Disease Management of Quercetin and Its Natural Derivatives

Subjects: Medicine, Research & Experimental
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Sepsis is a syndrome of organ dysfunction caused by an uncontrolled inflammatory response, which can seriously endanger life. There is still a shortage of specific therapeutic drugs. Quercetin and its natural derivatives have received a lot of attention recently for their potential in treating sepsis.

Keywords: sepsis ; quercetin and its derivatives ; anti-inflammatory ; antioxidant

1. Quercetin

Multiple studies have provided direct or indirect evidence supporting the therapeutic potential of quercetin in sepsis. The mechanism of action involves the negative regulation of intracellular ROS levels and the NF-κB signaling pathway, effectively suppressing the excessive production of inflammatory factors, including TNF-α, IL-1β, and COX-2 [1][2].

In a rat model of colorectal cancer depression, quercetin exhibited antidepressant effects by reducing the expression levels of TNF-α and IL-1β in serum and the medial prefrontal lobe. It also increased the expression of BDNF (brain-derived neurotrophic factor) protein and acted on the tyrosine kinase receptor B/β-catenin axis, demonstrating its potential for treating depression [3].

Quercetin has also shown promise in reducing inflammatory factors in the hippocampus of mice in a chronic unpredictable stress model. It inhibits the secretion of COX-2, reduces the expression of nitric oxide, and restores hippocampal function, thereby exerting an antidepressant effect [4]. Studies have suggested that quercetin may inhibit the neuroinflammation–apoptosis cascade and neuronal apoptosis in the hippocampus. It has been found to inhibit the increase in TNF-α and IL-6 expression in the hippocampus of an olfactory bulb-removed rat model, indicating its potential antidepressant mechanism [5].

Research conducted by Sul et al. demonstrated that quercetin effectively reduced the levels of ROS in lung epithelial cells induced by LPS [6]. It also inhibited the nuclear translocation of NF-κB, resulting in a decrease in the levels of inflammatory cytokines, such as TNF-α, IL-1, and IL-6, which were elevated after LPS stimulation.

Furthermore, quercetin has been found to inhibit the activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome, which is involved in inflammatory responses. It reduces excessive ROS production and downregulates the expression of NLRP3, cleaved caspase-1, IL-1β, and N-gasdermin D (N-GSDMD) in macrophages. Quercetin also suppresses TLR2/myeloid differentiation factor 88 (Myd88) and p-AMP activated protein kinase (AMPK) upregulation induced by LPS/ATP in macrophages [7].

Quercetin can regulate immune responses in X-linked inhibitor of apoptosis protein (XIAP) deficiency by inhibiting IL-1β secretion and reducing IL-18 production. It has been shown to decrease levels of IL-1β and IL-18 in mice after LPS challenge [8]. Quercetin activates the Nrf2 signaling pathway, enhancing the expression and activity of Nrf2 through various mechanisms. It directly associates with Keap1, a negative regulator of Nrf2, preventing its degradation and promoting stability and functionality. Quercetin also offers protection against cytotoxicity induced by benzo[a]pyrene (B[a]P) and mitigates DNA adduct formation through aromatic hydroxylase receptor (AhR) and Nrf2 activation [9].

Severe sepsis, especially septic shock, causes extensive ischemia–reperfusion (I/R) injury [10], which often occurs in the kidney, brain, gut, lung, myocardium, retina, etc. Quercetin has been found to alleviate I/R injury by activating Nrf2 through the MAPK and phosphoinositide 3-kinase (PI3K)/ protein kinase B (PKB, also known as AKT) signaling pathways [11]. Furthermore, Li et al. demonstrated in a recent study that quercetin ameliorated neurological deficits and reduced infarct size in rats after cerebral I/R injury by regulating the PI3K/AKT/NF-κB signaling pathway and upregulating the proportion

of M2 polarization of macrophages (microglia) [12]. In addition, it also reduces senescence-associated secretory phenotype (SASP) factors and senescence phenotype in nucleus pulposus cells under IL-1β treatment, thereby mitigating intervertebral disc degeneration (IDD) [13]. It upregulates the expression of Nrf2, resulting in elevated levels of antioxidant enzymes and reduced renal injury [14]. Moreover, quercetin enhances the activity of antioxidant enzymes, such as superoxide dismutase (SOD) and catalase, reducing oxidative stress and protecting against cellular damage [15].

