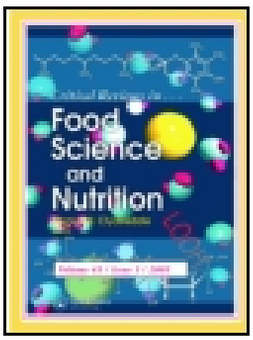

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

# A minireview of quercetin: from its metabolism to possible mechanisms of its biological activities

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**To cite this article:** Hande Gül Ulusoy & Nevin Sanlier (2019): A minireview of quercetin: from its metabolism to possible mechanisms of its biological activities, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2019.1683810

**To link to this article:** https://doi.org/10.1080/10408398.2019.1683810

Published online: 04 Nov 2019.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2019.1683810

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REVIEW



# A minireview of quercetin: from its metabolism to possible mechanisms of its biological activities

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**ABSTRACT**

Quercetin, one of the most taken flavonoid with diet, belongs to the family of flavonols in which kaempferol and myricetin are also found. Quercetin occurs as a glycoside (with linked sugars) or as an aglycone (without linked sugars). Although quercetin has many different forms in nature, the form found in plants is quercetin-3-O-glucoside, which generally functions as a pigment that gives color to a multitude of fruits and vegetables. The recent literature has been reviewed using PubMed, Science Direct, and Embase databases. In this article, we reviewed quercetin with respect to chemical properties, absorption mechanism, metabolism, bioavailability, food sources, bioactivities, and possible health-promoting mechanisms. Quercetin is known as an antioxidant, anti-inflammatory, cardioprotective, and anti-obesity compound. It is thought to be beneficial against cardiovascular diseases, cancer, diabetes, neurological diseases, obesity, allergy asthma, and atopic diseases. Further clinical studies with large sample sizes are needed to determine the appropriate dose and form of quercetin for preventing diseases.

**KEYWORDS**

biological activities; diseases; health; quercetin

## Introduction

Polyphenols are naturally occurring chemical compounds in plants. Polyphenols, comprising more than 8000 compounds in total, are divided into 2 main groups: flavonoids, and non-flavonoids (lignans, stilbenes, phenolic acids, non-phenolic metabolites, and other polyphenols) (Singla et al. 2019). Flavonoids, which are separated into subgroups, including flavanols, flavanonols, flavanones, flavones, flavonols, isoflavones, anthocyanins and anthocyanidins, are natural antioxidants capable of removing free radicals (Simioni et al. 2018; Durazzo et al. 2019; Singla et al. 2019).

A wide range of physiological functions of flavonoids has been investigated since their bioactivities were first determined about 80 years ago (Kawabata, Mukai, and Ishisaka 2015). Differences in dietary flavonols result from the binding of phenolic-OH groups and added sugars in different positions. All flavonols, including quercetin, have a common 3-hydroxyflavone backbone (Kelly, 2011). Quercetin, part of the flavonol subclass of flavonoids, is common in nature and is found in many foods such as vegetables, fruits, and tea (Ross and Kasum 2002; Nishimuro et al. 2015).

Quercetin, which has many different forms in nature, is found in plants as quercetin-3-O-glucoside, which usually acts as a pigment giving color to fruits and vegetables (Miles, McFarland, and Niles 2014). Quercetin exhibits antioxidant activity both *in vitro* and *in vivo*. It is thought that quercetin prevents cardiovascular and other diseases through scavenging free radicals, inhibiting lipid peroxidation, and other antioxidative effects (Kobori et al. 2009). In addition, quercetin can be effective in many diseases such as diabetes, neurological disorders, and obesity (Kelly 2011). Therefore, this minireview was conducted to evaluate the relationship between quercetin and health.

### *Definition and chemical properties of quercetin*

Flavonoids, a broad family of plant compounds, have a similar flavon backbone of hydroxyl [OH] groups bound to a three-ring molecule. Their basic structure consists of two aromatic rings, called A and B, and a heterocyclic ring called 3-carbon chain C, which combines these two rings (Eid, & Haddad, 2017), (Figure 1). Flavonoids occur either as glycosides, with bound sugars (glycosyl groups), or as aglycones, without bound sugars (Ross and Kasum 2002). Flavonoid subclasses and examples thereof are given in Table 1. Quercetin, whose closed formula is $C_{15}H_{10}O_7$, is a flavonol, one of the six subclasses of flavonoid compounds (Li et al. 2016; Ross and Kasum 2002). Since quercetin has an –OH group in the 3,5,7,3 and 4′ positions, it is known as 3,3′,4′,5,7- pentahydroxyflavone (3,3′,3′,5,7-pentahydroxy-2-phenylchromen-4-one) (Kelly 2011). The most common form of quercetin, which is usually found glycosylated, is rutin (Yalçın et al. 2016).

The sugar-free structure of quercetin is called aglycone. This structure's color is yellow. Although it is insoluble in cold water, aglycone has poor solubility in hot water and has good solubility in alcohol and oil (Li et al. 2016). The

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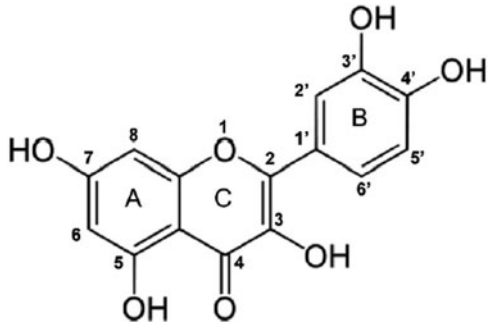


**Figure 1.** Chemical structure of quercetin (D'Andrea 2015).

**Table 1.** Flavonoid subclasses and its examples (Ross and Kasum 2002).

| Subclasses | Examples |
|---|---|
| Flavons | Apigenin, Chrysin, Luteolin |
| Flavonols | Kaempferol, Myricetin, Quercetin |
| Flavons | Hesperidin, Naringenin |
| Flavols (Catechin) | Epicatechin, Gallocatechin |
| Anthocyanidins | Cyanidin, Malvidin, Pelargonidin |
| Isoflavones | Genistein, Daidzein |

glycoside structure of quercetin is formed by the addition of a glycosyl group (a sugar, such as glucose, rhamnose, or routine) instead of an -OH group (usually at position 3). The presence of a glycosyl group (quercetin glycoside) increases water solubility compared to quercetin aglycone (Kelly 2011).

