Quercetin: A Flavonoid with Antioxidant, Anti-Inflammatory, and Anti-Apoptotic Properties - A Review

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ABSTRACT

Flavonols are a diverse group of polyphenolic compounds found abundantly in a variety of fruits and vegetables, offering a wide range of bioactive benefits. One of the most prominent flavonols, quercetin, is commonly present in foods such as onions, apples, tea, cabbage, cauliflower, berries, and nuts. Quercetin is particularly well-known for its potent antioxidant properties, which help neutralize harmful free radicals and protect cells from oxidative damage. As a result, quercetin is often included in nutraceutical and cosmeceutical formulations designed to support health and prevent age-related degenerative diseases. It also exhibits anti-inflammatory effects, beneficial for conditions like arthritis and cardiovascular disease, and has anti-apoptotic activity, promoting cell survival in diseases such as cancer and neurodegeneration. This review highlights quercetin's multifaceted biological benefits, focusing on its antioxidant, anti-inflammatory, and anti-apoptotic properties. Through a deeper understanding of quercetin's properties, this work contributes to the growing body of knowledge surrounding natural compounds and their role in modern medicine and health.

Keywords: Quercetin, antioxidant, anti-inflammatory, anti-apoptotic

INTRODUCTION

Plants and their parts have been utilized for centuries, valued for their aromatic, flavoring, and medicinal properties. Compared to pharmaceutical products, plants and their phytoconstituents offer numerous advantages. Plant extracts and their constituent phytoconstituents have been shown to exhibit a range of biological activities, including antidiabetic, antihyperlipidemic, free-radical scavenging, and anti-inflammatory effects. Free radicals often play a significant role in the development of metabolic disorders, ultimately impacting quality of life. Fortunately, nature provides a balanced environment that fosters a healthy lifestyle. In recent decades, there has been a notable increase in research focused on identifying compounds with antioxidant activity, which can help mitigate the harmful effects of free radicals [1]. Oxidative stress is a crucial factor in the development of various chronic diseases, including cardiovascular diseases, diabetes, neurodegenerative diseases, and cancer. Prolonged exposure to elevated levels of pro-oxidant factors can lead to structural damage to mitochondrial DNA and functional alterations in enzymes and cellular structures, resulting in aberrant gene expression. Modern lifestyle factors, such as consuming processed foods, exposure to chemicals, and lack of exercise, contribute significantly to oxidative stress. However, medicinal plants with antioxidant properties have been utilized for their potential to treat or prevent various human pathologies, where oxidative stress is a contributing factor [2, 3, 4]. Recent

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research has revealed that nature boasts an impressive array of flavonoids, with over 4000 distinct types identified to date. These flavonoids are further categorized into several subclasses, including flavonols, flavanones, flavones, catechins, isoflavones, anthocyanidins, dihydroflavonols, and chalcones [,4, 6, 45].

Quercetin is a potent antioxidant flavonol that belongs to the broader flavonoid group. It is commonly found in its glycoside form, known as quercetin glycoside. The quercetin aglycone, the non-glycosylated form of quercetin, has the ability to conjugate with various sugars such as glucose, xylose, or rutinose. This conjugation occurs through the attachment of these sugars to one of quercetin's hydroxyl groups, resulting in the formation of diverse quercetin glycoside forms [7, 8, 9]. Quercetin-3-O-glycoside is primarily responsible for the pigmentation of flowers, vegetables, and fruits, imparting color to these plant-based foods [10, 11]. In terms of nutritional content, quercetin is predominantly present in the form of glycosides, rather than as aglycones, which are the non-glycosylated forms of quercetin [12, 13]. Quercetin is presently authorized by the United States Food and Drug Administration for use as a dietary supplement [14, 15, 16].

