Quercetin

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Scientific Name

3,3',4'5,7-Penthydroxyflavone.

Background

Quercetin is a flavonol, belonging to the class of flavonoids, that occurs ubiquitously in foods of plant origin, such as red wine, onions, green tea, apples, berries, and *Brassica* vegetables (cabbage, broccoli, cauliflower, turnips). Quercetin is also found in *Gingko biloba*, St. John's wort, and American elder.

Also known as: Bioflavonoid, Bioflavonoid Complex, Bioflavonoid Concentrate, Bioflavonoid Extract, Bioflavonoïde, Bioflavonoïde de Citron, Bioflavonoïdes de Citron, Citrus Bioflavones, Citrus Bioflavonoid, Citrus Bioflavonoids, Citrus Flavones, Citrus Flavonoids, Complexe de Bioflavonoïde, Concentré de Bioflavonoïde, Extrait de Bioflavonoïde, Extrait de Bioflavonoïdes de Citron, Flavones de Citron, Flavonoid, Flavonoïde, Meletin, Mélétine, Quercetin Dihydrate, Quercetina, Quercétine, Sophretin, Sophrétine.

CAUTION: See separate listings for Chrysin, Diosmin, Hesperidin, Methoxylated Flavones, and Rutin.

History

People Use This For

Orally, quercetin is used for atherosclerosis; hypercholesterolemia; hypertension, coronary heart disease; vascular insufficiency; diabetes; cataracts; allergic rhinitis; peptic ulcer; schizophrenia; inflammation; asthma; gout; viral infections; chronic fatigue syndrome (CFS); preventing cancer; treating chronic, bacterial prostatitis, and improving function of kidney transplants. It is also used to increase exercise endurance and improve athletic performance.

Intravenously and intraperitoneally, quercetin is used for treating cancer.

Safety

POSSIBLY SAFE ...when used orally and appropriately short-term. Quercetin has been safely used in amounts up to 500 mg twice daily for up to 12 weeks (481, 1998, 1999, 16418, 16429, 16430, 16431). ...when used intravenously and appropriately. Quercetin has been safely used in amounts less than 722 mg (9564, 16418). Higher amounts may be nephrotoxic.

POSSIBLY UNSAFE ...when used intravenously in large amounts. Doses greater than 722 mg are reported to cause nephrotoxicity (9564, 16418).

PREGNANCY AND LACTATION: Insufficient reliable information available; avoid using.

Effectiveness

See detailed evidence summary

POSSIBLY EFFECTIVE

Prostatitis. Clinical research shows that taking quercetin orally reduces pain and improves quality of life, but does not seem to affect voiding dysfunction in patients with chronic, nonbacterial prostatitis (481).

INSUFFICIENT RELIABLE EVIDENCE to RATE

Cardiovascular disease. Population research shows that increasing dietary intake of quercetin from food sources such as tea, onions, and apples, is associated with a significantly reduced risk of heart disease-related mortality in elderly men (7726). However, preliminary clinical research shows that quercetin 1 gram daily for 28 days does not significantly improve platelet

aggregation, thromboxane B2 production, blood pressure, heart rate, or serum lipid levels compared to placebo in healthy people (1998).

Exercise performance. Preliminary clinical research shows that taking quercetin 500 mg twice daily for 3 weeks before, and continuing during an endurance run or cycling event does not attenuate muscle damage, soreness, or inflammation (16429, 16431).

Exercise-induced respiratory infections. Preliminary clinical research shows that taking quercetin 500 mg twice daily for 3 weeks before, and continuing during 3 days of prolonged, intense cycling reduces the incidence of upper respiratory infections in the 14 days following the heavy exercise (16430).

Hypercholesterolemia. Preliminary clinical research shows that short-term use of quercetin supplements for 1 month does not reduce low-density lipoprotein (LDL) cholesterol, total cholesterol, or increase high-density lipoprotein (HDL) cholesterol (1998, 1999).

