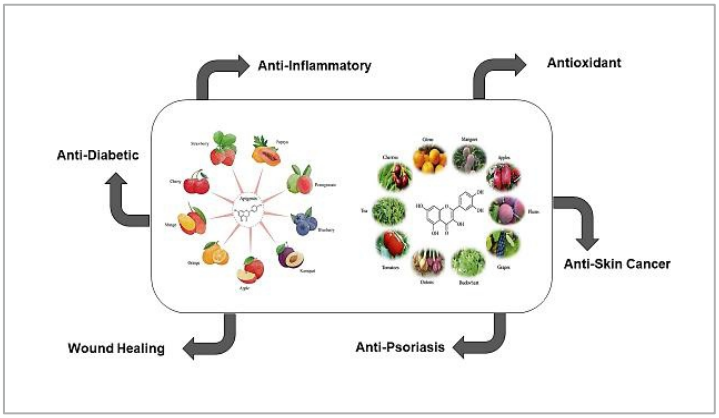
ABSTRACT

Apigenin and Quercetin have gained significant attention due to their abundance in fruits and vegetables, as well as their pharmacological properties. These naturally occurring flavonoids are widely researched because of their low toxicity and diverse biological activities. Apigenin is found in parsley, celery, chamomile, and oranges, whereas Quercetin is abundant in apples, onions, berries, and tea. Both compounds exhibit strong antioxidant properties by scavenging free radicals, reducing oxidative stress, and preventing cellular damage. Their anti-inflammatory effects are mediated through the inhibition of pro-inflammatory cytokines, suppression of NF-κB signaling pathways, and modulation of immune responses. Furthermore, they have demonstrated significant potential in wound healing by promoting collagen synthesis, enhancing fibroblast proliferation, and improving tissue regeneration. Additionally, both flavonoids have shown promise as anti-psoriasis agents by modulating keratinocyte proliferation and reducing inflammatory markers. Their anti-cancer activities have been extensively studied, with evidence supporting their role in inhibiting tumor growth, inducing apoptosis, and suppressing metastasis in various cancer models. Moreover, their anti-diabetic properties are attributed to their ability to regulate glucose metabolism, improve insulin sensitivity, and reduce oxidative damage associated with diabetes-related complications. This review aims to provide comprehensive insights into the pharmacological applications of Apigenin and Quercetin, emphasizing their various properties. By exploring their mechanisms of action and potential therapeutic applications, this research offers a scientific foundation for further studies and the development of novel formulations for medical and pharmaceutical use. Their diverse benefits highlight the need for more in-depth investigations to optimize their clinical applications and enhance their bioavailability.

Keywords: *Flavonoids, Anti-inflammatory, Antioxidant, Anti-psoriasis, Anticancer*

Graphical Summary



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Introduction

Flavonoids are quite an important class of natural substances. Specifically, these are a type of secondary metabolic by-products from crops that have a polyphenolic framework as well as are frequently found in vegetables, fruits, and some beverages [1]. These substances provide plants with a defense against diseases, UV rays, and herbivores [2]. Anthocyanins, flavones, flavanols, flavanones, dihydroflavonols, chalcones, aurones, flavan, proanthocyanidins, isoflavonoids, etc. represent a few of the classes into which flavonoids are classified [3].

The name "apigenin" comes from the genus Apium, which belongs to the family Apiaceae, which is primarily composed of aromatic floral plants like parsley, carrot, along with celery. Apigenin (Figure 1) is present principally as glycosylated in significant amount in parsley, celery, onions, oranges, chamomile, thyme, oregano, basil, and tea, beer, and wine [4]. One of the most prevalent flavonoids in plants is apigenin. Versulin, 4′,5,7-trihydroxyflavone, is the different name for this substance [5]. Apigenin belongs to the subclass of flavonoids called flavones, based on the chemical makeup of its backbone [6]. Because of apigenin's exceptional effects on malignant vs normal cells and low intrinsic toxicity, there is a growing curiosity regarding it as a health-beneficial drug, in recent times [7]. Human daily consumption of this phytochemical is thought to vary from 0.0 to 18.0 mg [8]. Certain Asteraceae plants have been found to contain apigenin, including *Artemisia* [9], *Achillea* [10], *Matricaria* [11], and *Tanacetum* [12] genera. Apigenin can also be identified across multiple genera of the family Lamiaceae that involves *Sideritis* [13] and *Teucrium* [14].