The origin of the name "quercetin" is derived from the Latin term "*Quercetum*," meaning Oak Forest, and it belongs to the flavonol category [17, 18]. Notably, flavonols, including quercetin, are not produced by the human body. According to the International Union of Pure and Applied Chemistry (IUPAC) nomenclature system, the formal name for quercetin is 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-1-benzopyran-4-one [19]. However, its informal name, quercetin, has become the prevalent term. Quercetin is also known as 3,3′,4′,5,7-pentahydroxyflavone and exhibits relatively high bioavailability compared to other phytochemicals. Estimates suggest that the average daily dietary intake of quercetin ranges from 5 to 40 milligrams per day [20, 21, 22]. Quercetin is a multifaceted plant molecule that has demonstrated a wide array of pharmacological activities, including anticancer, antiviral, and anti-inflammatory properties [23]. Its therapeutic potential extends to the treatment of various disorders, such as allergic reactions, metabolic issues, eye diseases, cardiovascular conditions, and arthritis. Moreover, quercetin has been recognized for its anticancer properties, with several studies indicating its efficacy as a cancer-preventing agent. Quercetin has also been found to possess psychostimulant properties. It has also been documented to exhibit several beneficial effects, including preventing platelet aggregation, reducing capillary permeability, inhibiting lipid peroxidation, and enhancing mitochondrial biogenesis [24].

Quercetin's effectiveness is impacted by its poor water solubility. To address this, quercetin is often stabilized as quercetin glycosides, where glycosyl groups are attached. These groups are released during digestion, allowing quercetin to be absorbed by the body. Several strategies can enhance quercetin absorption. Consuming quercetin with a fatty meal has been shown to improve absorption. Additionally, vitamin C has been found to not only improve quercetin absorption but also increase plasma quercetin blood levels. [25]. Quercetin has been found to accumulate in various organs, including the lungs, liver, kidneys, and small intestines, with notable concentrations. In contrast, lower levels of quercetin have been detected in the brain, heart, and spleen. The elimination of quercetin from the body occurs through the renal, fecal, and respiratory systems [26]. Despite its well-documented health benefits, quercetin has been reported to have a relatively short half-life in buffered solutions, such as body fluids. This limited half-life may impact the duration of quercetin's therapeutic effects and its overall bioavailability. [27, 28]. To address the issue of quercetin's short half-life, researchers conducted a study where quercetin was covalently conjugated into a polymethacrylic acid backbone. The resulting conjugate was then tested on HeLa cancer cells. A range of analytical techniques, including FT-IR, UV-Vis, Gel Permeation Chromatography, and the Folin-Ciocalteu test, were employed to characterize the conjugate. The antioxidant properties of the conjugate were evaluated using the DPPH test, while the viability experiments were conducted using the trypan blue exclusion assay. The results showed that the conjugate exhibited a functionalization degree of 2.01 mg of quercetin per gram, an IC50 of 2.62 mg/ml in the DPPH assay and induced 90% cell death after one-day treatment. In contrast, free quercetin achieved only 40% cell death after three days. The study concluded that polymer conjugation significantly enhances quercetin stability, leading to sustained activity of the flavonoid [27,29,30,31].

Sources of Quercetin

Quercetin is a naturally occurring flavonoid that is commonly found as a secondary metabolite in plants. Since the production of synthetic flavonoids is not currently practiced, plants serve as the sole source of quercetin [32].

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Quercetin is abundant in various fruits and vegetables, including apples, honey, raspberries, onions, red grapes, cherries, citrus fruits, and green leafy vegetables. Notably, onions contain the highest concentration of quercetin among all fruits and vegetables [33, 34]. The quercetin content in onions appears to be influenced by factors such as the bulb color and type [33] with the peel containing approximately 77 times more quercetin than the edible part of the plant [35]. Onion skin's bioactive compounds can be extracted through a variety of approaches, including solvent extraction, ultrasound-assisted extraction, microwave-assisted extraction, and the combined use of strong pulsed light with subcritical water extraction [35, 36, 37]. The preparation and storage of food can significantly impact the quercetin content. Specifically, cooking methods such as frying and boiling can lead to a decrease in quercetin levels. Boiling, in particular, is a major contributor to the reduction of quercetin due to two primary factors: thermal degradation and the leaching action of boiling water [38, 39].

