

Overviews of Biological Importance of Quercetin: A Bioactive Flavonoid

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ABSTRACT

Antioxidants are substances that may protect cells from the damage caused by unstable molecules such as free radicals. Flavonoids are phenolic substances widely found in fruits and vegetables. The previous studies showed that the ingestion of flavonoids reduces the risk of cardiovascular diseases, metabolic disorders, and certain types of cancer. These effects are due to the physiological activity of flavonoids in the reduction of oxidative stress, inhibiting low-density lipoproteins oxidation and platelet aggregation, and acting as vasodilators in blood vessels. Free radicals are constantly generated resulting in extensive damage to tissues leading to various disease conditions such as cancer, Alzheimer's, renal diseases, cardiac abnormalities, etc., Medicinal plants with antioxidant properties play a vital functions in exhibiting beneficial effects and employed as an alternative source of medicine to mitigate the disease associated with oxidative stress. Flavonoids have existed over one billion years and possess wide spectrum of biological activities that might be able to influence processes which are dysregulated in a disease. Quercetin, a plant pigment is a potent antioxidant flavonoid and more specifically a flavonol, found mostly in onions, grapes, berries, cherries, broccoli, and citrus fruits. It is a versatile antioxidant known to possess protective abilities against tissue injury induced by various drug toxicities.

Key words: Antioxidant, bioflavonoid, free radical, quercetin

INTRODUCTION

Plants and plant parts are used for its scent, flavor, or therapeutic properties. There are a number of advantages associated with using plants and plant phytoconstituents as opposed to pharmaceutical products. The plants extracts and its phytoconstituents are proven for its biological activities such as antidiabetic, antihyperlipidemic, free-radical scavenging, and anti-inflammatory activities. Most of the time, free-radical are playing an important role in the development of metabolic disorders, and it affects the quality of life. Nature is a balanced system providing a balanced environment to have a good and healthy life. The search leading to compound with antioxidant activity has increased in the last few decades.^[1] The plant such as *Curcuma domestica valetton*, *Cuscuta reflexa*, *Daucus carota*, *Embllica officinalis*, *Foeniculum vulgare*, *Glycyrrhiza glabra*, *Mangifera indica*, *Momordica charantia*, *Ocimum sanctum*, *Psoralea corylifolia*, *Santalum album*, *Solanum nigrum*, *Swertia chirayita*, and *Withania somnifera* are known for its antioxidant activity and these plants showed significant biological activities against disease such as diabetes, hypercholesterolemia, and inflammatory disorders.^[2,3]

Quercetin is one of the important bioflavonoids present in more than twenty plants material [Table 1] and which is known for its

anti-inflammatory, antihypertensive, vasodilator effects, antiobesity, antihypercholesterolemic and antiatherosclerotic activities.^[4,5] Free-radical are one of the key factors for the development of the diseases such as hypertension, vascular disorders, and metabolic syndrome. Disease caused by free-radical and oxidant is summarized in Table 2. The objective of this review is to compile the biological and pharmacological importance of quercetin, a bioactive flavonoid.

Free-radical and Health

The production of physiological amount (low or moderate concentrations) of free-radical is essential to fight against an unfavorable environment. Indeed, phagocytes release free radicals to destroy pathogenic microbes. The free radicals such as nitric oxide (NO), superoxide anion, and related reactive oxygen species (ROS) play an important role as regulatory mediators in signaling processes. In higher organisms, NO and ROS regulate vascular tone, oxygen tension in control of ventilation, and erythropoietin production.^[6] Free radicals can be produced from enzymatic and nonenzymatic reactions. The respiratory chain, phagocytosis, prostaglandin synthesis, and the cytochrome P450 system are involved in enzymatic reactions generating free radicals and oxygen initiates the nonenzymatic reactions.^[7] ROS and reactive nitrogen species are generated from either endogenous such as immune cell activation, inflammation, mental stress, excessive exercise, ischemia, infection, cancer, aging, or exogenous sources such as air pollution, water pollution, cigarette smoke, alcohol, heavy metals, transition metals, pharmaceutical substances/pharmacological agents,