Furthermore, recent research has identified apigenin as a key active ingredient in a number of other plants used for medicinal purposes, such as *Gentiana veitchiorum* Hemsl. [15], *Endodesmia calophylloides* Benth as well as *Hymenostegia afzelii* (Oliver) Harms[16], *Alphonsea elliptica* Hook.f. & Thomson [17], Wedelia *chinensis* (Osbeck) Merr. [18], along with *Carduus crispus* Guirão ex Nyman [19]. Apigenin has additionally been discovered in other species as a biologically active molecule, including *Portulaca oleracea* L. (Portulacaceae), *Combretum erythrophyllum* (Combretaceae), *Scutellaria barbata* D. Don (Lamiaceae), *Marrubium globosum* ssp. *Libanoticum* (Lamiaceae), *Gentiana veitchiorum* (Gentianaceae)[20].

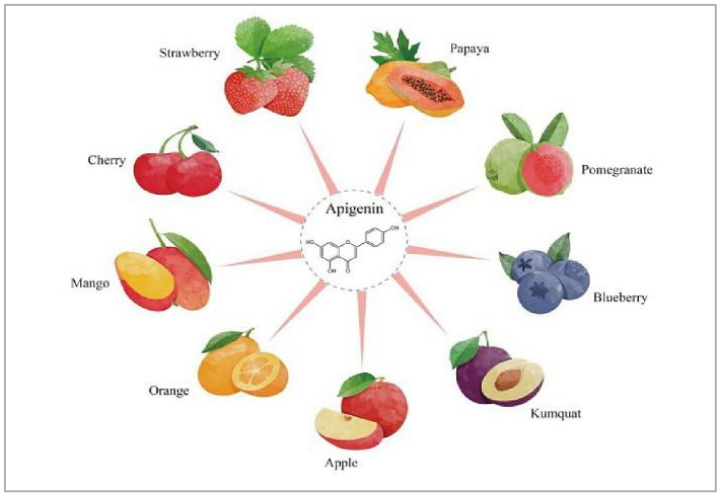

Figure 1. Source of Apigenin.

The flavonoid quercetin's Latin name, "Quercetum," implies "oak forest". Quercetin is a flavonol that the human body does not synthesize [21]. It acts as a potent molecule which is capable of being utilized to address a wide range of health issues [22]. Quercetin (2-(3,4-dihydroxy phenyl)-3,5,7-trihydroxychromen-4-one) is a dietary flavonoid that belongs to the flavonols subgroup [23]. It is a key plant molecule that has anti-atopic, antiviral, anti-inflammatory and also pro-metabolic properties. It has also been shown to have a variety of anticancer properties. Also has a psychostimulant property, and has also been reported to increase mitochondrial biogenesis, reduce lipid peroxidation, capillary permeability and to mitigate platelet aggregation [24,25].

Quercetin is also a promising component that has the potential to prevent lifestyle-related diseases (Figure 3) [26]. The estimated daily intake of quercetin in the diet is 5-40 mg/day [27]. *Hypericum perforatum*, *Ginkgo biloba*, and elderberry are all plants with medicinal properties that contain quercetin [28-30]. Plants containing quercetin involves *Camellia sinensis* (Theaceae), *Morus alba* (Moraceae), *Calamus scipionum* (Calamoidaceae), *Centella asiatica* (Apiaceae), *Allium fistulosum* (Amaryllidaceae), *Moringa oleifera* (Moringa), *Nasturtium officinale* (Brassicaceae), *Hypericum hiricinum* (Clusiaceae), *Brassica oleoracea* (Brassicaceae), *Apium graveolens* (Apiaceae), *Coriandrum sativum* (Apiaceae), *Lactuca sativa* (Asteraceae), *Allium cepa* (Liliaceae), *Capparis spinosa* (Capparaceae), *Hypericum perforatum* (Hyperiaceae), *Prunus domestica* (Rosaceae), *Asopargus officinalis* (Aspargaceae), *Malus domestica* (Rosaceae), *Vaccinium oxycoccus* (Ericaceae), *Prunus avium* (Rosaceae), *Solanum lycopersicum* (Solanaceae), *Brassica oleoracea* (Brassicaceae), *Ginkgo biloba* (Ginkgoaceae), *Vitis vinifera* (Vitaceae) along with *Sambucus canadensis* (Adoxaceae) [31-35]. The richest source of quercetin is onion, one of the most popular vegetables, both edible and medicinal [36]. Other sources include grapes, cherries, apples, mangoes, citrus fruits, buckwheat, plums, tomatoes, and tea [37,38] (Figure 2). Table 1 and Table 2 depict the potential biological effects of quercetin and apigenin, respectively, and their proposed mechanism of action.