Quercetin is considered an excellent anti-asthmatic agent. In a rat asthma model experiment, quercetin (50 mg/kg) reduced IL-6 and TNF-α and increased IL-10 in the lung tissues of asthmatic mice compared to dexamethasone (2.5 mg/kg). It also alleviates oxidative stress and inflammation, especially in tissues [16]. In conclusion, quercetin modulates the expression of proinflammatory and anti-inflammatory cytokines, promoting a more balanced immune response. It also offers various pharmacological benefits for sepsis, improving cardiovascular health by lowering blood pressure and lipid levels. Quercetin prevents thrombosis and reduces the risk of cardiovascular disease by inhibiting clot formation, platelet aggregation, and platelet activation markers [17][18]. Furthermore, quercetin maintains the integrity of the endothelial barrier, reducing organ dysfunction, and improving outcomes in sepsis.

2. Miquelianin

Miquelianin (quercetin 3-*O*-glucuronide), a flavonoid glycoside compound, is present in plants of the Asteraceae and Moraceae families. It possesses unique characteristics, such as the addition of a glucuronic acid moiety to the quercetin molecule, which enhances its antioxidant properties. Recent studies have indicated that treatment with 0.1 μM miquelianin can effectively reduce the production of ROS and modulate various signaling pathways, including cAMP, RAS, and ERK1/2 [19]. Additionally, it has been shown to regulate the expression of genes associated with heme oxygenase 1 (HO-1), matrix metalloproteinase (MMP)-2, and MMP-9, suggesting its potential neuroprotective effects.

Studies have demonstrated that miquelianin can cross the blood–brain barrier (BBB) and reduce the production of β-amyloid (Aβ) peptides in primary cultured Tg2576 mouse models of Alzheimer's disease [20]. Moreover, it interferes with the initial protein–protein interactions necessary for the formation of neurotoxic Aβ oligomers, specifically Aβ1-40 and Aβ1-42, further supporting its potential as a therapeutic agent. Recent research has also highlighted the role of miquelianin in promoting neurogenesis by upregulating the time-resolved Kerr rotation (TrkR) and PI3K/AKT signaling pathways. Mice supplemented with nuciferine leaf polyphenol extract (NLPE), enriched in miquelianin, exhibited increased numbers of stem cells and neurons. In vitro experiments using miquelianin-treated HT22 and SH-SY5Y cells demonstrated enhanced neurite outgrowth and elevated TrkR and PI3K/AKT levels, indicating its potential in the treatment of neurodegenerative diseases [20][21].

Furthermore, miquelianin exhibits immunomodulatory effects by inhibiting the Th2 immune response and displaying antiallergic properties. It has been shown to suppress cytokine production and IL-2 by Th2 cells while upregulating the expression of HO-1 in splenocytes [22]. In vitro experiments have demonstrated its ability to inhibit CD4+ T-cell proliferation and induce HO-1 expression through the ROS and the C-Raf–ERK1/2–Nrf2 pathway. In a mouse model of atopic dermatitis, miquelianin effectively alleviated symptoms by inhibiting the Th2 immune response.

3. Reynoutrin

Herbs containing reynoutrin (quercetin-3-xyloside) are recognized for their potential anti-inflammatory, antioxidant, and antiviral effects, particularly against hepatitis C virus [23]. Notably, reynoutrin has displayed promising potential in improving ischemic heart failure (IHF) by targeting S100A1 [24]. In an experimental rat model of left anterior descending (LAD) ligation-induced heart failure, reynoutrin was administered at different doses, and its impact on various aspects, including cardiac function, inflammatory factors, oxidative stress, cardiomyocyte apoptosis, and myocardial fibrosis, was comprehensively evaluated. The results revealed significant improvements in cardiac function, a reduction in the release of inflammatory factors, alleviation of oxidative stress, attenuation of cardiomyocyte apoptosis, and mitigation of myocardial fibrosis in IHF rats treated with reynoutrin [24][25].

However, it is important to note that while reynoutrin has been isolated and identified from various plants in several studies [24][26][27], there is limited evidence available to fully support its antioxidant and anti-inflammatory effects. Further investigations are required to elucidate and provide more comprehensive evidence of these effects.

4. Rutin

Rutin, also known as quercetin-3-rutinoside or sophorin, is a flavonoid compound commonly found in various plants [28]. Extensive research has been conducted on rutin, highlighting its potential as a promising active ingredient derived from medicinal plants.

