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Review Article

QUERCETIN: DERIVATIVES, BIOSYNTHESIS, BIOLOGICAL ACTIVITY, PHARMACOLOGICAL AND THERAPEUTIC EFFECTS

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ABSTRACT

In this review, the general properties, derivatives and biosynthesis, pharmacological and therapeutic effects, and biological activities of quercetin were examined to shed light on future studies. The literature search has revealed that the effects of quercetin, which is formed from different substrates, also vary. It has been observed that quercetin can be used in the treatment of diseases such as allergy, prostate, arthritis, neurodegenerative diseases, diabetes mellitus, osteoporosis, asthma and hypertension. In addition, it has been observed that quercetin has biological activities such as anticancer, antioxidant, and antimicrobial activities. In the literature, there is no detailed information about daily intakes and doses for human use. In this context, it is thought that quercetin may be an important compound in in vivo and in vitro studies due to its different pharmacological and biological potentials.

KEYWORDS: Bioflavonoids, Biological activity, Quercetin, Pharmacology, Phenolic compounds.

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1. Introduction

Phenolic compounds, also known as secondary metabolites, are characterized as chemical compounds containing one or more aromatic rings and one or more hydroxyls in their structure. Plant secondary metabolites, also known as phytochemicals, are compounds synthesized by plants through natural processes that protect them against stress conditions, insects and other pests, microorganisms, and other abiotic factors [1-3]. Phenolic compounds found in various organs of plants are abundant in plant-based foods and beverages as well as plants [4-6]. Stilbenoids, lignans, phenolic acids, tannins, and flavonoids represent some of the most significant examples of phenolic compounds [7-12].

2. Quercetin and its properties

Bioflavonoids are chemical compounds that have attracted the special attention of researchers for the past 30 years. They are abundant in many fruits such as apples and pears, in many vegetables such as broccoli, cabbage,

and in many beverages such as tea and wine. Flavonoids are one of the most common plant-derived polyphenol compounds. Flavonoids have the general structure of a 15-carbon skeleton consisting of two phenyl rings (A and B) linked by a heterocyclic ring (C, ring containing embedded oxygen). Furthermore, flavonoids manifest as aglycones, glycosides, and methylated derivatives. Flavonoids are classified into six subgroups, namely flavones, flavonols, flavanols, flavanones, isoflavones, and anthocyanins, based on the oxidation state of the central C ring. More than 4000 different flavonoids have been identified, many of which are responsible for the attractive colors of flowers, fruits, and leaves [7,9,13-15].

The compound with the structure of (3,3',4',5,7-pentahydroxyflavone) is commonly referred to as quercetin. The molecule in question contains five hydroxyl groups at positions 3, 5, 7, 3', and 4. The term quercetin is derived from the Latin word quercetum. Quercetin is also referred to as oak forest or quercus oak. The form of quercetin found in fruits is usually glycone or carbohydrate conjugates that act as a pigment that gives color to many fruits and vegetables (quercetin-3-O-glucoside, quercetin-

3-rutinoside, etc.). They have various functions in plants, such as giving flavor and aroma to fruits, flowers and vegetables, helping color development, helping pollination, and repelling harmful insects. Rutin and thujin are among the quercetin glycone conjugates. Rutin is also known as quercetin-3-rutinoside in academic literature. Thujin is also known as quercitrin, quercetin-3-L-rhamnoside, and 3-rhamnosyl quercetin [16-22]. Quercetin is a bioflavonoid. The compound is a pentahydroxy flavonoid and possesses five hydroxyl groups located at positions 3, 3', 4', 5, and 7, and is characterized by the formula $C_{15}O_{10}O_7$ (Fig 1) [23]. Quercetin is one of the most common flavonoids found in edible vegetables, fruits, and wine. In addition, it acts as an antibacterial agent, antioxidant, and as a protein kinase inhibitor [24].