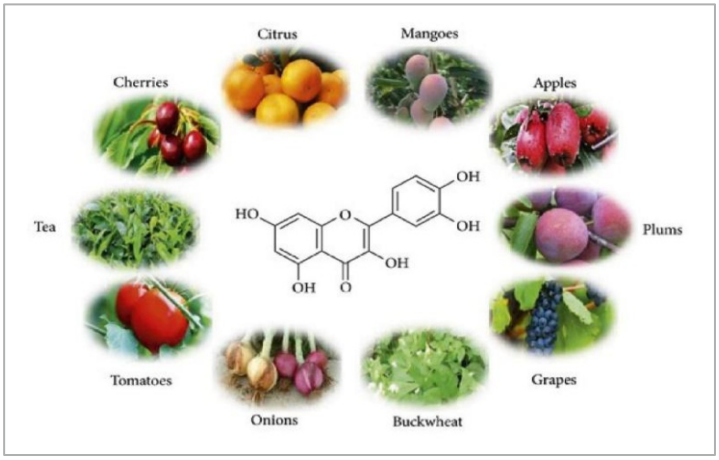

Figure 1. Source of Quercetin.

Table 1. Possible biological effects of quercetin and their anticipated mechanism of actions

Application	Drug	Mechanism of Action
Anti-inflammatory	Quercetin	Impedes pro-inflammatory cytokines like IL-1β, IL-6, TNF-α and inflammation mediators like nitric oxide and catalase. Decreases inflammatory reactions mediated by c-Jun N-terminal kinase and Erk1/2 and suppress LOX and COX. Inhibits action of I-κB-phosphorylation and NF-κB translocation, reporter gene transcription, and AP-1 action.
Anti-oxidant	Quercetin	Scavenges free radicals, ROS and RNS. Increases level of aldo-keto reductase and glutathione transferase, raise level of intracellular GSH, induce intracellular p38 MAPK pathway. Increase enzymes like catalase and superoxide dismutase (SOD), chelating copper and iron, prevent oxidative stress-induced cell death and suppress nitric oxide synthase and oxidases enzymes.
Anti-skin cancer	Quercetin	Inhibits MAP kinase and PI3K signaling, increases apoptosis and decreases cell viability, boosts UVB-induced NF-κB nuclear translocation, decreases MEK–ERK signaling, reduces Bcl-2 expression, potentiating caspase-3 activity, inhibits transcription 3 (STAT3) activator, oxidative stress induced by UVB and damage of DNA.
Anti-psoriasis	Quercetin	Reduces the levels of TNF-α, IL-17 and IL-6, MDA growth, PASI scores and drops the temperature of psoriasis-like abrasions.
Anti-diabetic	Quercetin	Inhibits α-amylase and α-glucosidase, lowers level of serum blood glucose, raises the levels of insulin, reduces the level of oxidative stress, elevate the expression of GLUT4 and phosphorylation of both AMPK/Akt and PI3K/Akt.
Wound healing	Quercetin	Fibroblast proliferation, collagen deposition, accelerates closure of wounds, promotes regeneration of epithelial layer, reduces oxidative stress, raises the levels of VEGF, Increase TGF-β1, GAP-43, IL-10, CD31, PCNA, and α-SMA, decrease levels of TNF-α, blocks MAPK pathway and increases keratinocyte recovery.