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Table 1: Source of quercetin

Plant name	Family	Geographical distribution	Traditional use
<i>Morus alba</i>	Moraceae	China	Diet
<i>Camellia sinensis</i>	Theaceae	Southeast Asia	Analgesic, antiviral, antispasmodic, antidiabetic, bronchodilator
<i>Allium fistulosum</i>	Amaryllidaceae	China	Spring onions as food ingredient
<i>Calamus scipionum</i>	Calamoideae	Brunei, Sumatra	Source of cane
<i>Moringa oleifera</i>	Moringa	Tropical, subtropical areas	Multipurpose medicinal use antihypertensive, antibacterial, antiinflammatory
<i>Centella asiatica</i>	Apiaceae	India	Wound healing
<i>Hypericum hircinum</i>	Clusiaceae	Britian	Antioxidant
<i>Hypericum perforatum</i>	Hypericaceae	Europe	Neurological effects, major depressive disorders
<i>Apium graveolens</i>	Apiaceae	Europe, North Africa, Siberia and the Caucasus	Anti-inflammatory, antibacterial, lowers blood pressure, and blood glucose
<i>Brassica oleracea</i> var. <i>italica</i> (Broccoli)	Brassicaceae	Europe and Asia	Edible plant. Prevents fluid retention and cancer
<i>Brassica oleracea</i> var. <i>sabellica</i> (Kale)	Brassicaceae	Europe	Neuropathy, reduces blood glucose, reduces risk of stroke
<i>Coriandrum sativum</i>	Apiaceae	Southern Europe, Northern Africa to Southwestern Asia	Reduces blood pressure, cholesterol, and dyspepsia
<i>Lactuca sativa</i>	Asteraceae	Mediterranea, Siberia	Iron deficiency anemia, osteoporosis
<i>Allium cepa</i> (red onions)	Liliaceae	Italy	Antioxidant, cardioprotective, immune stimulation
<i>Nasturtium officinale</i>	Brassicaceae	Globally distributed	Reduces risk of cancers
<i>Asparagus officinalis</i>	Asparagaceae	Egypt, European Union, China, Mexico	Antiulcer, antitussive, antineoplastic
<i>Capparis spinosa</i>	Capparaceae	Europe	Antiatherosclerotic agent, disinfectants, vermifuges
<i>Prunus domestica</i>	Rosaceae	Europe, China, the United states	Laxatives
<i>Malus domestica</i>	Rosaceae	North America	Decrease the risk of cardiovascular disease and cancer
<i>Solanum lycopersicum</i>	Solanaceae	Latin America	Food supplement and salads
<i>Vaccinium oxycoccus</i>	Ericaceae	North America	Urinary tract infections
<i>Prunus avium</i>	Rosaceae	Europe, Anatolia, Maghreb, and Western Asia	Astringent, diuretic, and tonic

Table 2: Disease caused by free-radical and oxidant

Human system	Disease
Central nervous system	Stroke Alzheimer's Depression
Cardiovascular system	Hypertension Atherosclerosis Cardiomyopathy
Respiratory system	Asthma
Excretory system	Renal failure
Skeletal system	Arthritis Rheumatism
Metabolic system	Diabetics
Multiorgans	Cancer Inflammation Aging

and radiation.^[7,8] Excess production of free-radical alters the cellular functions and induces chronic and degenerative diseases.

Antioxidants

Antioxidants inhibit the oxidation reaction of other molecules that can produce free radicals. These antioxidants are natural or synthetic supplement which helps to improve the free radicals induced pathological conditions. Vitamin A, Vitamin C, and Vitamin E are dietary antioxidants, commonly present in vegetables and fruits which help to inhibit the free radicals.^[9] Many plant flavonoids have rich antioxidant properties which are used for the treatment of inflammatory disorders.