A study examining the effects of post-harvest light treatment on onions revealed that light exposure significantly enhances quercetin content. The results showed that blue light conditions yielded the highest quercetin content, while fluorescent light resulted in the lowest levels. Furthermore, it was found that UV light not only decontaminates peeled onions but also increases the content of quercetin and quercetin glucoside in onions after light treatment. Additional findings indicated that red, blue, and UV-A light treatments also elevate quercetin concentrations, although to a lesser extent than white light. The study demonstrated that quercetin content in onions can be doubled after harvest through the use of UV light lamps. [40].

Food Source	**Quercetin Content (mg/100g)**
Capers	233.00
Onions	22.00
Cocoa Powder	20.00
Cranberries	14.00
Asparagus, cooked	7.61
Lingonberries	7.40
Blueberries	5.05
Apple, Red Delicious	4.70
Green Tea	2.69
Cherries	2.64
Broccoli, raw	2.51
Apple, Fuji	2.02
Black Tea	1.99
Red Grapes	1.38

Figure 1. Sources and content of quercetin in different fruits.

Adapted from: Larson, A., Symons, J. & Jalili, Thunder. (2010). Quercetin: A Treatment for Hypertension?—A Review of Efficacy and Mechanisms. *Pharmaceuticals*. 3. 10.3390/ph3010237. [41].

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Chemical Structure of Quercetin

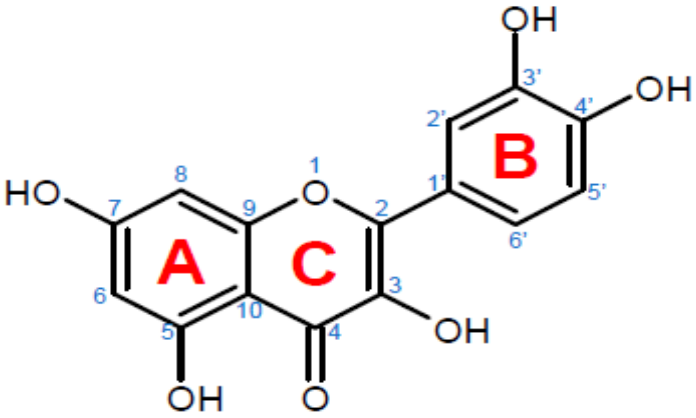

Figure 2. Chemical structure of quercetin with numbered carbon atoms (blue) and marked rings (red) on the general flavonoid backbone structure.

Adapted from: Neamtu, A.-A., Maghiar, T.-A., Alaya, A., Olah, N.-K., Turcus, V., Pelea, D., Totolici, B.D., Neamtu, C., Maghiar, A.M. & Mathe, E. (2022). A Comprehensive View on the Quercetin Impact on Colorectal Cancer. *Molecules*. 27, 1873. [42].

The chemical structure of pure quercetin is characterized as an unconjugated aglycone, lacking a carbohydrate moiety (Figure 2). In contrast, quercetin found in food sources, such as onions, exists in a glycoside form, featuring a sugar group in its structure [41, 43, 44]. Supplemental forms of quercetin typically consist of quercetin aglycone, although some products may also contain small amounts of a glycoside called rutin. The bioavailability of quercetin is influenced by the form in which it is ingested. Research has shown that glycoside forms of quercetin exhibit better absorption compared to quercetin aglycone. However, studies have also found that both forms are readily bioavailable [41, 9].

The antioxidant properties of quercetin can be attributed to its unique chemical structure [45, 46, 47]. Specifically, the following features play a crucial role: a hydroxyl group located on the third carbon, a double bond between the second and third carbons, a carbonyl group on the fourth carbon, and polyhydroxylated A and B aromatic rings. These structural components collectively contribute to the potent antioxidant properties of quercetin. [45].

Properties of Quercetin

Antioxidant properties of quercetin

Oxidative stress, which arises from an excess of oxidants relative to antioxidants, is a key factor in the progression of many common diseases [48, 49] and oxidant compounds are known to contribute to the development of various diseases in the human body. To combat oxidative stress, synthetic antioxidants need to be supplied from external sources to support the body's internal antioxidant defences. Due to their therapeutic potential and natural origin, medicinal plants are recognized as a primary source of natural antioxidant phytocompounds [50]. Consequently, antioxidant compounds have become increasingly important in preventing oxidation-associated diseases and disorders [5, 50]. Quercetin is renowned for its exceptional antioxidant properties [5, 47]. It is the most potent antioxidant flavonoid found in nature, providing protection to the body against free radicals [5, 51, 52, 53].

