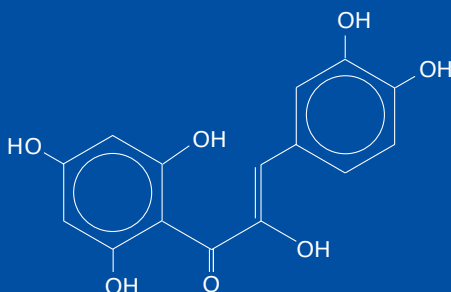


Quercetin



Quercetin Chalcone

Quercetin and Quercetin Chalcone

Quercetin

Introduction

Quercetin is widely distributed in the plant kingdom and is the most abundant of the flavonoid molecules. It is found in many often-consumed foods, including apple, onion, tea, berries, and brassica vegetables, as well as many seeds, nuts, flowers, barks, and leaves. It is also found in medicinal botanicals, including *Ginkgo biloba*, *Hypericum perforatum* (St. John's Wort), *Sambucus canadensis* (Elder), and many others, and is often a component of the medicinal activity of the plant. Quercetin appears to have many beneficial effects on human health, including cataract prevention, cardiovascular protection, as well as anti-cancer, anti-ulcer, anti-allergy, antiviral, and anti-inflammatory activity.

All flavonoids have the same basic chemical structure – a three-ringed molecule with hydroxyl (OH) groups attached. A multitude of other substitutions can occur, giving rise to more than 4,000 identified flavonoids. Flavonoids often occur in foods as a glycoside – with a sugar molecule (rhamnose, glucose, galactose, etc.) attached to the C ring. Quercetin is the aglycone (without the sugar molecule) of a number of other flavonoids, including rutin, quercetrin, isoquercetin, and hyperoside. These molecules have the same structure as quercetin except they have a specific sugar molecule in place of one of quercetin's hydroxyl groups on the C ring. This difference can dramatically change the activity of the molecule, as activity comparison studies have identified other flavonoids as often having similar effects as quercetin, but quercetin usually having the greatest activity.

Pharmacokinetics

Few human quercetin absorption studies exist. It appears only a small percentage of quercetin is absorbed after an oral dose; only two percent according to one study.¹ A study of quercetin absorption in ileostomy patients revealed absorption of 24 percent of the pure aglycone and 52 percent of quercetin glycosides from onions;² however, no intestinal permeability values were obtained in this group, and thus the results might not be reliable. Absorbed quercetin is transported to the liver bound to albumin,³ where some may be metabolized via hydroxylation, methylation, sulphation, or conjugation.⁴ Unabsorbed quercetin undergoes bacterial metabolism in the intestinal tract, where it is converted into phenolic acids.

Mechanisms of Action

Flavonoids, as a rule, are antioxidants, and a number of quercetin's effects appear to be due to its antioxidant activity. Quercetin scavenges oxygen radicals,^{5,6} inhibits xanthine oxidase,^{7,8} and inhibits lipid peroxidation *in vitro*.^{9,10} As another indicator of its antioxidant effects, quercetin inhibits oxidation of LDL cholesterol *in vitro*,^{11,12} probably by inhibiting LDL oxidation itself, by protecting vitamin E in LDL from being oxidized or by regenerating oxidized vitamin E.¹³ By itself, and paired with ascorbic acid, quercetin reduced the incidence of oxidative damage to human lymphocytes and neurovasculature structures in skin, and inhibited damage to neurons caused by experimental glutathione depletion.^{14,15}

Quercetin's anti-inflammatory activity appears to be due to its antioxidant capacity, its inhibitory effects on inflammation-producing enzymes (cyclooxygenase, lipoxigenase), and the subsequent inhibition of inflammatory mediators including leukotrienes and prostaglandins.¹⁶⁻¹⁸ Inhibition of histamine release by mast cells and basophils¹⁹⁻²¹ also contributes to quercetin's anti-inflammatory activity.