Hypertension. Preliminary clinical research suggests that taking quercetin aglycone, 365 mg twice daily, produces a small, 5-7 mmHg, decrease in blood pressure in people with untreated, mild hypertension (16424). Whether this is clinical significant is not clear.

Kidney transplantation. Preliminary clinical research suggests that a combination of quercetin 20 mg and curcumin 480 mg taken once or twice daily, starting within 24 hours of kidney transplantation and continuing for one month, in combination with anti-rejection drugs, improves early function of the graft and reduces serum creatinine (16420).

Lung cancer. Epidemiologic studies suggest that a high dietary intake of quercetin and related flavonols might reduce the risk of lung cancer, especially in male smokers (16426, 16427).

Ovarian cancer. An epidemiologic study suggests that there is no association between quercetin and related flavonol intake and the risk of ovarian cancer risk (16428).

Pancreatic cancer. Epidemiologic studies suggest that a high dietary intake of quercetin and related flavonols might reduce the risk of pancreatic cancer, especially in male smokers (16426, 16427).

More evidence is needed to rate quercetin for these uses.

Dosing & Administration

- **Adult**

  Oral:

  - **General**: A dose of 500mg quercetin two times daily is a common dose found in the literature and popularly used for allergy, asthma, gout and insect bites. Bioavailability studies have investigated the effects of 100-300mg quercetin as quercetin-4'-O-beta-D-glucoside supplements (16419), onion supplements, quercetin-4'-O-glucoside supplements, quercetin-3-O-rutinoside supplements and buckwheat tea (37291). 1.85 MBq (50microCi) of (14)C-quercetin both orally (100mg, 330mcM) and intravenously has been given (iv; 0.3mg, 1mcM) to healthy volunteers (70313). Based on anecdotal evidence, quercetin should be taken 20 minutes before meals.
  - **Acute diarrhea**: In a randomized, double-blind, clinical study, capsules containing 500mg of a phytodrug (QG-5), standardized in its content of quercetin, were administered every eight hours during three days (70318).
  - **Cardiovascular disease**: Healthy men and women with cholesterol levels of 4.0-7.2mM/L consumed four capsules daily of a quercetin-containing supplement (1.0g quercetin daily) for 28 days (1998).
  - **Chronic prostatitis**: 500mg twice daily Prosta-Q® (containing quercetin, as well as papain and bromelain proposed to enhance absorption) has been used in clinical trials and was well tolerated for one month (481).
  - **Chronic venous insufficiency**: AS195 marketed as Antistax® Venenkapseln was used as a quercetin-rich agent in doses of 360 to 720mg taken once daily for 12 weeks, and was well tolerated in one study (70356). Two film-coated tablets have been taken once daily for 42 days (360mg daily) (70355). Different oral doses of Venoruton powder (0.5, 1, 2 or 4g), which contains quercetin as an ingredient, have been used (70354). Bioflavonoid quercetin 500mg twice daily for one month has also been studied (481).
  - **Hypertension**: 365mg quercetin aglycone tablets have been taken twice daily for 28 days (16424).
  - **Immune function (after intense exercise)**: A dose of 500mg powdered quercetin has been taken twice daily for three weeks by male cyclists (16429, 16430).
  - **Interstitial cystitis**: One capsule of Cysta-Q complex (containing quercetin, bromelain and papain; equivalent to 500mg of quercetin) has been taken twice a day for four weeks (70309). Six soft gels of CystoProtek® have been taken daily for six months with greater oral absorption of CystoProtek® (equivalent of 900mg quercetin) achieved by combining with kernel olive oil extract due to the high lipophilicity of the quercetin (42346).