The antioxidant properties of quercetin are closely tied to its chemical structure, particularly the presence and location of hydroxyl (–OH) substitutions and the catechol-type B-ring [54, 55, 56, 57]. The structural features that contribute to quercetin's potent antioxidant capacity include the presence of an ortho-dihydroxy or catechol group in the B-ring, a 2,3-double bond, and hydroxyl substitutions at positions 3 and 5 [45]. Growing evidence

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has demonstrated that quercetin, with its distinct hydroxylation form at positions 3, 5, 7, 3', and 4', as well as a catechol B-ring, possesses all the structural properties characteristic of an antioxidant agent [58].

Thiyagarajan et al. developed an analytical methodology for qualitative and quantitative determination of quercetin from fenugreek leaves. They assessed the potential of quercetin as a natural antioxidant source. The antioxidant activity of isolated quercetin was compared to ascorbic acid, a standard molecule. The results showed that quercetin's antioxidant activity was evident from the decrease in DPPH radical absorbance, similar to ascorbic acid. This antioxidant activity occurred through the reaction between quercetin and free radicals, resulting in the scavenging of radicals by hydrogen donation. Notably, the isolated quercetin exhibited increased antioxidant activity with higher treated concentrations [59]. Quercetin's antioxidant activity is attributed to its ability to directly scavenge reactive oxygen species (ROS) [60, 61, 62]. In addition to its direct ROS scavenging activity, quercetin also exhibits indirect antioxidant effects through two distinct pathways. One of these pathways involves the induction of glutathione production, which serves as a hydrogen donor for the enzyme superoxide dismutase (SOD). SOD utilizes glutathione to capture superoxide anions (O^2-), converting them into hydrogen peroxide (H_2O_2), which is then further decomposed into water (H_2O) [63, 64]. On the other hand, quercetin can modulate the non-enzyme-dependent antioxidant defense system pathways. This modulation leads to a decrease in the levels of reactive oxygen species (ROS), further highlighting quercetin's indirect antioxidant effects [60].

Evidence shows that quercetin boosts the antioxidant defence system. When administered at 5 mg/kg to both normal and hyperuricemic rats, it significantly raised the serum's total antioxidant capacity (FRAP value) and reduced the heightened malondialdehyde levels in hyperuricemic rats. This effect was due to its ability to inhibit liver enzymes XO and XDH, responsible for uric acid synthesis, thereby substantially lowering serum uric acid levels in hyperuricemic rats [65]. Another investigation into the inflammation caused by monosodium urate crystals in rats found that quercetin at 200 and 400 mg/kg doses reduced malondialdehyde levels while increasing the activity of antioxidant enzymes such as glutathione peroxidase, catalase, and superoxide dismutase [66]. Treatment with 0.3 mmol/kg quercetin in mice experiencing galactose-induced oxidative stress resulted in an increase in serum total antioxidant capacity. The levels of antioxidant enzymes like superoxide dismutase, catalase, and glutathione peroxidase were elevated, and their mRNA expression levels also increased. In addition, quercetin reduced the serum concentrations of malondialdehyde and nitric oxide [67].

Quercetin may provide neuroprotective benefits by inhibiting oxidative stress-mediated neuronal damage. Oxidative stress is a major contributor to neurodegenerative disorders and vascular pathologies in the brain. Quercetin's radical-scavenging and metal-chelating activities make it a potential therapeutic agent [68, 69, 70]. Quercetin may also offer protection against neurodegenerative diseases caused by oxidative stress and apoptosis, highlighting its potential as a neuroprotective compound [71].

Quercetin has emerged as a promising compound for the development of anti-Alzheimer's disease (AD) formulations. Its neuroprotective effects against oxidative stress and excitotoxicity are attributed to its ability to regulate apoptosis mechanisms. The neuroprotective actions of quercetin in the context of AD involve multiple mechanisms. These include inhibition of amyloid-β (Aβ) aggregation, inhibition of intracellular neurofibrillary tangles (NFTs) formation, inhibition of amyloid precursor protein (APP), inhibition of cleaving enzyme (BACE1), and inhibition of acetylcholinesterase (AChE). Additionally, quercetin attenuates oxidative stress in AD [72] by down-regulating microglia proliferation within the hippocampus of AD model mice. This improves memory and cognitive and emotional dysfunction in mice [73, 74].