## Absorption, metabolism, and bioavailability of quercetin

Absorption of quercetin glycoside ranges from 3 to 17% after a 100-mg dose in healthy subjects (Simioni et al. 2018). Rutin and other quercetin glycosides that are bound to oligosaccharide or polysaccharide are absorbed in the lower part of the digestive system (the large intestine) as aglycones via deglycosylation by enterobacteria. On the other hand, quercetin monoglycosides such as isoquercitrin and quercetin-4'-glucoside (Q4'G) are absorbed in the upper part of the intestine (the small intestine) after enzymatic hydrolysis by gut microbiota-derived $\beta$-glucosidase and/or lactase-phlorizin hydrolase (LPH) in the intestinal mucosa. Some of the quercetin monoglycosides can be absorbed by sodium-dependent glucose transporter-1 (SGLT-1). An overview of quercetin absorption in the intestine is given in Figure 2. These metabolites are let into the digestive tract via multi-drug-resistance-associated protein 2 (MRP-2) and subsequently transported to the liver through blood vessels, where they are exposed to secondary metabolism. In addition, part of the quercetin taken by diet is also transported via the lymphatic pathway (Terao, Kawai, and Murota 2008).

For all flavonoids the gut microbiota plays a crucial role in absorption (Williamson 2017). In the gut microbiota, degradation of quercetin by many bacteria (*Eubacterium ramulus, Clostridium orbiscindens, Eubacterium oxidoreducens, Butyrovibrio* spp.) has been reported (Tamura et al. 2017; Luca et al. 2019). Quercetin forms into easily absorbable low molecular weight phenolic compounds such as 3,4-dihydroxyphenylacetic acid, 3-(3-hydroxyphenyl)propionic acid, 3,4-dihydroxybenzoic acid and 4-hydroxybenzoic acid (Santangelo, Silvestrini, and Mancuso 2018; Luca et al. 2019).

After absorption, quercetin is metabolized in various organs, including the small intestine, colon, liver, and kidney. Metabolites of quercetin (methylated, sulfated, and glucuronated forms) are formed in the small intestine and liver by biotransformation enzymes as a result of phase II metabolism. The quercetin metabolism results in the formation of phenolic acids in the small intestine and colon, along with the fragmentation of the quercetin skeletal structure (Boots, Haenen, and Bast 2008).

For physiological functions, conjugated quercetin metabolites in plasma or other tissues or deconjugated aglycone in specific tissues are used (Nishimuro et al. 2015). The quercetin metabolites are found in human plasma as glucuronide or sulfate (methylated or unmethylated, respectively) (Murota et al. 2007). Moreover, quercetin and its metabolites can cross the blood-brain barrier (Wang et al. 2016). Quercetin-3-O-$\beta$-D-glucuronide, the main metabolite of quercetin, is transported to target tissues via plasma to exert their biological activity (Kawabata, Mukai, and Ishisaka 2015). The half-life of quercetin metabolites varies from 11 to 28 hours, which is quite high (Boots, Haenen, and Bast 2008). Furthermore, quercetin has high bioavailability compared to other phytochemicals. The intake of quercetin from supplements instead of from foods during meals decreases quercetin's bioavailability (Guo and Bruno 2015).

Since the dietary form of quercetin is different from the supplementary form of quercetin (quercetin aglycone), it is not yet clear whether both forms have the same biological effects. In a randomized, double-blind, crossover study, 100 g of red onion containing 47 mg of quercetin glycoside and a supplement containing 554 mg of quercetin aglycone were administered to 6 healthy adult male subjects at 3-day intervals, and no significant differences were found between both groups in 24-hour urinary excretion of quercetin. However, it was determined that 166-mg quercetin supplementation was equivalent to 10-mg quercetin aglycone in onion (Shi and Williamson 2015).

Excretion of quercetin is by feces and urine. It can also be eliminated from the lungs when taken in high doses (Li et al. 2016). The excretory products of quercetin are 3-hydroxy phenylacetic acid, hippuric acid, and benzoic acid (Guo and Bruno 2015).

## Sources of quercetin

Quercetin is one of the most taken flavonols. Although previous reports (Hollman et al. 1995; Suganthy et al. 2016) indicate that quercetin intake accounts for 60-75% of total dietary flavonoids, Xiao et al. (2018) stated that quercetin intake constitutes approximately 60-75% of total flavonols, not total dietary flavonoids. Quercetin is widely found in different varieties of fruits and vegetables (Alinezhad et al. 2013). Onions, apples, and wine are considered to be quite rich in quercetin. It has been reported that quercetin occurs also in plant species such as tea, pepper, coriander, fennel,

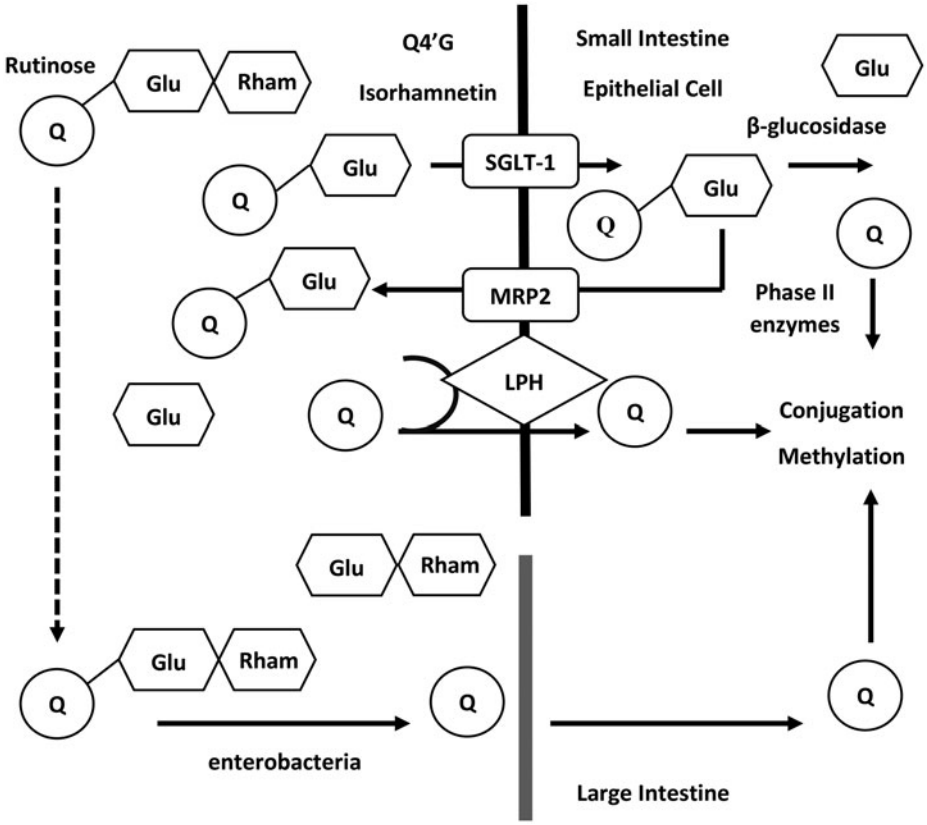


**Figure 2.** Absorption of quercetin from the intestine (Adapted from Terao, Kawai, and Murota 2008).
Q: quercetin aglycone, Glu: Glucose, Glu-Ram: Rutinose, SGLT 1: Sodium-dependent glucose transporter, MRP 2: multidrug-resistance-associated protein 2, LPH: lactase phlorizin hydrolase

radish, and dill (Nabavi et al. 2015). The quercetin content of some foods is given in Table 2.