Table 2. Potential biological effect of apigenin and their proposed mechanism of actions

Application	Drug	Mechanism of Action
Anti-inflammatory	Apigenin	Inhibits CXCL1/KC and CCL2/MCP-1 expression, TNF-α-induced NF-κB and JNK activation, reduce the expression of COX-2 and the production of NO induced by lipopolysaccharide, inhibits TNF-α-induced upregulation of E-selectin, intracellular adhesion molecule-1, vascular cellular adhesion molecule-1, and expression for the gene IL-1β, prevents phosphorylation of ERK/MAPK, and p38 pathways and inhibits expression of ICAM-1, IL-8, ROS and IL-6.
Antioxidant	Apigenin	Increases GCLM, GCLC, and HO-1 gene transcription through ARE /Nrf2/ ERK2 signaling pathways, GSH-to-oxidized GSH ratio, intracellular GSH levels, lowers the levels of malondialdehyde, remove endogenous ROS, increase the expression of AMPK and Nrf2 and protects against DNA damage.
Anti-skin cancer	Apigenin	Increases production of ROS, reduces SOD, GSH levels and ERK 1/2 and FAK function, down-regulating STAT3 signaling, suppression of Twist1, MMP-2, -9 and VEGF G2/M cell cycle arrest, restricts cell proliferation and induce apoptosis, suppression of the Akt/mTOR pathway, inhibits COX-2, decreases expression of receptors EP1, EP2 and prostaglandin PGE2 and increases terminal differentiation.
Anti-psoriasis	Apigenin	Reduces the cytokine levels, increase stratum corneum hydration and produce skin structural proteins like loricrin, filaggrin and involucrin.
Anti-diabetic	Apigenin	Increases insulin secretion, neutralizes ROS, prevents the activity of α-glucosidase, lowers ICAM-1 levels, serum lipid, blood glucose, malonaldehyde levels and insulin resistance index and increases Superoxide dismutase.
Wound healing	Apigenin	Wound re-epithelialization, enhances inflammation and increase wound closure.

1. Physical characteristics of Apigenin

Apigenin exists as a crystalline solid having yellow color with a melting point between 345°C and 350°C. The chemical formula for apigenin is $C_{15}H_{10}O_5$, (Figure 3) and its molecular weight is 270.24 [39]. Naturally, apigenin is often present in two different forms, pure and glycosylated. The large amount of the hydroxyl groups present in pure apigenin promotes degradation and makes it unstable, in contrast, glycosylated forms tend to be highly stable. For a long period of time, apigenin in its pure form must be stored at -20°C. Apigenin glycosides have higher water solubility due to their increased polarity and stability [40-42]. Organic solvents such as dimethyl sulfoxide (DMSO), ethanol as well as dimethylformamide (DMF) dissolve it, but in water, it is practically insoluble [43,44].

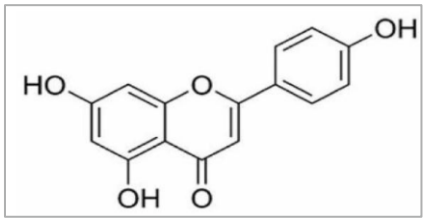

Figure 2. Chemical structure of Apigenin.

2. Physical characteristics of Quercetin

Quercetin is a bitter-tasting, crystalline solid having yellow color and is known to be soluble within glacial acetic acid as well as alkaline solutions but insoluble in water. It is also only marginally soluble in alcohol [45-47]. Their flavone nucleus is made up of two rings of benzene connected through a heterocyclic pyrone ring. Plants are the only sources of flavonoids because animals cannot synthesize the nucleus of flavones. Quercetin, as well as over 2,000 more flavonoids are p-glycoside condensation products [48-51]. Its molecular formula is $C_{15}H_{10}O_7$ depicted in Figure 4 [52].

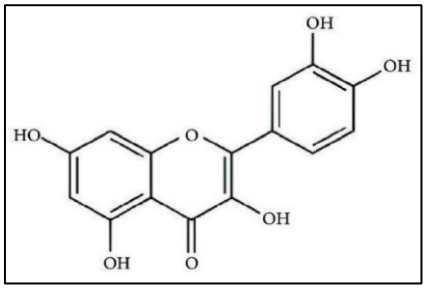

Figure 3. Chemical structure of Quercetin.

3. Therapeutic Potential of Apigenin and Quercetin

Apigenin and quercetin are naturally occurring phytochemicals with various therapeutic potentials, including anti-inflammatory, antioxidant, antiviral, and anticancer properties. Both have demonstrated promise in managing various diseases and improving overall health (Figure 5). Mechanisms of action of both Apigenin and Quercetin are as follows.