Diabetes is directly involved in oxidative stress production. A study was conducted to investigate the effects of oxidative stress and evaluate the antioxidant effect of quercetin nanoparticles (QUNPs) in streptozotocin (STZ)-induced diabetic (type II) rats. The study involved treating STZ-diabetic rats with QUNPs (10 and 20 mg/kg bw/day) for 7 weeks. The effects on renal enzymes, antioxidant markers, total protein, albumin, and kidney tissues were analyzed. The results showed that QUNPs significantly increased the serum activity of antioxidant enzymes (MDA, CAT, GR, and GPx) in normal rats. However, STZ had an opposite effect on these enzymes, which was ameliorated by QUNPs treatment. Additionally, QUNPs administration improved altered kidney tissues in STZ-diabetic rats. [75]. Similar results were observed elsewhere [76, 77, 78, 79]. Quercetin exhibits a range of antioxidant properties, including the ability to scavenge free radicals, transfer electrons, chelate metals, and inhibit superoxide radicals [80]. Aside from its possible direct antioxidant effect, quercetin may enhance

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cellular defenses against oxidative stress by activating pathways such as Nrf2-ARE and inducing the antioxidant/anti-inflammatory enzyme paraoxonase 2 (PON2). Moreover, quercetin has been demonstrated to activate sirtuins (SIRT1), trigger autophagy, and serve as a phytoestrogen, mechanisms that likely underlie its neuroprotective actions [81, 82].

Diabetes Mellitus (DM) is closely linked to a weakened antioxidant defence system [83, 84, 85]. A study explored the antioxidant effects of quercetin supplementation on blood sugar control, lipid profiles, and oxidative stress markers in patients with type 2 diabetes. The findings revealed that quercetin supplementation significantly enhanced total antioxidant capacity (TAC) in the treatment group compared to the placebo group. Furthermore, quercetin supplementation led to a notable reduction in oxidized LDL (ox-LDL) cholesterol. The study concluded that quercetin supplementation improved antioxidant status in patients with type 2 diabetes, although it had no significant impact on blood sugar control or lipid profiles. [83].

Researchers Jiao Wang et al. investigated quercetin's antioxidant effects on ovarian aging in a Chinese study. They administered quercetin to menopausal rat models at varying doses for 90 days and monitored estrous cycles. Additionally, lab tests examined ovarian cells treated with quercetin and hydrogen peroxide. Hormone levels, including luteinizing, follicle-stimulating, progesterone, and estradiol, were measured using radioimmunoassay. Western blot testing was used to analyze the expression levels of oxidative stress-related genes, specifically catalase and glutathione synthetase, in ovarian cells. The in vivo study revealed quercetin had no significant effect on ovarian structure, hormone production, or estrous cycle in menopausal rats. However, in vitro results showed quercetin significantly improved cell viability reduced by H_2O_2-induced oxidative stress and enhanced expression of oxidative stress-related proteins decreased by H_2O_2. The authors concluded quercetin boosts ovarian antioxidant capacity by upregulating oxidative stress-related genes, both in vivo and in vitro [86]. Bioactive phenols like quercetin can help defend against pro-oxidative damage by scavenging reactive oxygen species (ROS) [87].

Anti-inflammatory properties of quercetin

Inflammation is a natural response of the body's immune system [88, 89] designed to combat harmful invaders and repair damaged tissues. The main goal is to maintain homeostasis, and under normal conditions, the immune system produces both pro-inflammatory and anti-inflammatory mediators [90]. This protective mechanism involves recognizing and eliminating threats, paving the way for healing. Inflammation can be either acute or chronic [88, 91].