The polyphenolic profile of fruits and vegetables depends on the plant species, growing conditions, harvest conditions, and manner of storage (Etxeberria et al. 2013). High-temperature storage reduces the quercetin content of foods. For example, quercetin content of onions that are stored at 100 °C declines up to 25–33%. In contrast, the quercetin content of strawberries that are stored at 20 °C for 9 months shows an increase of about 32%. Compared with plants grown in greenhouses, plants that are exposed to ultraviolet rays have higher quercetin content due to the defense mechanisms of the plants (Suganthy et al. 2016). The levels of quercetin aglycone in organically grown tomatoes are higher than those of tomatoes grown using the traditional method (Chen et al. 2016).

The consumption of quercetin varies between countries. The daily intake of flavonoids can vary between 5 and 80 mg. Among the foods that affect the level of quercetin intake, fruit, vegetables, and tea are the most consumed sources (Chen et al. 2016). In the United States, 13 mg of flavanoid is taken per day, and it is found that approximately one-third of it is quercetin; in China, 4.37 mg quercetin is taken per day (Sampson et al. 2002; Sun et al. 2015). In a cross-sectional study involving 14711 adults in China, using the frequency of food consumption, a daily intake of quercetin of 20.9 ± 2.32 mg was found (Yao et al. 2019). The intake level can be as high as 250 mg/day in individuals who consume plenty of tea, fruit, and vegetables, which are rich in flavonoid (Simioni et al. 2018).

Quercetin intake from foods or supplements increases the plasma quercetin concentration (Nishimuro et al. 2015). In the study, the level of blood plasma flavonoid increased as flavonoid intake increased (Zamora-Ros et al. 2011). Therefore, it can be said that a daily intake of quercetin-rich foods increases the bioavailability of quercetin and contributes to the prevention of lifestyle-related diseases (Nishimuro et al. 2015). It is also stated that quercetin enhances the acids and anti-inflammatory agents produced by bifidobacteria through enhancing the probiotic effects of *Bifidobacterium* species, thus helping to protect intestinal health (Kawabata, Mukai, and Ishisaka 2015).

## Quercetin effects on health

Flavonoids, present in plant-based foods, are known for lowering the risk of health disorders mainly because of their antioxidant activity (Shahidi and Ambigaipalan, 2015). Quercetin is reported as bioactive substance with antioxidant, anti-inflammation, antihypertensive, antiobesity, antihypercholesterolemic, antiatherosclerotic, anticancer, and antitumor properties (David, Arulmoli, and Parasuraman 2016; Li et al. 2016). Potential effects of quercetin on health depend on the amount of its daily intake and forms of quercetin (Wang et al. 2019). For example, the antioxidant

Table 2. Quercetin content of some foods (mg/100 g) (Guo and Bruno 2015; Miltonprabu et al. 2017; Nabavi et al. 2015; D'Andrea 2015).

| Foods (100 g) | Quercetin content (mg) | Foods (100 g) | Quercetin content (mg) |
|---|---|---|---|
| Capers | 233.84 | Blueberries | 5.05 |
| Hot pepper (yellow) | 50.73 | Apple (red) | 4.7 |
| Red lettuce | 40.27 | Tomato | 4.56 |
| Cocoa powder | 20 | Green tea | 2.69 |
| Hot pepper (green) | 17.7 | Cherry | 2.64 |
| Onion (red) | 17.22 | Brocoli | 2.51 |
| Cranberry | 14 | Black tea | 1.99 |
| Onion (yellow) | 12.65 | Grapes (red) | 1.38 |
| Asparagus | 7.61 | Wine (red) | 1.04 |
| Lingonbery | 7.4 | Wine (white) | 0.04 |

activity of the quercetin conjugates is about half of the antioxidant activity of the quercetin aglycone (Hollman et al. 2011). On the other hand the quercetin glycoside exhibits more anti-inflammatory action than other forms of quercetin (Wang et al. 2019). Moreover, the dose of flavonoid, which can have a significant effect on health, used in particularly *in vivo* studies is unfortunately about 10–60 times the daily amount of flavonoid taken by diet. This is also the case for quercetin (Serban et al. 2016).

## Antioxidant properties

In a normal state, the endogenous antioxidant network provides adequate protection against reactive species, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS). However, when an imbalance occurs between the production and defense of reactive species, a condition called oxidative stress arises. Oxidative stress can lead to an increase in oxidative damage and may result from excessive production of free radicals and degradation of ROS or the endogenous antioxidant defense system (Boots, Haenen, and Bast 2008). Due to their ability to remove free radicals and reactive derivatives and consequently to reduce oxidative stress and related damage, exogenous antioxidants have been recommended for various health benefits (Halliwell, 1996; Diplock et al. 1998).

Quercetin is one of the most important dietary antioxidants (Boots, Haenen, and Bast 2008). It is one of the best scavengers of ROS such as $O^{2-}$ and RNS such as $NO^{\cdot}$ and $ONOO^{-}$. While cleaning free radical derivatives, quercetin produces, by means of oxidation, reactive products known as o-quinone/quinone methides. O-quinone/quinone methide can be transformed back to the quercetin form by other antioxidants. In the absence of glutathione or ascorbate, o-quinone/quinone is toxic. Therefore, adequate levels of plasma glutathione or ascorbate should be present in high-dose quercetin supplements (Askari et al. 2012).