  Parenteral (Intravenous/Intramuscular):

  - **General**: In a Phase I trial, administration of quercetin by short intravenous infusion at escalating doses (first dose level was 60mg/m^2) at three-week intervals demonstrated dose-limiting nephrotoxicity at the 10th dose level of

1,700mg/m^2, but no myelosuppression was observed. At the preceding dose level of 1,400mg/m^2, five patients were treated at three-week intervals, and another eight patients were treated on a once-weekly schedule; overall, two of ten evaluable patients had renal toxicity, one at grade 2 and one at grade 4 (9564). Based on pharmacokinetic study, Ferry et al. concluded that administration of quercetin by intravenous bolus appears safe at a dose of 1,400mg/m^2, given at three-week or weekly intervals.
    - **Cancer**: A dose of 400mg of QC12 (equivalent to 298mg of quercetin) orally on day one and intravenously in normal saline on day 14 have been studied in cancer patients (70310).

- **Children**
    - Insufficient available evidence.

- **Standardization & Formulation**
    - Most studies of quercetin have been based on calculating the quercetin content in flavonoid-rich foods, not on quercetin preparations as supplements, although a few studies reported supplement use (1998). Examples of quercetin content in foods and beverages that have been investigated in healthy human subjects include: 750mL red wine, 50g fried onions, or 375mL of black tea provided similar amounts of quercetin (14-16mg) (8976); a 150g onion (*Allium cepa*) cake was reported to contain 89.7mg quercetin and one 300mL cup of black tea contained 1.4mg quercetin (66763); a black currant and apple juice (750, 1,000, and 1,500mL) corresponded to an intake of 4.8, 6.4, and 9.6mg quercetin (31718); black tea solids (4g) were comparable to approximately 440mg (0.7mM) quercetin-3-rutinoside (8976); 1,600mL tea (type not specified) provided 49mg quercetin and 129g fried onions provided 13mg quercetin (36597); 220g onions provided 114mg quercetin (1999).

Adverse Effects

Report an Adverse Reaction to Quercetin

General: Quercetin, being a common food component, is generally safe and well tolerated at usual dietary intake. However it has been associated with headache, gastrointestinal effects, hematoma, and nephrotoxicity at higher-level intake. Intravenous administration of quercetin has resulted in flushing, sweating, dyspnea, nausea, and vomiting (9564). AS195 film-coated tablets (contains red vine leaf extract, rich in quercetin) were very well tolerated during one trial, as their global tolerability was assessed for most patients as good or satisfactory by both the patients and investigators (70356).

⊞ **Dermatologic**

⊞ **Gastrointestinal**

⊞ **Hematologic**

⊞ **Musculoskeletal**

⊞ **Neurologic/CNS**

⊞ **Pulmonary/Respiratory**

⊞ **Renal**

Toxicology

- **Gastrointestinal**: There is documentation of intravenous administration of quercetin associated with flushing, sweating, dyspnea, nausea, and vomiting (9564). When given at 1,700mg/m^2, quercetin caused emesis by the tenth dose; this effect did not respond to HT3 (serotonin) antagonists and dexamethasone (9564). AS195 (contains red vine leaf extract, rich in quercetin) film-coated tablets were very well tolerated during one trial, as their global tolerability was assessed for most patients as good or satisfactory by both the patients and investigators (70355).
- **Pulmonary/Respiratory**: Doses as high as 2,000mg/m^2 intravenous infusion of quercetin have been associated with severe dyspnea lasting as long as five minutes (9564).
- **Renal**: Quercetin has not been well-studied therapeutically intravenously. However, there are studies of the pharmacokinetics of intravenous administration. Single intravenous doses of 100mg/m^2 were well tolerated (70310). Higher doses (1,400mg/m^2/week) were associated with renal toxicity in 20% of subjects (70304). In a Phase I trial, administration of quercetin by short intravenous infusion at escalating doses (first dose level was 60mg/m^2) at three-week intervals demonstrated dose-limiting nephrotoxicity at the 10th dose level of 1,700mg/m^2, but no myelosuppression was observed. In contrast, administration of quercetin by intravenous bolus appears safe at a dose of 1,400mg/m^2, given at three-week or weekly intervals based on pharmacokinetic study (9564).
- **Carcinogenicity**: Concern had been expressed about the possible tumorigenic effect of quercetin. A study by the National

Toxicology Program found an increase in renal adenomas in male F344/N rats. This study has been criticized on the basis that the additional sections that revealed the adenomas in the active treatment arm of the study may not have been employed in the placebo arm. Quercetin is not currently classified as a carcinogen (70343, 70304).