Flavonoids as Antioxidant

flavonoids (the term is derived from the Latin word “flavus,” meaning yellow) are phenolic substances which exhibit biological activities including antiallergenic, antiviral, anti-inflammatory, and

vasodilating actions. Flavonoids are mostly found in fruits, vegetables, and certain beverages that have versatile beneficial antioxidant effects.^[10] Approximately, more than 3000 varieties of flavonoids have been identified, and it has aroused particular interest recently because of their potential beneficial effect on human health reported to have antiviral, anti-allergic, antiplatelet, anti-inflammatory, antitumor, antioxidant, and treatment of neurodegenerative disorders.^[11] Flavonoids are categorized into six classes according to the chemical structure into flavonols, flavones, flavanones, flavanols, isoflavones, and anthocyanidins.^[12]

Flavonoids can prevent injury caused by free radicals by scavenging of ROS, activation of antioxidant enzymes, metal chelating activity, reduction of α -tocopheryl radicals, inhibition of oxidases, and mitigation of oxidative stress caused by NO, increase in uric acid levels and increase in antioxidant properties of low-molecular antioxidants.^[13] Flavonoids are also act as prooxidants and promoting the oxidation of other compounds.

Quercetin

The name quercetin (3,3',4',5,7-pentahydroxyflavone) [Figure 1] comes from the Latin word “Quercetum” which means Oak Forest, belongs to the class called flavonols that cannot be produced in the human body.^[14] It is yellow color and is poorly soluble in hot water, quite soluble in alcohol and lipids and is insoluble in cold water. Quercetin is said to be one of the most widely used bioflavonoids for the treatment of metabolic and inflammatory disorders.

It is one of the most abundant dietary flavonoids found in fruits (mainly citrus), green leafy vegetables as well as many seeds, buckwheat, nuts, flowers, barks, broccoli, olive oil, apples, onions, green tea, red grapes, red wine, dark cherries, and berries such as blueberries and cranberries. The highest concentrations of flavonols were found in vegetables such as onions and broccoli, fruits such as apples, cherries, and berries, and drinks such as tea and red wine.

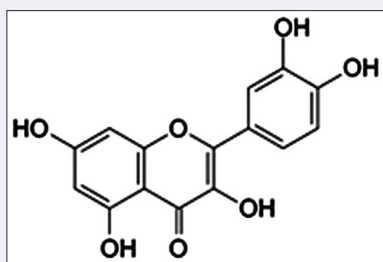


Figure 1: Structure of quercetin

Antioxidant Properties of Quercetin

Quercetin, a plant-derived aglycone form of flavonoid glycosides, has been used as a nutritional supplement and may be beneficial against a variety of diseases. Some of the beneficial effects include cardiovascular protection, anticancer, antitumor, anti-ulcer, anti-allergy, anti-viral, anti-inflammatory activity, anti-diabetic, gastroprotective effects, antihypertensive, immunomodulatory, and anti-infective.^[14]

Quercetin can also protect against environmental causes of free radicals such as smoking. Cigarette tar is a source of free radicals which has been found to damage erythrocyte membranes. It was also found that quercetin and its conjugate metabolites could protect erythrocytes from the membranous damage that is caused by smoking.^[15]

Pharmacological Importance of Quercetin

Anti-inflammatory

When parts of our human body exposed to harmful or irritating stimuli, there is a biological response called inflammation which plays a role in self-protection; the aim is to remove damaged cells, pathogens, or any harmful stimuli and begins the healing process. Inflammation does not necessarily mean infection. In most cases, infection is caused by a virus, bacteria, or fungus while inflammation process is the body's response trying to heal itself. One of the core most remarkable properties of quercetin is its ability to modulate inflammation. Quercetin inhibits inflammatory enzymes cyclooxygenase (COX) and lipoxygenase thereby decreasing inflammatory mediators such as prostaglandins and leukotrienes.^[16,17]