It is thought that this antioxidant property of quercetin is due to the catechol group in the beta ring and the -OH group in position 3 of the AC ring (Heijnen et al. 2002). In many cell types, quercetin shows comprehensive protective effects against oxidative stress caused by oxidation of lipid, lipoprotein fragments, and various other factors (Sakanashi et al. 2008). In a study conducted by Machha et al. (2007), rats were given quercetin for 6 weeks, and quercetin treatment was found to decrease the levels of plasma malondialdehyde (MDA) and 4-hydroxyalkyne (4-HNE) in diabetic rats while increasing superoxide dismutase activity and total antioxidant capacity (Machha et al. 2007). Nuclear factor erythroid 2-related factor 2 (Nrf2), which binds to antioxidant response elements (AREs), is an important signaling pathway against oxidative stress. Nrf2-ARE pathway induces antioxidant enzymes such as catalase, glutathione reductase (GR), glutathione S-transferase (GST), heme oxygenaase-1 (HO-1), thioredoxin reductase (TrxR), and superoxide dismutase (SOD). Quercetin enables expression of antioxidant enzymes through activation of the Nrf2-ARE signaling pathway (Costa et al. 2016; Dong et al. 2017; Marunaka 2017). Quercetin, which also known as an efficient iron chelator, protects cells against oxidative damages that caused from iron overloading. The anti-carcinogenic effect of quercetin is associated with the chelating effect of iron as well as its antioxidant effect. It has been reported that quercetin-metal complexes might possess even greater anticancer and antibacterial activities than free quercetin (Xiao et al. 2018).

Glutathione and glutathione dependent enzymes form the endogenous antioxidant system in the gut (de Barboza et al. 2017). Since intestinal calcium absorption depends on the amount of glutathione in the intestine, when the production of reactive oxygen species in the intestine increases, the amount of glutathione decreases and calcium absorption is inhibited (de Barboza, Guizzardi, and de Talamoni 2015; Moine et al. 2018; de Barboza et al. 2017). Quercetin may be used to provide normal redox status in diseases associated with intestinal oxidative stress, such as irritable bowel syndrome and celiac disease. While quercetin is maintaining normal redox status, it promotes calcium absorption (de Barboza et al. 2017).

## Allergy asthma and atopic diseases

Asthma is a chronic inflammatory disease characterized by mucosal inflammation, bronchial hyperactivity, and increased mucus production. Oxidative damage and many harmful factors of the respiratory tract play a role in the pathogenesis of asthma. Antioxidants are effective against the pathogenesis of asthma by preventing oxidative damage via different mechanisms (Elibol and Şanlıer 2017). Nowadays interest in flavonoids, especially quercetin with well-known antioxidant properties, is rapidly increasing. It has been reported that higher quercetin intake was

associated with lower asthma incidence. Moreover, at least two apples consumption per week was associated with stronger inverse relationship with asthma incidence than other quercetin sources such as onion, tea, and red wine (Mlcek et al. 2016).

Quercetin has been found to play a role in scavenging free radicals that can lead to cell death by damaging DNA and cell membranes. It has also been reported that quercetin may inhibit the production and release of histamine and other mediators responsible for the development of allergic reactions in mast cells and thus may be effective against asthma (Sakai-Kashiwabara and Asano 2013). In a study conducted on neonatal asthmatic rats, 50 mg/kg quercetin glycosides treatment significantly reduced TNF-α, IL-6, inducible nitric oxide synthase (iNOS) through reducing the mRNA expression levels. Moreover, treatment with quercetin glycosides significantly reduced total leukocytes, eosinophils, nitric oxide (NO), and apoptosis (Zhu et al. 2019).

In a study, it was emphasized that quercetin may have an important role in the treatment of respiratory inflammatory diseases such as asthma by means of its ability to regulate the Th1 (T helper type 1)/Th2 (T helper type 2) balance (Rogerio et al. 2010). Quercetin, which suppress eosinophil activation, may also have important role on the management of eosinophil-mediated diseases such as allergic rhinitis and asthma (Sakai-Kashiwabara and Asano 2013). In addition, some studies have reported that quercetin attenuates clinical symptoms (e.g., bronchial hyperreactivity) in asthma patients (Dorsch et al. 1992; Rogerio et al. 2007). In a study conducted *in vivo*, it was reported that quercetin (100 µM), the natural PDE4 selective inhibitor, could significantly reduce airway resistance and provide therapeutic relief of asthma symptoms (Townsend and Emala 2013).

### Cardiovascular diseases

One of the main mechanisms by which flavonols can reduce cardiovascular risk is their vasodilator and antihypertensive effect. Along with these diseases having a major impact on morbidity, they are also among the major causes of death worldwide (Perez et al. 2014). Cardiac output, blood volume, the nervous system, and the angiotensin system all play a role in the regulation of blood pressure (Marunaka et al. 2017). It is thought that quercetin can decrease blood pressure by decreasing oxidative stress, improving the renin-angiotensin-aldosterone system (RAAS), and improving vascular function (Larson, Symons, and Jalili 2012). It is stated that the anti-hypertensive effect is significant when quercetin is taken by individuals with hypertension or pre-hypertension at doses of 500 mg/day and above (Serban et al. 2016). In Cancer Prevention Study II Nutrition Cohort even low consumption of flavonoids-rich foods was associated with a low risk of cardiovascular disease (Serban et al. 2016).

Another cardiovascular disease is atherosclerosis, resulting in vasoconstriction of the vessels with fat accumulation. Vascular inflammation or reactive oxygen species damage and LDL oxidation play a role in the formation of fat plaques that contribute to the etiology of atherosclerosis (Kawabata, Mukai, and Ishisaka 2015; Li et al. 2016). Quercetin, which has the ability to increase the bioavailability of endothelium-derived nitric oxide, enhance vascular function (Patel et al. 2018). Quercetin has been shown to inhibit of LDL oxidation, reduce of adhesion molecules and other inflammatory markers. In addition to its antioxidant effect, quercetin acts as vasodilator and platelet anti-aggregator (Patel et al. 2018). Quercetin regulates cholesterol homeostasis through elevating hepatic cholesterol 7α-hydroxylase which is a key enzyme in the conversion of cholesterol to bile acids. However, quercetin did not affect the activity of hepatic β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase which is a rate-limiting enzyme involved in cholesterol synthesis (Zhang et al. 2016). In a study conducted on apolipoprotein E-deficient mice fed a high-fat diet, quercetin has been shown to accelerating reverse cholesterol transport which is defined as cellular cholesterol transport from peripheral tissues to liver. Underlying mechanism of this is the enhanced levels of expression ATP-binding cassettes (ABC) A1 and G1 which are engaged in the efflux of cellular cholesterol (Cui et al. 2017).