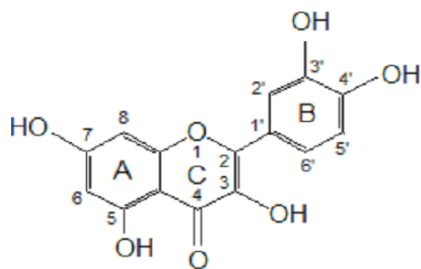


Fig 1. Molecular formula of quercetin

3. Quercetin derivatives and biosynthesis

Precursors of quercetin were obtained by the alkaline hydrolysis of pentamethyl ether from cuttings of *Fagopyrum tataricum* plant after 24 hours of exposure to light, followed by the separation of veratric acid (Fig 2A). Additionally, precursors of quercetin were obtained from shikimic acid, (Fig 2B) phenylalanine, (Fig 2C) and cinnamic acid (Fig 2D) in the same study [22,25-30]. Furthermore, the biosynthesis of coumarin occurs through the phenylpropanoid metabolic pathway. Initially, cinnamic acid is synthesised from phenylalanine; this reaction is catalysed by the highly important enzyme phenylalanine ammonia-lyase. The glycosylation of quercetin involves the attachment of glucose moieties to the 3, 5, 7, 3', and 4 hydroxyl groups, resulting in the formation of larger quercetin glycosides. If quercetin binds to galactose at position 3-OH, it forms quercetin 3-O-galactoside. On the other hand, if the rhamnosyl group binds to position 3-OH or 7-OH, it forms quercetin 3-O-rhamnoside and quercetin 7-O-rhamnoside, respectively. Additionally, α -L-rhamnopyranosyl-(1 \rightarrow 6)- β -D-glucopyranose binds to position 3-OH of quercetin. The compound quercetin undergoes methylation to form

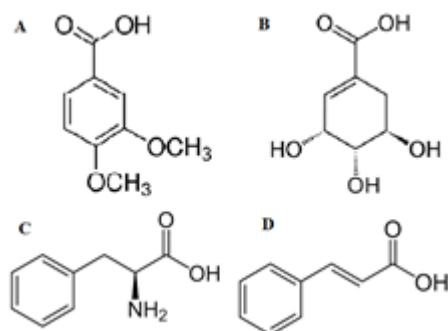


Fig 2. Molecular formulas of veratric, shikimic, cinnamic acids and phenylalanine

various derivatives, including ramnetin 7-O-methyl quercetin, dimethyl quercetin, isorhamnetin, 3-methyl-quercetin, isorhamnetol, isorhamnetin 3-O-rutinoside, isorhamnetin 3-O-rutinoside-7-O-glucoside, and isorhamnetin 3-O-rutinoside-4'-O-glucoside. Additionally, when a glucose molecule is attached to the 3 position of structure of quercetin, tamarixetin 3-O- β -D-glucoside derivatives are formed [22,25-30].

4. Pharmacological and therapeutic effect

It has been reported in the literature that quercetin is used in the treatment of disorders such as allergic asthma, prostate cancer, neurodegenerative diseases, diabetes, osteoporosis, hypertension, eye disorders, coronary heart diseases, hay fever, gout, gastric ulcer, impaired sperm function and reproductive hormone dysfunction, testicular injury, atherosclerosis and rheumatoid arthritis [31-53]. Studies conducted in South Korea and China have reported that 40 μ M quercetin has an effect on MUC5AC expression induced by human neutrophil elastase (HNE) in human airway epithelial (HBE16) cells. It has also been reported that 7.5 mg/kg quercetin inhibits specific airway resistance (sRaw) and leukocyte aggregation. As a result, it has been reported that it may be beneficial in the treatment of asthma by reducing the uptake of neutrophils and eosinophils into the lungs [31,32]. In studies conducted in China, the LC50 value of quercetin proliferation of human prostate cancer PC-3 and LNCaP cells was reported to be 22.12 μ M for PC-3 and 23.29 μ M for LNCaP. It has also been reported that Cyclin D and E, CDK2, cdc25c are down-regulated and p21, p53, p18 and p27 up-regulated in the 50-200 μ M dose range [33,34]. Studies conducted in India, Japan and South Korea have reported that 0.5-50 mg/kg quercetin protects from oxidative stress and neurotoxicity caused by neurotoxic attacks. It has also been reported that quercetin protects cells from H_2O_2 - and xanthine (X)/xanthine oxidase (XO)-induced damage at LC50 values of 0.6-0.7 μ g/mL [35-37]. In studies conducted in Ukraine and Saudi Arabia, it has been reported that quercetin in the dose range of 10-50 mg/kg restores the basic parameters of carbohydrate metabolism, reduces blood sugar and glycosylated hemoglobin in experimental type 1 diabetes mellitus and type 2 diabetes combined with obesity. It has also been reported to have a sugar-lowering activity when applied for 2-4 weeks [38,39].