Figure 4. Multi-facet applications of Apigenin and Quercetin.

3.1 Anti-inflammatory activity

Apigenin's anti-inflammatory properties have drawn more attention recently in both *in vitro* as well as *in vivo* studies [53]. It was discovered to significantly inhibit CXCL1/KC and CCL2/MCP-1 expression, and also TNF-α-induced NF-κB and JNK activation [54]. Additionally, apigenin reduced the expression of cyclooxygenase-2 (COX-2) and the production of nitric oxide (NO) induced by lipopolysaccharide (LPS), as well as TNF-α-induced upregulation of E-selectin, intracellular adhesion molecule-1 (ICAM-1), and vascular cellular adhesion molecule-1 (VCAM-1) [55].

Numerous cytokines, including IL-1β, IL-4, IL-6, IL-5, INF-γ, TNF-α, MIP-1α (Monocyte inflammatory protein), MCP-1α (Monocyte chemotactic protein), as well as ICAMS are also related to inflammatory reactions. Apigenin's potential function in suppressing the expression of multiple cytokine genes have been linked to several signal transduction-related protein kinases, such as ERK, MAPK, and PKC. The DNA binding capacity of certain transcription factors like Fos-Jun, AP-1, and NF-B is controlled by the inhibition of these molecules [56]. It was discovered that monocyte derived chemokine (MDC) contributes a significant part in recruitment of T-helper 2 (Th) cells during allergic reactions [57,58]. Apigenin inhibits the THP-1 cells' production of IP-10 as well as MDC, as well as prevents the phosphorylation process of the c-JNK, ERK/MAPK, and p38 pathways [59]. Apigenin's anti-inflammatory studies showed a noteworthy rise in IκBα protein expression, which in turn suppresses NF-κB activation as well as inflammatory factors expression (ICAM-1, COX-2, IL-8, ROS and IL-6) and also MUC-2 expression [60,61]. Apigenin substantially reduces the quantity of the copies of TNF-α mRNA and also inhibited the expression of the gene IL-1β and demonstrating a role in the prevention of inflammatory disease [62].

Studies have indicated that quercetin is a long-half-life anti-inflammatory flavonoid [63,64]. Quercetin prevents lipopolysaccharide (LPS)-induced production of tumour necrosis factor alpha (TNF-α) in macrophages [65]. The inflammatory enzymes lipoxygenase (LOX) and cyclooxygenase (COX) can both be suppressed by quercetin [66]. Quercetin has been shown to inhibit the action of I-κB-phosphorylation, NF-κB translocation, reporter gene transcription, and AP-1 action, thus, it combats inflammatory conditions. It additionally has an effect on the functions of the signaling pathways AP-1, NF-B, and JNK [67]. Quercetin aids in the stabilization of basophil and mast cell's cell membranes, preventing these cells from releasing pro-inflammatory as well as allergy-causing agents [68]. Quercetin's anti-inflammatory qualities originate primarily from the way it can prevent the actions of pro-inflammatory cytokines which include IL-1β, IL-6, and TNF-α, as well as mediators of inflammation such as nitric oxide and catalase [69]. Quercetin inhibits the production of nuclear factor B (NFB) translocation and even interleukin-6 (IL-6) as well as, nitric oxide (NO), reducing the inflammatory reactions mediated by c-Jun N-terminal kinase (JNK) and Erk1/2 [70].

3.2 Antioxidant activity

Apigenin is an antioxidant which scavenges peroxyl radicals and quenches singlet oxygen [71]. An imbalance involving the production and removal of reactive oxygen species, or ROS, has been linked to cellular oxidative stress, which is the primary root of numerous chronic illnesses [72]. The primary defense towards electrophilic stress and cellular oxidative is the stimulation as well as the participation of the Nrf-2 anti-oxidant signaling route. After binding to the anti-oxidant response element (ARE) in nucleus, Nrf-2 activates a variety of enzymes which can lead to detoxification as well as eradication of electrophilic agents and reactive oxidants [73-75]. A subsequent study discovered that apigenin can reduce oxidative stress by increasing GCLM, GCLC, and HO-1 gene transcription through the ARE /Nrf2/ ERK2 signaling routes. Apigenin further increases the GSH-to-oxidized GSH ratio, intracellular GSH levels [76]. Apigenin was shown to enhance the longevity of cells along with reduction to the damage of tissues in general by raising resistance to oxidative stress activators.