In a study, it was found that a treatment of 50 mg/kg quercetin in rats for 14 weeks reduces atherosclerosis and oxidative stress (Lara-Guzman et al. 2012). In a systematic review, it was reported that quercetin doses above 50 mg/day significantly decrease blood triglyceride levels but had no significant effect on other plasma lipids (Sahebkar 2017). By its anti-inflammatory effect, quercetin plays a key role in the reduction of cardiovascular risk factors such as fibrinogen and C-reactive protein. It has also been suggested that quercetin inhibits the proliferation and migration of aortic smooth muscle cells (Suganthy et al. 2016).

### Cancer

The use of chemotherapeutic components such as flavonoids along with a diet against cancer has been increasing in recent years. One of the chemotherapeutic components is quercetin, with its free radical scavenging, antioxidant, and anti-inflammatory effects (Rauf et al. 2018). Quercetin has an anti-carcinogenic effect by stimulating apoptosis, inhibiting the cell cycle, and promoting the release of matrix metalloproteinase. Growth suppression, stimulation of cell aging and death, and telomerase and antiproliferative effects have also been shown. Besides, quercetin reduces tumor cell adhesion, metastasis, and angiogenesis (Russo et al. 2012; Lan et al. 2017). Quercetin can also inhibit tumor growth and development through epigenetic modulations. It is associated with inactivation of oncogenes that play a role in the onset of cancer development and activation of tumor suppressor genes (Carlos-Reyes et al. 2019).

Breast cancer is the most common form of cancer in women worldwide and is the third most common cancer-related death. Lei et al. (2018) compared the efficacy of a high dose of SN-38, the anti-cancer drug metabolite in AGS cells, which are gastric cancer cells, with a low dose of SN-38 in combination with quercetin. The combination of

quercetin and SN-38 was reported to regulate angiogenesis and epithelial-mesenchymal transition (EMT)-related factors. In the study, it was concluded that the combination of quercetin and a low-dose anti-cancer drug was more effective in inhibiting the progression of gastric cancer cells (Lei et al. 2018). Growth inhibition via the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway and activation of caspase-3 and caspase-9 are also involved in the effects of quercetin against gastric cancer (Shen et al. 2016).

In a study of MCF-7 breast cancer cells that were given 50 $\mu$M/mL quercetin for 24 hours, it has been shown that quercetin can suppress the viability and proliferation of MCF-7 cells by activating apoptosis and necropsy signaling pathways. It has been reported that quercetin can induce non-apoptotic necroptosis and can be used as a potential agent in apoptosis-resistant cancers (Khorsandi et al. 2017).

It is reported that quercetin can inhibit prostate cancer cell growth and metastasis both *in vitro* and *in vivo* (Yang et al. 2015; Tummala et al. 2017). Because flavonols such as quercetin are structurally similar to androgen, they can interact with androgen receptors. This interaction of quercetin is associated with anti-carcinogen activity against prostate cancer (Tummala et al. 2017). Quercetin demonstrates chemotherapeutic and chemopreventive effects against prostate cancer by inhibiting the phosphatidylinositol 3-kinase (PI3K)/AKT and insulin-like growth factor (IGF) signaling pathways, as well as by regulating the extracellular-signal-regulated kinase 1/2/c-Jun N-terminal kinase/mitogen-activated protein kinase (ERK-1/2/JNK/MAPK) signaling pathway (Yang et al. 2015).

In a study evaluating the effect of 0, 25, 50, and 100 mg/kg quercetin injections on dose-dependent tumor growth in mice, it was reported that quercetin at higher doses was associated with a further reduction in tumor growth. It was concluded that quercetin could be used against osteosarcoma due to its anti-carcinogenic effects (Lan et al. 2017).

Hashemzaei et al. (2017) evaluated the anti-cancer activity of quercetin on colon carcinoma CT-26 cells, prostate adenocarcinoma LNCaP cells, human prostate PC3 cells, pheochromocytoma PC12 cells, estrogen receptor-positive breast cancer MCF-7 cells, acute lymphoblastic leukemia MOLT-4 T cells, human myeloma U266B1 cells, human lymphoid Raji cells, and ovarian cancer CHO cells. In the study, it was concluded that quercetin can induce apoptosis in all types of cancer cells (Hashemzaei et al. 2017). Most studies evaluating the effects of quercetin on cancer consist of *in vitro* and *in vivo* experiments. Therefore, studies on humans are needed (Rauf et al. 2018).

## Diabetes

Glucose transporter type 4 (GLUT4) is responsible for the uptake of blood glucose into muscle cells (Bryant, Govers, and James 2002). Dietary polyphenols capable of inducing translocation of GLUT4 may promote glucose uptake in skeletal muscle cells and may be a potential compound for preventing or ameliorating diabetes (Kawabata, Mukai, and Ishisaka 2015; Chen et al. 2016). In a study, quercetin was shown to improve liver and pancreatic functions by inhibiting cyclin-dependent kinase inhibitor p21 (WAFl/Cipl) (Cdknla) gene expression and improving cell proliferation (Kobori et al. 2009). Aldose reductase is an enzyme that catalyzes the conversion of glucose into sorbitol, which has important roles in the eye. Diabetes plays an important role in the formation of cataracts (Kelly 2011). Quercetin is an *in vitro* inhibitor of aldose reductase and effectively blocks polyol accumulation in intact rat lenses that are incubated in a medium with a high concentration of sugar (Varma, Mikuni, and Kinoshita 1975; Chen et al. 2016).

Increased CYP2E1 protein in type 1 diabetes (T1DM) is considered to be the main cause of stress-induced liver injury. In a study on diabetic rats, 50 mg/kg/day quercetin treatment was found to significantly reduce CYP2E1 activity and to improve the pro-oxidant-antioxidant balance (Maksymchuk et al. 2017). In another study in diabetic rats, quercetin supplementation of 50 mg kg/day was shown to inhibit cytochrome c and caspase-3 activity and to increase the level of anti-apoptotic protein. It has been reported that quercetin can be used to prevent diabetic retinopathy by inhibiting oxidative stress and by exerting neuroprotective effects (Ola et al. 2017).

11$\beta$-hydroxysteroid dehydrogenase type 1 (11$\beta$-HSD1), which mediates the glucocorticoid hormone in target tissues for insulin action, is considered to be a regulator in glucose homeostasis. In a study comparing oral antidiabetic effects of flavonoids, 3-hydroxyflavone, chrysin, and quercetin, hypoglycemic and antidiabetic effects of quercetin were found to be significant. Besides, quercetin showed the most inhibitory effect against 11$\beta$-HSD1 (Torres-Piedra et al. 2010).