Studies conducted in China and the USA have reported that a concentration of 1 μ M quercetin has an effect on the proliferation, osteogenic differentiation and angiogenic factor secretion as well as osteoclastogenic factor secretion of ovariectomized (OVX) rat bone marrow-derived mesenchymal stem cells (rBMSCs). In addition, decreases in systolic (-7 mm Hg), diastolic (-5 mm Hg), and mean arterial pressures (-5 mm Hg) were reported after the administration of 730 mg quercetin for 28 days [40,41]. Studies conducted in the USA and China have reported that 200 μ M quercetin attenuates OVA-induced MC degranulation, eosinophil count, substance P concentrations, and mRNA IL-4/TNF- α expression in conjunctival tissue of AC mouse models. It has also been reported that significantly relaxed resistance (respectively, -32, n = 10; -47, n = 7; -82, n = 8) and conductivity (respectively, -20, n = 8; -32, n = 8; -72, n = 8) in coronary arteries were observed at 5.6, 8 and 30 μ M quercetin

concentrations [42,43]. In studies conducted in the USA and Pakistan, it has been reported that quercetin inhibits antigen and mitogen-induced histamine release from mouse mast cells and basophils of hay fever subjects. It has also been reported that 0.2425 mg/g quercetin may have a role in preventing gout [44,45]. In a study conducted in Turkey, it was reported that quercetin at a dose of 50 mg/kg was effective against gastric ulcer [46]. In studies conducted in Tunisia and China, it was reported that 50 μ M quercetin had an effect on human sperm DNA integrity and activation of caspase 3, the main apoptosis indicator, in 17 semen samples from 17 men. It has also been reported that quercetin at a dose of 25 mg/kg body weight reduces the activity of steroidogenic enzymes (3 β -HSD and/or 17 β -HSD) in a rat model of PCOS [47,48]. In a study conducted in Turkey, quercetin at a dose of 270 mg/kg was reported to be beneficial in the treatment of testicular injury [49]. Studies in the Netherlands and Indonesia reported that 19.3 μ M quercetin significantly reduced atherosclerosis by 40% in ApoE*3Leiden mice. In addition, 41.508 mg of quercetin obtained from plants has been reported to have anti-atherosclerotic effects [51]. In studies conducted in Egypt and South Korea, quercetin was reported to be effective against rheumatoid arthritis in mice when administered at 100 mg/kg. It has also been reported that quercetin administered at 166 mg to 20 patients has an effect against rheumatoid arthritis [52,53].

5. Biological activities

Table 2. Biological activity of quercetin [54-83].

Biological activity	Geographic regions
Antioxidant, antiviral, antimicrobial, antiprotozoal, anti-inflammatory, anticancer, hepatoprotective, cytotoxic	Serbia, India, China, Brazil, Iran, Saudi Arabia, South Africa, Malaysia, Scotland, USA, Japan, Turkey, Netherlands, Italy, Czech Republic, Spain, Sweden, Poland

5.1. Antioxidant activity of quercetin

Antioxidant compounds play an important role in reducing the effects of free radicals. [84]. Oxidizing compounds are compounds that do not show harmful effects at low levels but can become quite harmful as their levels rise [85]. The antioxidant defense system plays a role in suppressing oxidant compounds. In situations where antioxidants are insufficient, oxidative stress occurs [86]. Serious illnesses such as multiple sclerosis, cancer, cardiovascular disorders or Alzheimer's and Parkinson's diseases may manifest as a result of oxidative stress [87,88]. Supplementary antioxidants are significant agents for reducing the effects of oxidative stress [89]. In this review, the antioxidant potential of quercetin has been compiled from literature data. In a study conducted in Serbia, the antioxidant potential of quercetin was evaluated using DPPH, lipid peroxidation and FRAP tests. As a result of the study, it was reported that methylated quercetin metabolites showed high antioxidant activity by inhibiting lipid peroxidation [79]. A study conducted in India investigated the effects of quercetin against reduced glutathione, lipid peroxidation and hydrogen peroxide. As a result of the study, it was reported to have high activity [70]. Another study conducted in India reported that quercetin increased antioxidant enzymes in rats infected with prostate cancer [71]. In a study conducted in