The secret to apigenin's protective action has been found to be its capacity for removing endogenous ROS along with lowering the levels of malondialdehyde (MDA). Subsequent research indicates that apigenin decreased MDA and ROS levels, which in turn improved the activities of antioxidant enzymes like glutathione peroxidase (GSH-Px), catalase, and superoxide dismutase (SOD). Additionally, it increased the expression of antioxidant response proteins like AMP-activated protein kinase (AMPK) and nuclear factor erythroid 2-related factor 2 (Nrf2) [77,78]. Exposure to apigenin provides protection against DNA damage caused by H_2O_2 by influencing the ROS levels along with production of 8-hydroxy-2′ deoxyguanosine which could possibly explain its antioxidant properties [79].

Quercetin's hydroxyl group scavenges free radicals. The hydroxyl group within the molecule oxidizes free radicals by supplying active hydrogen to them, rendering them extremely stable and halting the oxidation of unsaturated fatty acids [80]. Because it's an antioxidant, quercetin scavenges ROS and RNS [81]. Certain antioxidant enzymes, including aldo-keto reductase and glutathione transferase, can be expressed more when quercetin is present. The quantity of quercetin directly correlates with the expression level [82]. Quercetin increases Nrf2 expression and nuclear exchange through influencing antioxidant enzyme activities, raising the level of intracellular GSH and inducing the intracellular p38 MAPK pathway, in order to boost the antioxidant capacity of the cell [83,84]. Enzymes like catalase and superoxide dismutase (SOD) levels increase, following quercetin administration. Thus, quercetin's likely modes of action in suppressing the functions of nitric oxide synthase (NOS) and oxidases enzymes involves eliminating free radicals and chelating metal ions like copper and iron [85]. Treatment with quercetin prevents oxidative stress-induced cell death [86].

3.3 Anticancer activity in the skin

Recently, apigenin has been widely investigated for its anti-cancer activities and low toxicity. Apigenin was reported to suppress various human cancers *in vitro* and *in vivo* through multiple biological effects, such as triggering cell apoptosis and autophagy, inducing cell cycle arrest, suppressing cell migration and invasion, and stimulating an immune response. Because of its origin, apigenin is generally considered to be one of the plant-based bioactive compounds that lowers the risk of cancer [87,88]. Treatment with apigenin increases production of reactive oxygen species (ROS), reduces SOD as well as glutathione (GSH) levels, triggering apoptosis induced by its intrinsic pathway [89]. Reduced ERK 1/2 and FAK function and reduced migration of cells are displayed by apigenin, making cells more susceptible to anoikis; detachment-induced apoptosis [90]. Additional research has assessed regarding STAT3 signaling impact on apigenin's anticancer properties on the cells with melanoma. Through down-regulating STAT3 signaling, apigenin inhibits invasion, migration, and metastasis. Alongside this, it was followed by the suppression of Twist1, MMP-2, -9 and VEGF, which are downstream targets of STAT3, under the influence of apigenin [91]. Apigenin causes a G2/M arrest in the cell cycle, which restricts cell proliferation and leads to apoptosis, which has been linked to apigenin-mediated suppression of the Akt/mTOR pathway [92]. Apigenin may prevent skin cancer development by inhibiting COX-2. Exposure to apigenin decreases the expression of receptors EP1 and EP2, prostaglandin PGE2 and increases terminal differentiation [93]. One well-known inhibitor of MAP kinase and PI3K signaling is quercetin.

In a dosage-dependent way, quercetin therapy increases apoptosis and decreases cell viability. Quercetin drastically influence PI3K/Akt pathway, boosts the UVB-induced NF-κB nuclear translocation and decreases MEK–ERK signaling. In mouse melanoma cells, quercetin caused apoptosis by potentiating caspase-3 activity and reducing B cell lymphoma 2 (Bcl-2) expression [94]. Quercetin's anti-melanoma properties could result from its inhibitory actions on the signaling transducer and transcription 3 (STAT3) activator which is an oncogenic protein [95,96]. Additionally, it has been shown that quercetin inhibits oxidative stress induced by UVB as well as damage of deoxyribonucleic acid (DNA), causing mouse epidermal cells to undergo apoptosis [97].