Inflammation is controlled by several key regulators, with nuclear-kappa factor B (NF-κB) playing a vital role [92, 93]. Tumour necrosis factor-alpha (TNF-α) activates NF-κB, triggering a cascade of pro-inflammatory responses. TNF-α amplifies inflammation by inducing genes involved in producing cytokines, chemokines, cell adhesion molecules, enzymes, and growth factors. Key enzymes induced by TNF-α include cyclooxygenases (COX-1 and COX-2), 5-lipoxygenase (5-LOX), and inducible nitric oxide synthase (iNOS), perpetuating the inflammatory response [94]. COX-2, 5-LOX, and iNOS regulate the biosynthesis of pro-inflammatory mediators, including prostaglandins, leukotrienes, and nitric oxide. These molecules trigger inflammation symptoms like vasoconstriction, vasopermeability, clotting, pain, and fever. TNF-α activates key signalling pathways: NF-κB, AP-1, MAPK, and apoptotic pathways. This regulates gene expression, differentiation, survival, and cell death. Over 100 cytokines influence the inflammatory response. Pro-inflammatory cytokines include IL-1β, IL-6, and IFN-γ. Anti-inflammatory cytokines, such as IL-10, IL-2, and TGF-β, promote immune tolerance [92, 95].

Prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with an increased risk of gastrointestinal and cardiovascular issues [96, 97] and are associated with associated with considerable morbidity and mortality [97]. As a result, there has been growing interest in the development of new anti-inflammatory drugs derived from natural sources. In this regard, flavonoids and their derivatives show promise as potential candidates due to their ability to interact directly with pro-inflammatory proteins, inhibit the expression of inflammation-related genes, and exert both antioxidant and pro-oxidant effects [98].

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Quercetin has been found to be a long-acting anti-inflammatory substance, demonstrating significant anti-inflammatory capabilities [99, 100, 52, 55]. Quercetin's anti-inflammatory potential is evident in multiple cell types, across animal and human models [101, 102]. Its benefits include mast cell stabilization and gastrointestinal cytoprotection. Quercetin also modulates inflammation and immunity through biphasic and regulatory actions. Furthermore, it exhibits immunosuppressive effects on dendritic cell function [103].

Several studies have demonstrated that quercetin suppresses the production of pro-inflammatory cytokines. For instance, it inhibits lipopolysaccharide-induced tumor necrosis factor-alpha production in macrophages [104, 105] and lipopolysaccharide-induced IL-8 production in lung A549 cells [106]. Quercetin also exerts anti-inflammatory effects by inhibiting the activity of enzymes involved in inflammation, such as cyclooxygenase and lipoxygenase [107]. Quercetin has been shown to suppress LPS-induced inflammation by inhibiting the Src- and Syk-mediated tyrosine phosphorylation of PI3K, thereby disrupting the formation of the TLR4/MyD88/PI3K complex and subsequent activation of downstream signaling pathways in RAW 264.7 cells [108], providing strong evidence that quercetin might act as a potent immunosuppressive agent, making it a promising candidate for managing chronic inflammation [109, 110, 111].

Quercetin demonstrated anti-inflammatory effects by reducing the production of inflammatory mediators, NO and TNF-α, in LPS-stimulated BV-2 microglial cells. This effect was mediated by the negative regulation of the transcription factor NF-κB [112]. Furthermore, quercetin inhibited iNOS expression and NO production in endotoxin/cytokine-stimulated BV-2 cells. Its anti-inflammatory action involved the down-regulation of various signaling molecules, including ERK, JNK, p38, Akt, Src, JAK-1, Tyk2, STAT-1, and NF-κB [113].

Quercetin and kaempferol demonstrated anti-inflammatory effects on bone marrow-derived macrophages (BMDM). They suppressed LPS-induced TNF-α secretion and iNOS expression, leading to decreased NO production [114]. This inhibitory effect was observed at concentrations of 25-50 μM for quercetin and 50-100 μM for kaempferol. Notably, both iNOS and TNF-α are regulated by the transcription factor NF-κB [115].