For the pathophysiological treatment of type 2 diabetes (T2DM), it is necessary to reduce blood glucose levels and improve insulin release. It is known that quercetin inhibits carbohydrate absorption by inhibiting digestive enzymes responsible for carbohydrate hydrolysis and glucose carriers in different forms *in vitro* and *ex vivo* (Eid and Haddad 2017). Quercetin has also been reported to help reduce numbness and pain in patients with T2DM and neuropathy (Simioni et al. 2018).

Dhanya et al. (2017) showed that the effect of quercetin on T2DM in skeletal muscle cells was not via the insulin signaling pathway but through the adenosine monophosphate kinase (AMPK) pathway. In addition, an increase in intracellular calcium was demonstrated. It has been shown that the mechanism of quercetin, similar to that of oral antidiabetic drug metformin, may be a potential component in the treatment of T2DM (Dhanya et al. 2017; Joshi et al. 2019). As a result, quercetin protects normal blood sugar with such mechanisms as an increase of AMPK, GLUT4 activation and insulin receptor count in muscle cells, pancreatic $\beta$ cell regeneration, repair of pancreatic oxidative damage, an increased glucokinase activity in the liver, and reduced absorption of glucose in the small intestine (Shi et al. 2019).

## Neurological diseases and sleep

Neurodegenerative diseases are growing burden on aging societies. Approximately 15 percent of the population over

65 suffer from Alzheimer's disease and 1 percent from Parkinson's disease (Scalbert et al. 2005). Parkinson's disease has a negative impact on quality of life, contributing to disability (Schneider, Iourinets, and Richard 2017). Many central nervous system disorders such as Alzheimer's disease, Parkinson's disease, and depression are associated with oxidative stress-induced neurodegeneration (Kawabata, Mukai, and Ishisaka 2015). However, there is still no disease-modifying treatment for Alzheimer's disease (Lane, Hardy, and Schott 2018).

After oral intake of quercetin, its conjugated forms, quercetin-3-O-glucuronide and isorhamnetin-3-O-glucuronide, are found in the brain. Quercetin aglycone is found hardly in the central nervous system (Babaei, Mirzababaei, and Nassiri-Asl 2018). Quercetin is known to have neuroprotective effects against oxidative and neurotoxic compounds *in vitro* and *in vivo* (Cai, Zhao, and Ratka 2011). As well as its direct antioxidant effect, quercetin provides neuroprotection against oxidative damage through activating Nrf2-ARE pathway (Costa et al., 2016). In addition to its antioxidant properties, quercetin shows anti-amyloidogenic effects in Alzheimer's disease (Ono et al. 2003; Ho et al. 2013).

Quercetin has been reported as anti-Alzheimer due to improving typical morphology of mitochondria, enhancing the memory impairments, protecting cognitive deficit, and reducing neurodegeneration. The protective effects of quercetin against neurological diseases are linked to the regulation of pathways such as paraoxonase-2, c-Jun N-terminal kinase (JNK), protein kinase C, mitogen-activated protein kinase (MAPK), and PI3K/Akt (Zaplatic et al. 2019). In several epidemiological studies, coffee consumption has been shown to reduce the risk of Parkinson's and Alzheimer's disease (Liu et al. 2012; Palacios et al. 2012; Qi and Li 2014). In a study investigating the neuroprotective effects of coffee components, it was reported that quercetin, flavones, chlorogenic acid, and caffeine protect SH-SY5Y cells from toxins and decrease TNF-α and IL-6 release from active microglia. It was concluded that quercetin, one of the coffee components, has the most protective effect against Parkinson's and Alzheimer's disease (Lee, McGeer, and McGeer 2016).

Degeneration of dopaminergic neurons in the *substantia nigra pars compacta* increases the likelihood of developing Parkinson's disease (Kawabata, Mukai, and Ishisaka 2015). Oxidative damage caused by dopamine metabolism, glutathione depletion, iron accumulation, and lipid peroxidation abnormalities is thought to be an important risk factor for Parkinson's disease (Dias, Junn, and Mouradian 2013). Quercetin has a role in Parkinson's disease by providing protective effects against lipid hydroperoxide- or 6-hydroxydopamine-induced oxidative stress in neuronal cell lines (Shirai et al. 2006; Mukai et al. 2012). While intraperitoneal administration of quercetin (200 mg/kg) in rats increased non-REM sleep in the dark periods of sleep, it resulted in a significant reduction in REM sleep. This effect of quercetin on sleep is thought to be due to the induction of the type A GABA (γ-aminobutyric acid) receptor activation (Kelly 2011).

### Obesity

Obesity, a global health problem, results from an imbalance in energy intake and expenditure, and this leads to adiposity with hypertrophy and hyperplasia of fat cells. Obesity is characterized by a state of chronic oxidative stress associated with overproduction of reactive oxygen species (ROS, e.g., hydrogen peroxide, peroxyl, superoxide anion) and subsequent reduction in antioxidant levels (Imessaoudene et al. 2016). Adipose tissue is not only a triglyceride storage organ but also an endocrine organ. Adipose tissue secretes cytokines and adipokines that contribute to the development of inflammation and oxidative stress (Fernández-Sánchez et al. 2011).

In recent years, basic evidence suggests that quercetin and other polyphenols improve obesity through different molecular pathways (Nabavi et al. 2015). Quercetin has been reported to inhibiting the gene expression of fatty acid synthase (FAS) and the activity of acetyl-CoA carboxylase (ACC). Quercetin, which can inhibit lipogenesis, also can suppress adipogenesis by inhibiting gene expression of peroxisome proliferator-activated receptor γ (PPAR γ) (Zhao et al. 2017). Isolated rat adipocytes have been shown to inhibit glucose uptake and to increase lipolysis. Quercetin has also been reported to reduce cell proliferation and cause apoptosis in 3T3-L1 preadipocytes (Ahn et al. 2008). Also by nuclear factor kappa B (NF-κB) regulation, proinflammatory factors and cytokines reduction, quercetin shows anti-obesity activity (Chen et al. 2016). In a systematic review and meta-analysis of 16 randomized controlled trials, quercetin supplementation significantly reduced total-cholesterol, LDL-cholesterol and C-reactive protein. However, it did not significantly reduce triglycerides, HDL-cholesterol, IL-6 and TNF-α (Tabrizi et al. 2019).