China, it was reported that quercetin prevents the increase of reactive oxygen species (ROS) level and prevents myocardial cell damage caused by oxidative stress [83]. In a study conducted in Brazil, it was reported that the dose of quercetin between 25-50 mg/kg is effective in terms of antioxidants [69]. In a study conducted in Iran, it was reported that quercetin reduces the effectiveness of ROS in nicotine addicts [76]. In another study conducted in Iran, it was reported that quercetin exhibited antioxidant activity in acute liver injury caused by tertiary butyl hydrogen peroxide [78]. Based on the antioxidant activity studies reported in the literature, it has been observed that quercetin could be an important antioxidant

5.2. Antimicrobial activity of quercetin

The increase in the number of diseases caused by microorganisms and the growing prevalence of resistant microorganisms have prompted researchers to focus on the discovery of new antimicrobial drugs [90,91]. In this context, a compilation of the reported antimicrobial activity studies of quercetin in the literature has been presented. In a study conducted in China, broiler chicks known as Arbour Acre were administered quercetin at doses of 0.2, 0.4, and 0.6 g/kg for a period of 42 days. As a result of the study, it was reported that it exhibited antibacterial activity against different bacterial strains such as *Salmonella enterica* serotype Typhimurium, *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *Helicobacter pylori*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Yersinia enterocolitica*, *Micrococcus luteus*, *Campylobacter jejuni* and *Escherichia coli* [80]. Quercetin used in a study conducted in Saudi Arabia was reported to exhibit antimicrobial activity against *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus niger* [73]. In a study conducted in China, the MIC (Minimum Inhibitory Concentrations) value of quercetin against *Streptococcus mutans*, *Streptococcus sobrinus*, *Lactobacillus acidophilus*, *Streptococcus sanguis*, *Actinobacillus actinomycetemcomitans* and *Prevotella intermedia* was reported to be between 1-8 mg/mL [64]. In another study conducted in China, it was reported that the MIC value of quercetin against *S. mutans* was 500 μ g/mL [77]. In a study conducted in South Africa, it was reported that the MIC value of quercetin-5,3'-dimethylether against *M. luteus* and *Shigella sonnei* was 25 mg/mL [59]. According to a study conducted in India, the MIC value of quercetin against *S. aureus* and *P. aeruginosa* was 20 mg/mL [75]. Within this context, it is believed that quercetin may serve as an antimicrobial agent against reported microorganisms.

5.3. Antiviral and antiprotozoal activities of quercetin

In a study conducted in Malaysia, it was reported that quercetin has an antiviral effect against the Japanese encephalitis virus (JEV), which causes Japanese encephalitis [66]. In a study conducted in Scotland, it was reported that quercetin and its derivatives are antivirals effective against human immunodeficiency virus (HIV), poliovirus, and Sindbis virus [60]. In a study conducted in the USA, it was reported that quercetin is effective in COVID-19 patients when taken together with vitamin C [82]. In a study conducted in Japan, it was reported that quercetin has effects against rhinovirus, Coxsackievirus, poliovirus, and echovirus [54]. In a study conducted in

Turkey, the effect of quercetin against *Trypanosoma brucei rhodesiense*, *Trypanosoma brucei brucei*, *Trypanosoma cruzi*, and *Leishmania donovani* parasites was investigated. As a result of the study, it was reported that the parasites used were inhibited [61]. In a study conducted in the USA, the leishmanicidal and trypanocidal activities of quercetin were examined. As a result of the study, the LC50 value has been reported to be 1.0 µg/mL and 8.3 µg/mL, respectively [55].