Interactions with Drugs

ANTIHYPERTENSIVE DRUGS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Mild • Occurrence = Probable • Level of Evidence = **B**

Quercetin can modestly decrease blood pressure in people with mild hypertension. Theoretically, it might have additive blood pressure lowering effects when used with antihypertensive drugs and increase the risk of hypotension(16424); use with caution.

CYCLOSPORINE (Neoral, Sandimmune)

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **B**

A small study in healthy volunteers shows that pretreatment with quercetin increases plasma levels and prolongs the half-life of a single dose of cyclosporine (Neoral, Sandimmune), possibly due to inhibition of p-glycoprotein or cytochrome P450 3A4 (CYP3A4) metabolism of cyclosporin (16434).

CYTOCHROME P450 2C8 (CYP2C8) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

There is preliminary evidence that quercetin inhibits CYP2C8 in vitro (16432, 16435). Inhibition of paclitaxel (Taxol) metabolism via CYP2C8 has been reported in vitro (16436). However, a small study in humans found no effect of quercetin on rosiglitazone (Avandia), which is also a CYP2C8 substrate (16432). Other substrates of CYP2C8 include amiodarone (Cordarone), docetaxel (Taxotere), tretinoins, repaglinide (Prandin), verapamil (Calan, Isoptin, Verelan, etc), and others.

CYTOCHROME P450 2C9 (CYP2C9) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

There is preliminary evidence that quercetin inhibits CYP2C9 in vitro (15549, 16433). Theoretically, use of quercetin along with drugs metabolized by these enzymes might result in reduced drug elimination, increased drug serum levels, and increased effects. Some substrates of CYP2C9 include celecoxib (Celebrex), diclofenac (Voltaren), fluvastatin (Lescol), glipizide (Glucotrol), ibuprofen (Advil, Motrin), irbesartan (Avapro), losartan (Cozaar), phenytoin (Dilantin), piroxicam (Feldene), tamoxifen (Nolvadex), tolbutamide (Tolinase), torsemide (Demadex), and warfarin (Coumadin).

CYTOCHROME P450 2D6 (CYP2D6) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

There is preliminary evidence that quercetin inhibits CYP2D6 in vitro (15549, 16433). Theoretically, concurrent use of quercetin and drugs metabolized by these enzymes might result in reduced drug elimination, increased drug serum levels, and increased effects. Some drugs metabolized by CYP2D6 include amitriptyline (Elavil), codeine, flecainide (Tambocor), haloperidol (Haldol), imipramine (Tofranil), metoprolol (Lopressor, Toprol XL), ondansetron (Zofran), paroxetine (Paxil), risperidone (Risperdal), tramadol (Ultram), venlafaxine (Effexor), and others.

CYTOCHROME P450 3A4 (CYP3A4) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

There is preliminary evidence that quercetin inhibits CYP3A4 (15549, 16433, 16435). Theoretically, concurrent use of quercetin and drugs metabolized by these enzymes might result in reduced drug elimination, increased serum levels, and increased effects. A small study in healthy volunteers shows that pretreatment with quercetin increased plasma levels and prolonged the half-life of a single dose of cyclosporine (Neoral, Sandimmune) (16434).