Quercetin was investigated in a mouse model of bone marrow-derived dendritic cells (DCs) stimulated by LPS. The results showed that quercetin downregulated TNF-α in a dose-dependent manner (6.25–50 μM). Additionally, quercetin decreased the secretion of various cytokines (IL-1α, IL-1β, IL-6, IL-10, and IL-12 p70) and chemokines (CCL-2, MIP-1α, MIP-1β, and RANTES). Quercetin's anti-inflammatory effects in DCs were attributed to its ability to decrease I-κB degradation and disrupt the activation of ERK, JNK, Akt, and NF-kB pathways. [116].

Quercetin exhibited anti-inflammatory effects in 3T3-L1 and RAW264.7 cell models. It inhibited ERK1/2, JNK, and p38MAPK signaling factors in a dose-dependent manner (6.25-25 μM). Additionally, quercetin suppressed the protein levels of CCL-2 and TNF-α, a pro-inflammatory cytokine and chemokine. It also decreased the secretion of IL-1β, IL-6, and NO, while increasing IL-10 secretion [117].

Quercetin and rutin, at a concentration of 20 μM, were found to significantly inhibit the expression of pro-inflammatory genes and proteins, including TNF-α, IL-1β, and COX-2, in human monocytic THP-1 cells, according to research by Wu et al [118]. Quercetin demonstrated anti-inflammatory effects on human umbilical artery smooth muscle cells (HUASMC) by reducing the expression of adhesion molecules (VCAM-1 and ICAM-1) and a chemokine (CCL-2) induced by TNF-α. However, its circulating metabolites did not exhibit the same effects, suggesting that quercetin itself is responsible for the observed anti-inflammatory activity [119]. Quercetin and its metabolites reduced COX-2 mRNA expression in colon cancer cells, with and without IL-1β stimulation. Specifically, quercetin and quercetin-3′-sulfate inhibited COX-2 activity at 10 μM [120]. Nair et al. studied the anti-inflammatory potential of quercetin on human peripheral blood mononuclear cells (PBMC). Results show that quercetin (1–50 μM) significantly inhibits TNF-α production and gene expression in a dose-dependent manner [121].

Mast cells, derived from hematopoietic progenitors, mature in tissues under specific microenvironmental conditions [122]. These cells play a pivotal role in triggering allergic reactions [123, 124] by releasing histamine, prostaglandin D2 (PGD2), leukotrienes (LT), various cytokines, and proteolytic enzymes [125, 126]. The primary function of mast cell secretions is to induce inflammation through the activation and recruitment of

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immune cells, as well as to mediate late-phase reactions [127, 128, 129, 130]. Quercetin has been shown to dampen the activation of the transcription factor NF-κB, thereby suppressing the downstream expression of pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-8. Furthermore, quercetin inhibits the activation of cytokines in mast cells triggered by IgE-mediated mast cell activation, particularly in extracts with high quercetin content [52, 131, 132].

Karliana et al. formulated a nanoparticle gel consisting of lecithin-quercetin injected into chitosan-tocopherol polyethylene glycol succinate (TPGS) to study its effects on osteoarthritis. Osteoarthritis was induced in rats, which were then treated with varying doses of quercetin administered through the nanoparticle gel. A significant reduction in inflammation and edema was observed at the highest dose, confirming quercetin's role in cartilage protection and inflammation reduction [133]. Other studies have also observed quercetin's anti-inflammatory roles in osteoarthritis [134, 135, 136, 137].

A Korean study explored the anti-inflammatory effects of galangin and quercetin in lipopolysaccharide-stimulated RAW264.7 macrophages and a 2,4-dinitrochlorobenzene-induced atopic dermatitis (AD) mouse model. The results showed that both compounds reduced nitric oxide production, interleukin-6, and nuclear factor NF-kB. Combination treatment significantly decreased inflammation, IgE levels, and ear thickness. The study suggests that quercetin and galangin may be effective therapeutic agents for AD, and their combination could be a novel strategy for preventing AD [138]. By modulating the levels of proinflammatory and anti-inflammatory cytokines, quercetin helps promote a more balanced immune reaction [139].