Rivera et al. (2008) administered 2 mg/kg or 10 mg/kg quercetin to obese rats. At the end of the study, dyslipidemia, hypertension, and hyperinsulinemia were observed in rats of both groups, but only the group that was given 10 mg/kg/day quercetin decreased in body weight (Rivera et al. 2008). Another study investigated the effect of a quercetin-rich dietary intake on obesity and hepatic fat accumulation in rats consuming a high-fat and cholesterol- and sucrose-rich Western diet. After 20 weeks of quercetin supplementation, there was a decrease in visceral and liver fat accumulation but no change in body weight. There was also a decrease in plasma TNF-α and hepatic thiobarbituric acid-reactive substances (Kobori et al. 2011). In a study conducted on mice fed a high-fat diet (HFD), quercetin has been shown to up-regulate uncoupling protein 1 (UCP1) in white/brown adipose tissues through activation of the AMPK/PPAR γ pathway. It has also been suggested that quercetin may be useful for preventing obesity (Choi, Kim, and Yu 2018). However, in a meta-analysis of quercetin effects on weight loss, it has been reported that quercetin did not significantly reduce body weight, body mass index (BMI), waist circumference, and waist to hip ratio (Huang et al. 2019) (Table 3).

**Table 3.** Human studies on the relationship between quercetin and health.

| Biological Activity | Study type | Study sample | Study method | Results |
|---|---|---|---|---|
| **Cardioprotective** (Zahedi et al. 2013) | Randomized, double-blind, placebo-controlled study | 72 women who have had T2DM for at least 3 years and whose ages range from 33 to 55 years | 500 mg/day quercetin or placebo 10 weeks intervention | Systolic blood pressure decreased significantly ($p = 0.04$) Diastolic blood pressure did not change significantly ($p = 0.19$) HDL-C significantly decreased in both groups Total cholesterol, LDL-C, triglyceride levels not significantly changed TNF-$\alpha$ and IL-6 levels were significantly decreased ($p = 0.01$ and $p < 0.0001$, respectively) |
| **Cardioprotective** (Pfeuffer et al. 2013) | Randomized, double-blind, placebo-controlled, single-center, cross-over study | 49 healthy males whose mean age is $59.4 \pm 0.9$ years, APOE genotype is 3/3 (n = 19) 3/4 (n = 22) and 4/4 (n = 8) | In a total of 6 capsules per day, 2 capsules per 3 main meals 150 mg/day quercetin dihydrate or placebo 8 weeks intervention after 3 weeks wash-out period 8 weeks intervention | Postprandial systolic blood pressure decreased significantly ($p = 0.044$) Postprandial triacylglycerol concentration significantly decreased and HDL-cholesterol concentration significantly increased ($p = 0.025$) Waist circumference reduced significantly about 0,63 cm ($p = 0.004$) TNF-$\alpha$ levels increased significantly ($p = 0.024$) Genotype-dependent effects only seen in waist circumference and BMI |
| **Cardioprotective** (Perez et al. 2014) | Randomized, double-blind, placebo-controlled, cross-over study | 15 healthy individuals (9 males, 6 females) whose mean age is $25.8 \pm 5.2$ years | 200 mg/day quercetin aglycone or 400 mg/day quercetin aglycone or placebo Each participant received three supplements with one-week intervals in the same day of the week and same hour of the day | Dose-dependent increase in plasma quercetin-3-O-glucuronide level after 2 hours quercetin aglycone supplementation of 200 and 400 mg/day (0.4 $\mu$M and 1 $\mu$M, respectively) Time-dependent increase in brachial artery diameter after 400 mg/day quercetin aglycone supplementation There was a significant increase in plasma glutathione level after 2 hours quercetin aglycone supplementation at 400 mg/day |
| **Cardioprotective** (Brüll et al. 2015) | Randomized, double-blind, placebo-controlled, cross-over study | 68 overweight or obese individuals (34 males, 34 females) whose mean age of $47.4 \pm 10.5$ years with, prehypertensive or stage 1 hypertension Those with a history of T2DM, inflammatory and cardiovascular disease are not included in the study | 162 mg/day of quercetin or placebo 6 weeks intervention after 6 weeks wash-out period 6 weeks intervention | While quercetin supplementation does not provide a significant change in blood pressure and endothelial function in the whole study population, cardioprotective effect showed a significant decrease in 24-hour systolic blood pressure in hypertensive individuals ($p = 0.022$) |
| **Cardioprotective** (Dower et al. 2015) | Randomized, double-blind, placebo-controlled, cross-over study | 37 healthy individuals (25 males, 12 females) whose mean age is $66.4 \pm 7.9$ years | 100 mg/day epicatechin or 160 mg/day quercetin-3-glucoside or placebo in randomized order with in the morning and evening with 2 capsules daily meals 4 weeks of intervention followed by a 4-week wash-out cycle | Supplementation of quercetin-3-glucoside did not provide a significant change in flow-mediated dilatation, insulin resistance and other cardiovascular disease risk factors |
| **Cardioprotective** (Bondonno et al. 2016) | Randomized, cross-over, dose-response study | 15 healthy individuals (6 male, 9 female) whose mean age is $60.8 \pm 9.3$ years People who smokes, | A minimum of 1-week wash cycle between each 5 times randomized intervention; 0 mg, 50 mg, | Increase in plasma total quercetin ($p < 0.001$) and isorhamnetin ($p = 0.005$) concentration after |

(*continued*)