Some other drugs metabolized by CYP3A4 include calcium channel blockers (diltiazem, nicardipine, verapamil), chemotherapeutic agents (etoposide, paclitaxel, vinblastine, vincristine, vindesine), antifungals (ketoconazole, itraconazole), glucocorticoids, alfentanil (Alfenta), fentanyl (Sublimaze), losartan (Cozaar), fluoxetine (Prozac), midazolam (Versed), omeprazole (Prilosec), lansoprazole (Prevacid), ondansetron (Zofran), propranolol (Inderal), fexofenadine (Allegra), amitriptyline (Elavil), amiodarone (Cordarone), citalopram (Celexa), sertraline (Zoloft), and numerous others.

P-GLYCOPROTEIN SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = **D**

There is preliminary evidence that quercetin inhibits the gastrointestinal P-glycoprotein efflux pump (16433, 16435). This inhibition might increase the bioavailability and serum levels of drugs transported by the pump, such as paclitaxel, diltiazem, cyclosporine, saquinavir, and digoxin (16434, 16435). A small study in healthy volunteers reported that pretreatment with

quercetin increased bioavailability and plasma levels after a single dose of cyclosporine (Neoral, Sandimmune) (16434). However, in another small study, several days of quercetin treatment did not affect the pharmacokinetics of saquinavir (Invirase) (16433).

Some other drugs transported by the pump include some chemotherapeutic agents (etoposide, vinblastine, vincristine, vindesine), antifungals (ketoconazole, itraconazole), protease inhibitors (amprenavir, indinavir, nelfinavir), H2 antagonists (cimetidine, ranitidine), verapamil, corticosteroids, erythromycin, fexofenadine (Allegra), loperamide (Imodium), quinidine, and others.

QUINOLONE ANTIBIOTICS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **B**

Theoretically, quercetin might competitively inhibit quinolone antibiotics by binding to the DNA gyrase site on bacteria (481). Quinolones include ciprofloxacin (Cipro), levofloxacin (Levaquin), ofloxacin (Floxin), moxifloxacin (Avelox), gatifloxacin (Tequin), and others.

WARFARIN (Coumadin)

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = **D**

Preliminary in vitro research shows that quercetin might increase serum levels of warfarin (Coumadin). Quercetin and warfarin have the same human serum albumin (HSA) binding site. Quercetin has stronger affinity for the HSA binding site and can displace warfarin, causing higher serum levels of warfarin (17213). Theoretically, quercetin might increase bleeding time and increase the risk of bleeding in patients who take warfarin.

Interactions with Herbs & Supplements

HERBS AND SUPPLEMENTS WITH HYPOTENSIVE EFFECTS: Quercetin can modestly decrease blood pressure in people with mild hypertension (16424). Theoretically, combining quercetin with other herbs and supplements with hypotensive effects might increase the risk of hypotension. Some of these herbs and supplements include andrographis, casein peptides, cat's claw, coenzyme Q-10, fish oil, L-arginine, lycium, stinging nettle, theanine, and others.

Interactions with Foods

None known.

Interactions with Lab Tests

None known.

Interactions with Diseases

KIDNEY DYSFUNCTION: Theoretically, intravenous quercetin may exacerbate kidney dysfunction (9563, 9564).