One area of focus has been rutin's beneficial effects in mitigating tau pathology. It has been found to inhibit tau aggregation, reduce cytotoxicity caused by tau oligomers, decrease proinflammatory cytokine production, protect neuronal morphology from harmful tau oligomers, and promote the uptake of extracellular tau oligomers by microglia. In a tau-P301S mouse model, rutin demonstrated therapeutic effects by reducing pathological tau levels, regulating tau hyperphosphorylation through increased expression of PP2A, inhibiting gliosis and neuroinflammation by downregulating the NF-κB pathway, preventing microglia-mediated synapse clearance, and rescuing synaptic loss [29]. Notably, rutin is able to effectively penetrate the BBB despite its limited water solubility and low bioavailability [30]. Its impact on the brain's nervous system is not through the regulation of the gut microbiome but rather through direct regulation of tau [29].

Rutin has also shown potential in modulating inflammation and oxidative stress responses in mice with colitis, as observed in a study by Liu et al. [31]. It significantly improved colonic permeability, as indicated by increased levels of tight junction proteins and decreased levels of FITC-dextran and endotoxin in the serum. Rutin exerted its anti-colitis effects by inhibiting the activation of the NF-κB pathway. Additionally, rutin partially restored the imbalance in the gut microbiota of mice with colitis. It increased the abundance of potential probiotics, such as *Faecalibaculum rodentium*, while reducing the levels of potentially disease-associated bacteria, such as *Romboutsia ilealis* and *Eubacterium fissicatena* group.

Data from a double-blind, placebo-controlled trial of rutin 500 mg daily for 3 months showed significant improvements in metabolic measures, brain-derived neurotrophic factor (BDNF), and markers of inflammation and oxidative stress in patients with type 2 diabetes mellitus (T2DM) [32]. These findings highlight the diverse therapeutic potential of rutin, particularly in the context of mitigating tau pathology and modulating inflammation and oxidative stress responses. Further research is needed to fully elucidate the molecular mechanisms and clinical applications of rutin in various disease conditions.

5. Isoquercetin

Isoquercetin (quercetin 3-glucoside) is a naturally occurring polyphenol that possesses antioxidant and anti-inflammatory properties, providing protection against oxidative stress and reducing inflammation [33]. It has demonstrated potential in mitigating ethanol-induced hepatotoxicity, oxidative stress, and inflammation through the Nrf2/ARE antioxidant signaling pathway. Additionally, it regulates the expression of nitric oxide by modulating the NF-κB transcription system [34]. Isoquercetin's high bioavailability and low cytotoxicity make it a promising candidate for preventing birth defects in diabetic pregnancies [35].

In a study by Zhou et al., isoquercetin not only enhanced spatial memory but also provided protection to hippocampal neurons in sleep-deprived mice. The study observed an increase in the levels of NLRP3 in sleep-deprived mice, which was subsequently alleviated by treatment with isoquercetin. Furthermore, isoquercetin exhibited an inhibitory effect on the upregulation of pyroptosis-related factors, such as NLRP3, caspase-1, apoptosis-associated speck-like protein containing CARD (ASC), IL-1β, IL-18, and GSDMD, induced by LPS [36].

A recent study by Zhang et al. investigated the therapeutic effects of isoquercetin on nonalcoholic fatty liver disease (NAFLD) in mice induced by a high-fat diet [37]. The study found that isoquercetin supplementation significantly regulated bile acid levels in the liver, serum, gut, and fecal samples of NAFLD mice. Additionally, it reduced the hepatic biliary sterols and triglyceride levels by 13.2% and 16.05%, respectively, in NAFLD mice. Isoquercetin achieved these effects by inhibiting FXR-Fgf15 signaling and promoting bile acid biosynthesis. It also modulated the receptors involved in bile acid transport, reabsorption, and excretion. Long-term intake of isoquercetin is suggested to have an intervention effect on the occurrence of fatty liver.

Moreover, a study on *Apocynum venetum* leaf extract (AVLE) showed that eight compounds, including isoquercetin, quercetin, rutin, and quercetin-3-*O*-glucuronide, in AVLE had protective effects against doxorubicin (DOX)-induced cardiomyocyte apoptosis [38]. AVLE administration mitigated DOX-induced oxidative stress, improved mitochondrial function, regulated apoptosis-related protein expression, and activated the AKT signaling pathway, thereby safeguarding against DOX-induced cardiotoxicity.

These findings highlight the potential therapeutic benefits of isoquercetin in various contexts, including hepatotoxicity, sleep deprivation, nonalcoholic fatty liver disease, and cardiomyocyte apoptosis. Further research is needed to explore its mechanisms of action and clinical applications.