**Table 3.** Continued.

| Biological Activity | Study type | Study sample | Study method | Results |
|---|---|---|---|---|
| | | have a BMI of $<18$ or $>35\ kg/m^2$, have a systolic blood pressure $\leq 100$ or $\geq 160$ mm Hg, have a diastolic blood pressure $\leq 50$ or $\geq 100$ mm Hg and history of cardiovascular disease are not included in the study | 100 mg, 200 mg, 400 mg quercetin-3-O-glucoside supplementation Endothelial function and blood pressure were measured 60 minutes before and after the supplementation and the blood sample was taken 90 min before and after the supplementation | quercetin supplementation No significant change in endothelial function, blood pressure and nitric oxide production in any of the doses |
| **Cardioprotective** (Burak et al. 2017) | Randomized, double-blind, placebo-controlled, cross-over study | 67 healthy nonsmoker college students (34 males, 33 females) whose mean age is $24.6 \pm 3.9$ years, have BMI 19–25 $kg/m^2$ Individuals whose serum TAG $\geq 200$ mg/dL and LDL cholesterol $\geq 160$ mg/dL were not included in the study | Minimum 3.3 g/day ALA + 190 mg/day quercetin or minimum 3.3 g/day ALA + placebo 8 weeks intervention after 8 weeks wash-out period 8 weeks intervention | Significant increase in serum ALA in both groups (ALA + placebo, +69.3%; ALA + quercetin, +55.8%) Significant increase in serum EPA in both groups (ALA + placebo, +37.3%; ALA + quercetin, +25.5%) Slight decline in serum DHA in ALA + quercetin group (−9.3%) No significant effect of quercetin found Fatty acid composition did not differ between genders |
| **Anti-inflammatory** (Heinz et al. 2010) | Randomized, double-blind, placebo-controlled study | 120 healthy women aged between 30 and 79 years | 500 mg/day quercetin or 1000 mg/day quercetin or placebo 12 weeks intervention | Supplementation of 500 or 1000 mg/day did not result in a significant change in plasma IL-6 concentration ($p = 0.208$) Plasma leukocytes ($p = 0.306$), neutrophil ($p = 0.103$), lymphocytes ($p = 0.867$), IL-6 ($p = 0.812$) and TNF-$\alpha$ ($p = 0.208$) levels did not change significantly |
| **Anti-inflammatory** (Boots et al. 2011) | Randomized, double-blind, placebo-controlled study | 18 nonsmoker individuals (12 male, 6 female) whose mean age is $45 \pm 10$ years with untreated sarcoidosis | Quercetin or placebo $4 \times 500$ mg/day for 24 hours following the wash-out period of 2 days | Plasma antioxidant capacity was significantly increased in the group receiving quercetin (3%, $p < 0.01$) Plasma TNF-$\alpha$/IL-10 and IL-8/IL-10 ratios were significantly decreased Quercetin showed better efficacy in patients with higher inflammation markers |
| **Anti-inflammatory** (Askari et al. 2012) | Randomized, double-blind, placebo-controlled study | 60 healthy and physically active males whose mean age is $21.0 \pm 1.6$ years | 500 mg/day quercetin + 250 mg/day vitamin C or just 500 mg/day quercetin or only 250 mg/day vitamin C or placebo 8 weeks intervention | Plasma CRP levels were significantly decreased in groups receiving quercetin + vitamin C ($p = 0.098$) and quercetin alone ($p = 0.095$) IL-6 levels were significantly decreased in the group receiving quercetin + vitamin C supplementation ($p = 0.049$) E-selectin levels were not significantly decreased in any group |
| **Anti-inflammatory** (Brüll et al. 2017) | Randomized, double-blind, placebo-controlled, cross-over study | 68 overweight or obese individuals (34 males, 34 females), whose mean age is $47.4 \pm 10.5$ years with prehypertensive or stage 1 hypertensive Those with a history of T2DM, inflammatory and cardiovascular disease are not included in the study | 162 mg/day of quercetin or placebo 6 weeks intervention after 6 weeks wash-out period 6 weeks intervention | Quercetin supplementation did not significantly change serum leptin and adiponectin concentrations compared to placebo Serum C-reactive protein, plasma TNF-$\alpha$, glucose, insulin, HOMA-IR, liver and kidney biomarkers, serum electrolytes did not change significantly |

(*continued*)

Table 3. Continued.

| Biological Activity | Study type | Study sample | Study method | Results |
|---|---|---|---|---|
| **Anti-inflammatory** (Javadi et al. 2017) | Randomized, double-blind, placebo-controlled study | 50 nonsmoking women with rheumatoid arthritis, age range 19–70 years | 500 mg/day quercetin or placebo | EMS, morning pain, postoperative pain decreased significantly ($p < 0.05$) DAS-28 and HAQ scores decreased significantly Plasma hs-TNFα levels were significantly decreased ($p < 0.05$) ESR was not significantly decreased ($p > 0.05$) |
| **Anti-obesity** (Lee, McGeer, and McGeer 2016) | Randomized, double-blind, placebo-controlled parallel study | 72 overweight or obese individuals (11 males, 61 females) placebo group whose mean age is 42.6 ± 9.4 years and intervention group whose mean age is 43.9 ± 8.9 years | Onion peel extract containing 50 mg (100 mg/day) quercetin or placebo 2 times daily 12 weeks intervention | Significantly reduced body weight and body fat ($p = 0.02$) |
| **Adiponectin-mediated insulin resistance and hormonal profile improving** (Rezvan et al. 2017) | Randomized, double-blind, placebo-controlled parallel study | 84 women whose age is between 20 and 40 years and whose BMI are between 25 and 40 kg/m$^2$ with polycystic ovary syndrome (PCOS) | 500 mg (1 g/day) quercetin or placebo twice a day 12 weeks intervention | Adiponectin decreased by 5,56% compared to placebo ($p = 0.001$) Testosterone significantly decreased ($p < 0.001$) Luteinizing hormone significantly decreased ($p = 0.009$) HOMA-IR significantly decreased ($p < 0.001$) Insulin significantly decreased ($p < 0.001$) |
| **Lowering plasma uric acid** (Shi and Williamson 2016) | Randomized, double-blind, placebo-controlled, cross-over study | 22 healthy males whose mean age is 29.9 ± 12.9 years with plasma uric acid mean 339 ± 51 μmol/L | 500 mg/day quercetin or placebo 4 weeks intervention after 4 weeks wash-out period 4 weeks intervention | Plasma uric acid concentration decreased significantly by 26.5 μmol/L |

## Conclusions and recommendations

Quercetin is the most common form of flavonols in nature and is found in foods such as vegetables, fruits, and tea. Quercetin has many molecular and physiological effects in various organisms, including humans. Quercetin may have key roles in combating asthma, diabetes, obesity, cardiovascular, neurological and inflammatory diseases.

Although quercetin is known to be mutagenic since the 1970s, quercetin has been shown in the recent literature to protect against genotoxicants and thus to be antimutagenic (Bischoff 2008). Even with doses as low as 150 mg per day, the plasma quercetin concentration increases significantly and shows biological effects. Quercetin can be taken from functional foods in amounts of up to 10–125 mg per serving and from supplementation of up to 200–1000 mg/day (Lesjak et al. 2018). It is thought that a supplementation lasting more than 4 weeks is required to show the effects of quercetin. The most effective dose of quercetin is 60 mg/kg/day, and this value is equivalent to approximately 4 g/day. However, quercetin can show biological activities even at lower doses, such as 500 mg/day and 1000 mg/day (Rezvan et al. 2017). In most studies, a dose of 1000 mg/day quercetin is divided into two parts per day (Kelly 2011). However, it is also stated that long-term supplementation at a dosage of 1000 mg/day may cause side effects such as headache, nausea, and tingling in extremities (Serban et al., 2016). The recommended daily intake for the flavonoid family is between 250 and 400 mg (Peluso and Palmery 2015).

The European Food Safety Authority (EFSA) suggests that there is insufficient evidence to prove the biological activities of quercetin (EFSA 2011). Further studies are therefore needed to determine the appropriate dose and form of quercetin for its effects on diseases.

## Disclosure statement

The authors declare no conflict of interest.

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