5.4. Anti-inflammatory activity of quercetin

In a study conducted in Serbia, the effect of quercetin and some of its derivatives only on the COX-2 AA pathway tamarixetin > quercetin = quercetin-3,4'-di-O-glucoside >isorhamnetin = quercetin-3-O-glucuronide > isorhamnetin-3-O -glucoside > quercetin3,5,7,3',4'penthamethylether has been reported [79]. In a study conducted in Brazil, it was reported that the dose of quercetin above 50 mg/kg shows anti-inflammatory effect [69]. In a study conducted in China, quercetin was reported to affect lipopolysaccharide-mediated tumor necrosis factor TNF-α and LPS development in lung A549 cells [72]. In a Dutch study, quercetin was reported to affect Src- and Syk-mediated phosphatidylinositol-3-Kinase (PI3K)-(p85) tyrosine phosphorylation and complex formation of Toll-like receptor 4 (TLR4)/MyD88/PI3 K [62].

5.5. Anticancer and cytotoxic activities of quercetin

In another study conducted in India, it was reported that quercetin suppressed cancer cell proliferation and regulated the expression of antiapoptotic proteins in prostate cancer rat model [70]. It was reported that quercetin used in a study in Italy showed chemoprotective activity against tumor cell lines [65]. In a study conducted in China, it was reported that quercetin was used against 4T1 breast cancer [63]. It has been reported that quercetin used in another study in China has effects on MCF-7 and MDA-MB-231 human breast cancer cell lines [74]. It has been reported that quercetin used in a study in Sweden exhibits intracellular metabolic activation to o-quinone, in which case quercetin has a cytotoxic effect partially dependent on the observed concentration [56]. It has been reported that quercetin derivatives used in a study in Italy have effects on C-26 tumor cells and mouse embryonic fibroblasts (MEF) [67]. In a study conducted in India, it was reported that quercetin, used in African green monkey kidney (Vero) cells, has an effect at 10-40 µg/mL [57]. Quercetin used in a study in Poland was reported to have effects on human glioblastoma A172 and LBC3 cell lines [82].

5.6. Hepatoprotective activity of quercetin

In study conducted in Iran, it was reported that quercetin showed hepatoprotective activity in acute liver injury caused by tertiary butyl hydrogen peroxide [78]. Quercetin used in a study conducted in the Czech Republic was reported to decrease plasma concentrations of alanine aminotransferase in rats treated with LPS [68]. In a study conducted in Spain, a dose-dependent decrease in blood pressure was reported when quercetin was used chronically in a hypertensive rat model [58].

6. Daily use, bioavailability and toxicity of quercetin

The daily intake of quercetin may be different with different foods. It also varies even in different intake

methods. As it is known, one of the main sources of quercetin is plants. Daily intake of quercetin between 5-100 mg can be achieved by consuming vegetables or fruits. Doses should be adjusted in clinical studies. These doses can vary between 500-1000 mg. Animal studies have provided evidence of accumulation of quercetin in the kidney, liver, small intestine, and lung. In some cases, attention should be paid to its intake depending on the function of the body. In many studies, it has been stated that a toxic side effect is not observed much with the increase in daily quercetin intake. There are almost no human trials of the safety of quercetin supplementation. There is a lack of information regarding the possible consequences of quercetin supplementation, particularly in pregnant or lactating women, children and adolescents. Besides that, since quercetin is a mutagenic agent, some studies have reported that quercetin taken in excess dosage has an effect on supporting tumor growth in nephrotoxic and estrogen-dependent cancers [92-99].

Consumption of natural products and functional foods that are sources of quercetin can be very beneficial for people to fight disease and improve their well-being. The health benefit of quercetin generally depends on its absorption in the body, and the benefit also varies depending on the amount of absorption [99]. Quercetin is a hydrophobic molecule with relatively low solubility in water (0.17-7 µg/mL), gastric juice (5.5 µg/mL), and small intestinal fluid (28.9 µg/mL) [100]. Accordingly, the amount of absorption may decrease due to the tendency to precipitate. In addition, oral use of quercetin is thought to be limited, potentially limiting its health benefits. Different studies should be conducted to increase the bioavailability of quercetin.

7. Conclusions

Many secondary metabolites attract attention with their different bioactive properties. In this study, the general properties of quercetin were emphasized. In many studies reported in the literature, quercetin has been proved to be an important metabolite, especially in terms of antioxidant, anticancer and antimicrobial activity. Quercetin has been observed to be taken by humans in different forms through plants. It has been determined that there are not many studies on daily use doses. In this context, clinical studies as well as in vitro and in vivo studies on quercetin should be strengthened.

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