6. Quercetin-3-O-Sambubioside

Quercetin-3-*O*-sanburoside is a glycoside derivative of quercetin that was mentioned in a study by Wang et al., which focused on the hepatoprotective effects of *Hedyotis diffusa Willd* [39]. The researchers observed significant protective effects against liver injury and identified quercetin-3-*O*-sambubioside as the key active compound. In vitro experiments further confirmed the compound's ability to reverse the decrease in cell viability caused by INH (isoniazid) and its effects on relevant targets.

In another study by Guo et al., the main active components of *Eucommia* male flower pollen were identified and analyzed [40]. Quercetin-3-*O*-picroside, quercetin-3-*O*-sansanoside, and quercetin-3-*O*-naringin were identified as the primary active compounds. The researchers performed purification and structure identification of these compounds and employed molecular docking methods to predict their activities. The effects of these compounds on ROS generation were evaluated using H_2O_2 stimulated with RAW264.7 cells as a model.

These studies highlight the potential therapeutic benefits of quercetin-3-*O*-sanburoside and related compounds, particularly in the context of hepatoprotection and antioxidant effects. Further research is needed to explore the mechanisms of action and the potential clinical applications of these compounds.

7. Quercitrin

Quercitrin (quercetin 3-rhamnoside) is a bioflavonoid compound, shows promise in the treatment of various diseases, particularly osteoarthritis (OA) [41][42]. It has been found to reduce the expression of MMP-13 and increase collagen II expression, promoting cell proliferation and delaying the degradation of the extracellular matrix (ECM). Notably, studies conducted on chondrocytes and SW1353 cells have yielded promising results. In an animal model of OA using rats with anterior cruciate ligament transection (ACLT), quercitrin was found to activate the p-110α/AKT/mTOR signaling pathway, leading to increased bone and tissue volume and enhanced cartilage thickness in the tibial subchondral bone. These positive effects are further supported by a decrease in the OARSI score, emphasizing quercitrin's potential for the prevention and treatment of early OA.

Quercitrin has also demonstrated hepatoprotective properties against acetaminophen (APAP)-induced liver injury [43]. This is achieved through the reduction of ROS levels, protection of the mitochondria, and the restoration of mitochondrial complex I activity. Animal models have shown that quercitrin effectively mitigated APAP-induced liver injury, resulting in improved liver function markers and reduced inflammation levels [43].

In a comprehensive study conducted by Sun et al., the molecular mechanisms of quercitrin were further explored in an inflammatory animal model induced by LPS [44]. The study focused on quercitrin's antidepressant effects, modulation of neuroinflammation, and influence on neuroplasticity. The administration of quercitrin (10 mg/kg) resulted in rapid and sustained antidepressant effects. Within two hours, signaling molecules related to neuroplasticity in the hippocampus were upregulated, while inflammatory pathways were suppressed. Quercitrin exhibited the ability to reduce cytokine levels, restore impaired signaling, and exert anti-inflammatory effects similar to those of a PI3K inhibitor. These findings highlight the diverse therapeutic potential of quercitrin, particularly in the domains of osteoarthritis, liver injury, and neuroinflammation.

Further investigations are warranted to deepen our understanding of the underlying mechanisms and expand the scope of the clinical applications of quercitrin.

8. Spiraeoside

Spiraeoside (quercetin 4'-*O*-glucoside) is a flavonoid glycoside compound that occurs naturally in plants. It has shown potential as a natural alternative for managing gout, a type of arthritis [45][46]. Research conducted on the marine seagrass *Halophila stipulacea* has revealed that the extract, which contains spiraeoside, reduced neutral lipid levels in zebrafish larvae [47]. In another study, spiraeoside derived from *Filipendula ulmaria* (L.) Maxim. was investigated for its inhibitory activity on monoamine oxidase (MAO), an enzyme targeted in gout treatment. Spiraeoside demonstrated inhibitory activity approximately 25 times greater than allopurinol, suggesting its potential as a natural alternative for managing gout [45].

Furthermore, spiraeoside has significant antioxidant and anti-inflammatory properties. It has shown promising inhibitory effects on aromatase, monoamine oxidase A/B, and angiotensin-converting enzymes. Additionally, spiraeoside exhibited strong inhibitory effects on the growth of HeLa cells, particularly at a concentration of 50 μg/mL [48]. Mechanistically, it was found to suppress the expression of Bcl-2 and Bid, promoting apoptosis through the activation of caspase-9/-3, and inhibited the expression of mu-2 related death-inducing gene (MUDENG).

These findings highlight the potential of spiraeoside in the management of gout and its ability to exhibit antioxidant, anti-inflammatory, and anti-cancer properties. Further studies are necessary to explore its therapeutic applications and mechanisms in greater detail.