3.4 Wound healing activity

Skin injuries caused by mechanical, chemical, or thermal damage are referred to as wounds [98]. Research has demonstrated that applying apigenin gel topically enhanced inflammation and speed up the process of wound re-epithelialization [99]. An *in vivo* investigation evaluated the impact of apigenin glycoside. Significant anti-inflammatory and wound-healing effects, including wound closure and re-epithelialization, were exhibited by the compound [100]. Research has shown that apigenin has a positive impact on the healing process of wounds; however, more research is required to assess the therapeutic effectiveness of apigenin along with its derived compounds as wound recovery compounds as a result of the lack of evidence [101].

Quercetin possesses a variety of biological actions such as angiogenesis, anti-inflammation, anti-oxidant, fibroblast proliferation, and collagen deposition, making it greatly helpful for healing wounds. Topical application of 0.3% of quercetin dramatically accelerates closure of wounds, promotes regeneration of epithelial layer, reduces oxidative stress, as well as exhibits early wound healing. Quercetin therapy additionally raises the levels of vascular endothelial growth factor (VEGF), transforming growth factor (TGF)-β1, GAP-43, IL-10, CD31, PCNA, and α-SMA levels and decrease the levels of TNF-α illustrating the possible mode of action of quercetin for wound treatment [102]. Furthermore, it was found that by blocking the MAPK pathway, quercetin therapy enhances wound healing [103]. The multiphase hydrogel method using quercetin-loaded liposomes has applications for healing wounds and dramatically reduces the time needed to close wounds [104]. Compared to conventional gel, quercetin-loaded hydrogel significantly increases keratinocyte recovery and fibroblasts and has a longer-lasting effect on chronic wound healing [105].

3.5 Diabetes treatment

Diabetes is a disease that is common throughout the world and affects people of all ages. According to global estimates of the number of people with diabetes in 2017, 451 million people are living with the disease and the number is rising more quickly than it did in the past [106]. Apigenin has anti-diabetic properties because it can increase insulin secretion [107]. Apigenin interacts with reactive oxygen species (ROS) in the cell and neutralizes them [108]. Postprandial hyperglycemia may be reduced by preventing the activity of vital hydrolyzing enzymes like α-glucosidase [109]. Apigenin significantly lowers ICAM-1 levels, serum lipid, blood glucose, malonaldehyde levels, along with insulin resistance index and improves antioxidant enzymes like superoxide dismutase, as well as impaired glucose tolerance [110].

Additionally, Apigenin administration reduces hepatic glucose-6-phosphatase, which is frequently elevated in diabetics [111]. Apigenin-6-C-(2"-O-α-L-rhamnopyranosyl)- β-L-fucopyranoside, isolated from the leaves of *Averrhoa carambola* L., after its oral administration, it has an immediate effect on reducing blood glucose levels and stimulating insulin secretion induced by the glucose [112].

Quercetin has been shown in studies to be an intriguing drug target in order to treat diabetes. Quercetin increases insulin sensitivity by improving the secretion of insulin, enhancing the metabolism of glucose, as well as promoting the proliferation of pancreatic β-cell [113]. Quercetin has additionally been discovered to inhibit α-amylase as well as α-glucosidase [114]. Because of its anti-inflammatory, hypoglycemic, antioxidant, and hypolipidemic properties, quercetin is believed to be used in the treatment of type 2 diabetes mellitus. Quercetin lowers blood glucose concentrations while also maintaining the number of β cells and the activity of islets cells. Experiments show that quercetin consumption aids in the treatment and prevention of diabetes mellitus [115,116]. Treatment with quercetin improves dyslipidemia, lowers the level of serum blood glucose, raises the levels of insulin, and reduces the level of oxidative stress [117]. Quercetin boosts uptake of glucose in the cells which are isolated via elevating the expression of GLUT4 and translocation of endogenous GLUT4 by increasing the phosphorylation of both AMP-activated protein kinase/Akt (AMPK/Akt) signal pathways and phosphatidylinositol-3-kinase/Akt (PI3K/Akt), consequently enhancing the elevation of the estrogen receptor-α, thereby enhancing the intake of glucose in skeletal muscle cells [118,119]. Quercetin has the potential to mitigate the disruption caused by hyperglycemia by regulating both endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) [120,121].