Aldose reductase, the enzyme that catalyzes the conversion of glucose to sorbitol, is especially important in the eye and plays a part in the formation of diabetic cataracts. Quercetin is a strong inhibitor of aldose reductase in the human lens.²²

Quercetin exerts antiviral activity against reverse transcriptase of HIV²³ and other retroviruses, and was shown to reduce the infectivity and cellular replication of herpes simplex virus type 1, polio-virus type 1, parainfluenza virus type 3, and respiratory syncytial virus (RSV).²⁴

Clinical Indications

Allergies

Quercetin's mast cell-stabilizing effects make it an obvious choice for use in preventing histamine release in allergy cases, similar to the use of the synthetic flavonoid analogue cromolyn sodium. Studies show quercetin's ability to inhibit histamine release stimulated by IgE-dependent ligands.²¹ Absorption of the pure aglycone quercetin is poor; however, much of quercetin's anti-allergy effects may be due to anti-inflammatory and anti-histaminic effects in the gut.

Cardiovascular Disease Prevention

Quercetin's cardiovascular effects center on its antioxidant and anti-inflammatory activity, and possibly by its ability to inhibit platelet aggregation.²⁵

The Zutphen Elderly Study investigated dietary flavonoid intake and risk of coronary heart disease.²⁶ The risk of heart disease mortality decreased significantly as flavonoid intake increased. Individuals in the upper 25 percent of flavonoid intake had a relative risk of 0.42 compared to the lowest 25 percent in this five-year follow-up study of men ages 65-84. The flavonoid-containing foods most commonly eaten in this study contained a high amount of quercetin (tea, onions, apples). In a cohort of the same study, dietary intake of flavonoids (mainly quercetin) was inversely associated with stroke incidence.²⁷ In a clinical trial of quercetin supplementation in healthy subjects, a marked increase in plasma quercetin levels was seen; however, no improvements were noted in selected risk factors for cardiovascular disease or thrombogenesis.²⁸

Inflammation

Quercetin is indicated in inflammatory conditions, as it inhibits formation of prostaglandins and leukotrienes, as well as histamine release. This may be especially helpful in asthma, as leukotriene B4 is a potent bronchoconstrictor. Patients suffering from chronic inflammatory conditions such as chronic prostatitis and interstitial cystitis show significant symptomatic improvement with oral quercetin supplementation (500 mg BID for one month).^{29,30}

Ulcer/Gastritis

Animal studies have shown quercetin to be protective of gastric ulceration caused by ethanol, probably by inhibiting lipid peroxidation of gastric cells^{31,32} and/or by inhibition of gastric acid secretion.³³ An interesting aspect of quercetin's anti-ulcer effect is that it has been shown to inhibit growth of *Helicobacter pylori* in a dose-dependent manner *in vitro*.³³

Cancer

Quercetin has been investigated in a number of animal models and human cancer cell lines, and has been found to have antiproliferative effects in numerous cancer cell types, including breast,³⁴⁻³⁷ leukemia,³⁸⁻⁴⁰ colon,⁴¹⁻⁴³ ovary,⁴⁴⁻⁴⁶ squamous cell,^{47,48} endometrial,³⁴ gastric,⁴⁹ and non-small-cell lung.^{50,51} It may also increase the effectiveness of chemotherapeutic agents.^{44,45} Phase one clinical trials show evidence of *in vivo* lymphocyte tyrosine kinase inhibition and anti-tumor activity of parenteral quercetin.⁵² More clinically oriented research needs to be done in this area to discover effective dosage ranges and protocols.

Diabetic Complications

Quercetin's antioxidant activity and aldose reductase-inhibiting properties make it a useful addition to diabetic nutritional supplementation, to prevent cataracts and neurovascular complications.

Side Effects and Toxicity

Early studies on quercetin reported that its administration to rats caused an increased incidence of urinary bladder tumors. Subsequent studies on rats, mice, and hamsters have been unable to confirm this finding.^{53,54}

Dosage

An oral dose of 400-500 mg three times per day is typically used in clinical practice. Since solubility is an issue in quercetin absorption,⁴ a new, water-soluble quercetin molecule, quercetin chalcone, might be used in smaller doses; typically 250 mg three times per day.

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