9. Rhamnetin

Rhamnetin is a quercetin derivative derived from *Coriandrum sativum* [49]. In the molecular structure of quercetin, the hydroxyl group's position is substituted by a methyl group, giving rise to rhamnetin. Sepsis caused by carbapenem-resistant *Acinetobacter baumannii* (CRAB), a pathogen resistant to current antibiotics and responsible for acute lung failure, has been extensively studied. In a study carried out by Lee et al., the potential therapeutic efficacy of rhamnetin in sepsis was underscored, presenting encouraging outcomes [50]. They demonstrated that rhamnetin effectively mitigated the uncontrolled inflammatory response in sepsis by inhibiting the release of IL-6 and NO in mouse macrophages stimulated by LPS, CRAB, and *Escherichia coli* (*E. coli*). Additionally, in a mouse model of sepsis with CRAB or *E. coli* infection, rhamnetin administration significantly reduced the bacterial load in organs and effectively alleviated lung injury, as evidenced by levels of inflammatory factors and histological analysis of lung tissue. In the meantime, rhamnetin exhibited remarkable anti-inflammatory activity with minimal cytotoxicity.

10. Tamarixetin

Tamarixetin (4'-*O*-methyl quercetin) is a methylated derivative of quercetin extracted from *Tamarix troupii*. It has been found to protect against cardiac hypertrophy, a compensatory response to a mechanical load that can lead to heart failure. In an anti-cardiac hypertrophy study, researchers demonstrated that tamarixetin effectively alleviated cardiac hypertrophy and ventricular dilatation in transverse aortic constriction (TAC) mice; a series of echocardiography parameters were improved, and hypertrophy markers, such as atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and myosin heavy chain 7 (Myh7) were significantly reduced [51]. It also inhibited phenylephrine-induced hypertrophy in cardiomyocytes and reduced oxidative stress and ROS production. It suppressed the expression of apoptosis and fibrosis-related genes, reversed remodeling in the stressed heart, and prevented nuclear translocation of the nuclear factor of activated T cells (NFAT) and activation of the PI3K–AKT signaling pathway.

11. Nepetin

Nepetin (6-methoxyluteolin) is a methylated derivative of quercetin that is derived from the flowers of *Inula japonica*, Inulae flos [52]. It has shown potential in managing various diseases, including Alzheimer's disease and T2DM [53][54]. In the context of sepsis, nepetin has demonstrated effectiveness against multiple infections. For example, Jing et al. identified nepetin (100 mg/kg) as an inhibitor of ClpP and a potential lead compound for treating methicillin-resistant *S. aureus* (MRSA) infection [55]. Nepetin effectively combated MRSA-induced pneumonia by inhibiting bacterial virulence.

Moreover, nepetin exhibits anti-inflammatory properties by reducing the secretion and mRNA expression of pro-inflammatory cytokines, such as IL-6, IL-8, and monocyte chemoattractant protein 1 (MCP-1). This effect is achieved through the inhibition of the NF-κB and MAPK signaling pathways. Additionally, nepetin can inhibit degranulation and the production of inflammatory molecules in bone marrow-derived mast cells [56].

Nepetin also shows potential in inhibiting osteoclast differentiation, formation, and bone resorption induced by RANKL. Studies have demonstrated its protective effect against bone destruction caused by excessive osteoclast activity. This protection is attributed to the inhibition of NF-κB and MAPK signaling pathways and prevention of the TNF receptor-associated factor 6 (TRAF6)-mediated ubiquitination of Beclin-1 [57].

12. Isorhamnetin

Isorhamnetin (3'-methylquercetin) is a flavonoid compound extracted from *Hippophae rhamnoides* (L.). Lee et al. discovered that isorhamnetin can activate the cystic fibrosis transmembrane conductance regulator (CFTR), offering a potential treatment for dry eye syndrome [58]. Their investigations showed that isorhamnetin significantly enhanced CFTR

chloride currents occurring in both wild-type and ΔF508-CFTR mice. Importantly, isorhamnetin had no impact on the intracellular cAMP levels or the activity of other ion channels. The topical application of isorhamnetin on mice's ocular surface led to CFTR activation and increased tear secretion. Isorhamnetin effectively reduced ocular surface damage and the expression of inflammatory markers in an experimental dry eye mouse model. This protective effect is attributed to the activation of the AKT/sirtuin 1 (SIRT1)/Nrf2/HO-1 pathway, mitigating apoptosis, inflammation, and oxidative stress [59].

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