3.6 Anti-psoriasis activity

Psoriasis is a severe, immunological skin condition which impacts millions worldwide [122]. Psoriasis occurs as a chronic inflammation-related skin condition that arises from both hyperproliferation of keratinocytes as well as dysfunctional differentiation. Furthermore, the predominant feature of psoriasis is the infiltration of Th17 cells that secrete inflammatory cytokines, like IL-23, into keratinocytes [123]. It had the biggest effect on reducing the cytokine levels in a psoriasis model. Apigenin-treated skin showed skin barrier recovery effects. It further boosts the condition of the skin through increasing stratum corneum hydration. Additionally, apigenin has an effect on the production of skin structural proteins such as loricrin, filaggrin and involucrin [124].

The drug quercetin has the potential to be anti-psoriasis beneficial in an imiquimod (IMQ)-induced psoriasis in animal model. The results showed that the quercetin therapy significantly improves worsening histology, lowers the temperature of psoriasis-like abrasions and reduces PASI scores. Moreover, quercetin effectively reduces the levels of tumor necrosis factor-alpha (TNF-α), IL-17 and IL-6, increases endogenous anti-oxidant enzymatic function as well as reduces MDA growth in mouse skin tissue caused by IMQ. Liposphere gel comprising *C. mukul* along with quercetin outperforms the cream with respect to its prolonged release and is helpful in the treatment of psoriasis [125-127].

4. Future Perspectives and Limitations

Flavonoids can be degraded by high temperatures, thus studies aimed at stabilizing apigenin therapeutics should be performed. The solubility of apigenin as a poorly water-soluble drug is only 0.0032 mg/ml in water and 0.001–1.63 mg/ml in high hydrophilic or nonpolar solvents, leading to a poor absorption in gastrointestinal tract. Apigenin is lipophilic and can be deactivated in the acidic environment of the gastrointestinal tract, leading to lower bioavailability, which limits its potential use in healthcare products and functional foods. Regardless of its broad-spectrum pharmacological effect on the skin, low hydrophilicity and poor percutaneous absorption are significant limitations to conventional topical delivery of quercetin. Therefore, the improvement in solubility and bioavailability is urgently needed for development and application of apigenin and quercetin. To overcome these defects, novel drug delivery platforms are suggested. One of the promising future anticancer approaches is the induction of cellular senescence, reported here to be easily achieved by extended low-dose treatments of apigenin. This kind of chemotherapy would selectively slay only those cells which are unable to respond properly to induce stress, such as cancer cells, due to their genomic instability. As a general limitation, there is very less clinical trial regarding the effect of apigenin and quercetin on a dermal disorder which shows the necessity for further research in this regard and for its translation into a clinically acceptable option for therapy.

5. Conclusion

Phytochemicals are plant products found in various vegetables as well as fruits. There are phenolic groups in the structure of such phytochemicals. This comprehensive review sheds light on the remarkable properties and diverse applications of apigenin and quercetin. Apigenin is an intriguing bioactive plant element that has been studied because of its potential medical benefits, which aid in its formation as a medicinal product for clinical trials. Apigenin possesses the potential to prevent or postpone the appearance of a variety of long-term illnesses. The bioflavonoid quercetin has a wide range of well-studied biological effects, including health promotion, physical and mental activity enhancement, and several distinct pharmacological effects. As a result of ongoing research, quercetin will likely become an innovative medication that may both prevent and cure a variety of illnesses. These flavonoids appear as multifaceted bioactive chemicals with promising anti-skin cancer, wound healing, and anti-diabetes benefits in addition to their strong anti-inflammatory, antioxidant, and anti-psoriasis properties. The extensive exploration of their uses in a variety of sectors, including health, wellness, and lifestyle issues, highlights their enormous therapeutic potential. As research continues to untangle the complexities of apigenin and quercetin, it is clear that both chemicals hold promise for tackling contemporary health concerns. The current review will lay the groundwork for future investigations that will certainly have significant consequences on the clinical results as well as the development of new products.

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