Nutrition scientists from Michigan State University explored the impact of dietary flavonoids such as quercetin in their general roles as systemic anti-inflammatory agents.^[18] Elevated C-reactive protein (CRP) levels are associated with numerous disease states such as obesity, heart disease, and lupus. It has been identified through this study that intake of certain foods can lower the levels of the inflammatory risk factor (CRP). In preclinical *in vitro* studies, quercetin showed a significant reduction in the levels of inflammatory mediators such as NO synthase, COX-2, and CRP in human hepatocyte-derived cell line.^[19] In rats, quercetin (80 mg equivalent dose) inhibited both acute and chronic inflammation and also showed significant antiarthritic activity against adjuvant-induced arthritis.^[20,21]

Askari *et al.* studied the effect of 2-month flavonoid quercetin (500 mg) supplementation in healthy male nonprofessional athletes with regular exercise, and the study results showed a significant decrease in the levels of CRP.^[22] However, in a pathological condition, quercetin did not show any significant alteration in the levels of CRP in women with rheumatoid arthritis (RA). The study was conducted for 8 weeks, and the RA patients were administered with quercetin 500 mg/day.^[23] In addition to that, quercetin having the ability to inhibit xanthine oxidase prevents

the accumulation of uric acid, which may help the subjects who are suffering from gout.^[24]

Cardiovascular disease prevention

Cardiovascular diseases have become a ubiquitous cause of morbidity and a leading contributor to mortality in most countries.^[25] It has been identified that diet plays a major role in the etiology of cardiovascular disease. Reported meta-analyses studies showed an inverse association between fruit and vegetable consumption and the occurrence of Stroke. Regular intake of fruit and vegetable consumption decreases the risk of stroke and coronary heart disease.^[26,27]

Plants are the richest source for bioflavonoids, minerals, vitamin, and many more which exhibits activity against metabolic and inflammatory disorders. Many flavonoids exert antihypertensive, anti-atherosclerotic, antiplatelet activity, and positive effects against endothelial dysfunction. Flavonoids existing over many years such as quercetin possess a wide spectrum of biological activities which may have a positive influence on cardiovascular diseases. In a study done by Greek cardiologists on thirty men who already had coronary heart disease (CHD) on the consumption of red grape polyphenol extract rich in quercetin caused an increase in flow-mediated dilation of major arteries, a potent indicator of improved endothelial health.^[28]

Quercetin inhibits the platelet aggregation and improves the health of the endothelium. In addition to that, it also protects against CHD and reduces the risk of mortality caused by low-density lipoprotein (LDL). It is known to exhibit important vasorelaxant properties on isolated arteries which helps to lower blood pressure and prevents the development of cardiac hypertrophy.^[29] Quercetin prevents damage to LDL cholesterol and studies revealed that people who consume high in flavonoid containing food supplements have lower cholesterol. In one of the study, it was found that people who consume quercetin and an alcohol-free red wine extract (which contains quercetin) inhibit LDL oxidation.^[30] Quercetin at 150 mg/day reduces systolic blood pressure and plasma oxidized LDL levels in overweight subjects who were at high risk of heart disease in the 6-week clinical trial.^[31]

Quercetin has a specific feature which inhibits fat accumulation in maturing human fat cells and simultaneously triggers apoptosis (programmed destruction) in existing fat cells.^[32,33] In addition, quercetin also blocks the uptake of glucose from the blood, blocks the fat cell production, and enhances fat cell necrosis.^[34,35] The dietary fiber intakes from cereals or from fruit were, independent of each other, inversely associated with the risk of CHD mortality. Ten grams of dietary fiber intake from cereals lowered CHD mortality risk by 29% and that of dietary fiber from fruit lowered CHD mortality risk by 35%.^[36,37]