Anti-apoptotic properties of quercetin

Apoptosis is a naturally occurring process of programmed cell death, essential for maintaining cellular homeostasis. It plays a vital role in eukaryotic development, cellular renewal, and tissue regeneration. Additionally, apoptosis helps eliminate unnecessary cells, preventing excessive immune responses and maintaining overall cellular balance [140]. Apoptosis is controlled by a complex signaling mechanism involving multiple protein families, including caspases, inhibitors of apoptosis proteins, BCL-2 family proteins, perforins, and granzymes. This pathway balances pro-apoptotic and pro-survival members to determine cellular survival or death. Disruptions in this pathway can lead to abnormal cell proliferation, contributing to cancer and autoimmune disorders [140, 141]. Apoptosis is marked by distinct morphological changes and biochemical processes, ultimately leading to the removal of cells without causing damage to nearby tissues [141].

Fang et al. investigated quercetin's effect on liver injury in acute on chronic liver failure (ACLF) rats. They evaluated apoptosis in liver tissues using TUNEL staining, which detects DNA fragmentation. The results showed a significant increase in TUNEL-positive cells in the ACLF group, which was reversed by quercetin treatment. Western blot analysis revealed changes in apoptosis-related proteins. Specifically, the ACLF group showed upregulation of pro-apoptotic Bax and cleaved caspases 9 and 3, along with downregulation of anti-apoptotic Bcl-2. Quercetin treatment reversed these changes [142].

Diabetic nephropathy is a major microvascular complication of diabetes mellitus [143, 144] and is the leading cause of end-stage renal disease, accounting for the majority of cases [145, 146]. Gomes et al. investigated the anti-apoptotic effects of quercetin in a C57BL/6J mouse model of diabetic nephropathy (DN) induced by streptozotocin (STZ). The results showed a significant increase in early and late apoptosis in diabetic mice compared to non-diabetic mice. However, treatment with quercetin reduced the progression from early to late apoptosis and decreased the percentage of apoptotic cells to levels similar to those in non-diabetic animals [147].

(-)Epigallocatechin gallate and quercetin in combination were reported to inhibit H_2O_2-induced apoptosis through modulation of the expression of apoptosis-related Bcl-2 and Bax in endothelial cells [148].

It has been demonstrated that quercetin-conjugated iron oxide nanoparticles (QNPs) enhance quercetin's (Qu) bioavailability in the brains of rats, leading to improved learning and memory in diabetic rats [149, 150, 151]. Yarjanli et al. conjugated quercetin to dextran-coated iron oxide nanoparticles (DNPs) and investigated changes in solubility, antioxidant, anti-inflammatory, and anti-apoptotic activities post-conjugation. Their findings revealed that Qu and QNPs exhibit similar antioxidant, anti-inflammatory, and anti-apoptotic effects against

H_2O_2-induced toxicity in PC12 cells. Notably, QNPs possess magnetic properties, enabling targeted tissue delivery [149].

Activation of JNK and ERKs, but not p38 kinase, is required for the H_2O_2-induced apoptosis. Suppression of the JNK-c-Jun/AP-1 pathway and the ERK-c-Fos/AP-1 pathway is involved in the anti-apoptotic effect of quercetin [152]. Research conducted by Chow et al. explored the mechanisms underlying quercetin's protective effects against oxidative stress-induced cytotoxicity in RAW264.7 macrophages. Their findings revealed that quercetin safeguards cells against H2O2-induced mitochondrial membrane potential decrease. Quercetin significantly blocked the activation of apoptotic proteins, including caspase 3, caspase 9, PARP, and D4-GDI, as confirmed by Western blotting and enzyme activity assays. Notably, the protective effect was specific to quercetin, as rutin and quercitrin did not exhibit similar effects. Furthermore, the study identified heme oxygenase 1 (HO-1) catalytic metabolites, particularly carbon monoxide (CO), as playing a crucial role in protecting cells against H2O2-induced apoptosis [153].

CONCLUSION

Quercetin is a polyphenolic flavonol abundant in fruits and vegetables, boasting antioxidant, anti-inflammatory, and anti-apoptotic properties beneficial to human health. However, its poor bioavailability limits its pharmaceutical applications. Nanoparticles offer a solution, enhancing bioavailability through their large surface area, customizable targeted delivery, improved bioavailability, enzymatic protection, and controlled release. These emerging techniques offer the potential for diverse formulations and uses of this flavonoid.

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