Neurodegenerative disorders

Neurodegenerative diseases such as Alzheimer's and Parkinson's disease as well as neuronal injury associated with stroke are associated with neuroinflammatory processes in the central nervous system. There has been intense interest recently in the potential of flavonoids to modulate neuronal function and prevent against age-related neurodegeneration.^[38] Flavonoids exert multiple beneficial effects on the vascular system leading to changes in cerebrovascular blood flow which are capable of changing neuronal morphology causing neurogenesis and angiogenesis. In addition to that, it also has the potential to protect neurons against injury induced by neurotoxins. The consumption of flavonoids rich food limits neurodegeneration and to reverse age-dependent loss in cognitive performance.^[39]

Quercetin along with with ascorbic acid reduces the incidence of oxidative damage to human lymphocytes and neurovascular structures in the skin and inhibits damage to neurons. It is known to protect

brain cells against the oxidative stress, which damages tissue leading to Alzheimer and other neurological conditions.^[14] Flavonoids believed to play a crucial role to protect neuronal injury.^[39] Flavonoid exerts neuroprotective actions within the brain including a potential to protect neurons against injury induced by neurotoxins. It also has additional ability to suppress neuroinflammation and promotes memory, learning, and cognitive functions. Flavonoids are also found to exhibit protective features capable of preventing more serious degenerative diseases and many forms of cerebrovascular disease associated with dementia and stroke effecting predominantly elderly people. Flavonoid-rich plant or food supplement improves the cognition functions and protects vulnerable neurons by enhancing existing neuronal function or by stimulating neuronal regeneration.^[40]

Cancer and apoptosis

Epidemiological survey showed diet with more vegetables and fruits have protective effect against cancer. Quercetin has potential anticancer properties which include antiproliferative, growth factor suppression, and antioxidant.^[41]

Quercetin has potent anticarcinogenic properties and known to contribute as apoptosis inductor whereby it decreases the growth of tumor in and brain, liver, colon, and other tissues and inhibits the spread of malignant cells.^[42,43] Cruz-Correa *et al.* studied the combination treatment with curcumin and quercetin on familial adenomatous polyposis (FAP) patients. The patients were administered with curcumin 480 mg and quercetin 20 mg orally 3 times a day for mean of 6 months. At the end of the study, curcumin and quercetin reduced the number and size of ileal and rectal adenomas with minimal adverse effects.^[44]

Quercetin inhibits hexavalent chromium (Cr[VI]), a chemical carcinogen-induced cell transformation such as cell visibility loss, ROS generation and MicroRNA-21 (miR-21) elevation in human colon cancer Caco-2-cells.^[45,46] Both *in vitro* and *in vivo* cancer studies, quercetin was said to have a beneficial effect against prostate cancer.^[47]

Ulcer and gastritis

The studies have shown that quercetin inhibits gastric acid secretion and lipid peroxidation of gastric cells thereby serves as gastroprotective agents. It also inhibits *Helicobacter pylori* infection.^[14] Suzuki *et al.* studied the antioxidant and antiulcer effect of quercetin 50 and 100 mg/kg against ethanol-induced gastric mucosal injury model in rats and results suggest that quercetin has favorable anti-ulcer activity. The anti-ulcer activity of quercetin due to its free-radical scavenging properties or its increased gastric mucus production.^[48,49]

Antibacterial and antiviral activity

Quercetin is known to exhibit antibacterial effects against almost all strains of bacteria, particularly affecting gastrointestinal, respiratory, urinary, and dermal system. Their anti-infective and antireplicative ability possibly contributes to the antiviral characteristics. Viruses which commonly respond to flavonoids are adenovirus, herpes simplex virus, Japanese encephalitis virus, and respiratory syncytial virus.^[50-52]

Allergies, asthma, hay fever, and hives

Quercetin exerts anti-allergy effects by inhibiting the release of histamine from mast cells and other allergic substance thus acting as a natural antihistamine. Quercetin's ability to prevent allergic effects has tremendous implications for the treatment and prevention of asthma and bronchitis. The cell membranes of mast cells which have been known to be an immune gateway to the brain as well as the environment and emotional stress.^[53]

Pharmacokinetics

Ferry *et al.* studied the pharmacokinetic properties of intravenous injection of quercetin on cancer patients at the dose levels of 60–2000 mg/m². From the study, the determined quercetin safety dose is 945 mg/m². In toxic dose, quercetin caused emesis, hypertension, nephrotoxicity, and reduction in serum potassium. The distribution and elimination half-life of intravenous quercetin is 0.7–7.8 min, and 3.8–86 min, respectively. The clearance is 0.23–0.84 L/min/m², and volume of distribution is 3.7 L/m².^[54] Erlund *et al.* studied the pharmacokinetic properties of 8, 20, and 500 mg quercetin aglycone orally in healthy volunteers.^[55] Graefe *et al.* also studied pharmacokinetic properties of quercetin at the dose levels of 200 mg. C_{max} and T_{max} of quercetin are 2.3 ± 1.5 µg/mL and 0.7 ± 0.3 h, respectively.^[56]

Clinical Effect of Quercetin

The ability of quercetin is claimed to exert many beneficial effects on health, including protection against various diseases such as osteoporosis, lung cancer, and cardiovascular disease. The studies showed that there has been a reduction in the risk of cardiovascular disease in subjects, who had a high intake of flavonoids. Progressive disorder of the lung parenchyma and airways or also known as chronic obstructive pulmonary disease (COPD) which happens to be the third-leading cause of death in the USA. Therapies thus far for COPD, unfortunately, is said to be partially effective with possibilities of side effects. Increasing evidence indicates that quercetin supplementation may be beneficial in its treating this condition. In the previous preclinical study, it has been demonstrated a 4-fold increase in plasma quercetin levels significantly decreased lung inflammation and prevented disease progression. The effects of quercetin and its derivatives against inflammation, *in vivo* models, suggest that it is a potent anti-inflammatory agent. In *in vivo* study in mice has been reported to show a reduction in the expression of inflammatory genes using a quercetin-enriched diet.^[54] In a 12 weeks clinical trial, quercetin (1000 mg/day) reduced the upper respiratory tract infection rates in middle and older age subjects.^[57]

Quercetin has been reported to have features of neuroprotection in rat brain when used in combination with fish oil. Subsequently, it has also been reported to show beneficial effects against neurodegenerative diseases.^[56,58] Quercetin with its radical scavenging potential is said to be capable of preventing cancer which is induced by oxidative stress.^[58]

Quercetin supplementation (150 mg/day) reduced systolic blood pressure and plasma oxidized LDL concentrations in overweight subjects in 5 weeks double-blind trial.^[31] In another study, quercetin does not affect the fasting serum concentration of total cholesterol and reduced the levels of high-density lipoprotein cholesterol and apoA1 in apoε4 carrier and reduced blood pressure in obese carriers of the apo ε3/ε3 genotype.^[59] Brüll *et al.* studied the effect of quercetin 162 mg/day on overweight-to-obese patients with prehypertension and Stage I hypertension and concluded that quercetin supplementation lower ambulatory blood pressure in patients with hypertension.^[60] Quercetin 500 mg/day also reduced systolic blood pressure in women with Type 2 diabetes.^[61] Cruz-Correa *et al.* studied the effect of quercetin (20 mg) and curcumin (480 mg) on FAP in five patients and found to be effective against FAP.^[44] Combination of quercetin (20 mg) and curcumin (480 mg) showed benefaction effect in patient who dependent cadaveric kidney recipients.^[62]

In another clinical trial, quercetin 250 mg (twice daily for 4 weeks; per oral) did not show any significant effect on oral lichen planus.^[63]

CONCLUSION

Quercetin is a flavonoid with antioxidant properties. The ability of quercetin is claimed to exert many beneficial effects on health, including protection against various diseases such as osteoporosis, lung cancer, and cardiovascular disease. The studies showed that there has been a reduction in the risk of cardiovascular disease in subjects, who had a high intake of flavonoids. Flavonols is the most prominent flavonoids in fruits and vegetables and of these, quercetin is the most commonly consumed in the human diet.

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Conflicts of interest

There are no conflicts of interest.

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