Mechanism of Action

- **Constituents**: Quercetin may affect membrane permeability and inhibit membrane-associated enzymes like ATPase, phospholipase A2 and prostaglandin cyclooxygenase. Quercetin stimulates Ca2+-ATPase activity at low concentration, while it inhibits it at high concentration. Quercetin also modifies eicosanoid biosynthesis, prevents platelet aggregation, promotes relaxation of cardiovascular smooth muscle, inhibits reverse transcriptase, promotes vasodilatation and platelet disaggregation (70345).
- **Adipogenesis**: Quercetin may affect adipocytes during specific stages of development, resulting in either inhibition of adipogenesis or induction of apoptosis (45451).
- **Allergic rhinitis**: After administration of a multi-ingredient nasal spray containing quercetin, all patients experienced a rapid and significant symptom relief of nasal symptoms, comparable to the effect of antihistamine and chromoglicate preparations, which several of the patients had used previously (70323). Quercetin may affect mast cell proliferation and secretory granule development (70322).
- **Anticancer properties**: Quercetin may interact synergistically with the effect of anti-cancer agents (70338, 70344, 70306). *In vitro* and animal studies have supported the hypothesis that quercetin may have anticarcinogenic and antiproliferative properties (67120). Quercetin reduced the growth of colon tumors in mice (63346), inhibited cancer cell growth *in vitro* (485, 70346), inhibited signal transduction targets, including tyrosine kinases, MEK/ERK, Nrf2/keap1, protein kinase C, and phosphatidyl inositol-3 kinase (9564, 70312, 70330), suppressed DNA synthesis, and blocked the progression of cell cycle from the G1 to the S phase (70336). Rodent studies have demonstrated that dietary administration of quercetin prevents chemically induced carcinogenesis, especially in the colon, whilst epidemiological studies have indicated that an intake of

quercetin may be associated with the prevention of lung cancer (70330). High quercetin intake was associated with decreased pancreatic cancer risk in male smokers not consuming supplemental alpha-tocopherol and/or beta-carotene (16427).

- Quercetin may be directly cytotoxic (70337). Quercetin reduced the increased signal transduction of PI kinase activity seen in malignant cells (70342). Quercetin has been shown to interact with some receptors, particularly an aryl hydrocarbon receptor, which is involved in the development of cancers induced by certain chemicals (70330). Quercetin binds to estrogen receptor type II and exerts a dose-dependent inhibition on cell growth in cell cultures. Type II estrogen receptors are found in normal cells and many a variety of carcinomas, including larynx, breast, melanoma, ovary, meninges, leukemia, and colorectum (70352, 70327). There is a negative association between urinary isoflavone excretion and breast cancer risk (70316). Hertog et al. conducted a cohort study examining the flavonoid intake from multiple dietary sources of 738 men with no history of cancer (age ranging from 65 to 84 years) and following up for five years (42909). No associations were found between the risks of any type of cancer when the highest and lowest quintiles of intake were compared. This study may have been underpowered to detect an association even if one was present. Quercetin also inhibits histamine release and induced accumulation of secretory granules in rat basophilic leukemia cells (70322). Quercetin down regulates the expression of mutant p53 protein, and inhibits the production of heat shock proteins and the expression of Ras proteins in rats (70304).
- **Antidepressant effects**: Quercetin is found in St. John's wort. Results from several studies showed that St. John's wort has a therapeutic effect in mild to moderate depression (203, 70301, 70341, 70340, 70339, 70340) and the strength of this effect depends on its hyperforin content (761). It is important to note that, although found in St. John's wort, quercetin alone was not studied in these experiments. Results from one study indicate that for the treatment of patients with a pre-existing conductive dysfunction or elderly patients, high-dose hypericum extract is safer with regard to cardiac function than tricyclic antidepressants (70348). Studies have also shown that hypericum may be an effective therapy for seasonal affective disorder (70349); quercetin is a component of St. John's wort, as is hypericum, and no conclusions were drawn regarding the effectiveness of quercetin as a potential therapy for SAD.
- **Anti inflammatory effects**: The flavonoid quercetin, found in the product CystoProtek®, has proposed anti-inflammatory properties and inhibits activation of mast cells (42346). Oral or intravesical administration of solutions containing quercetin reduced bladder inflammation in patients with interstitial cystitis (70335). Anti-inflammatory phytotherapy with quercetin has been used in the treatment of chronic prostatitis (70331). There is evidence that active aglycone may be generated from the quercetin glucuronide conjugates by enhanced beta-glucuronidase activity during inflammation (70330). In one study, however, daily oral supplementation of healthy humans with quercetin for two weeks did not affect inflammation (70332).
- **Antioxidant effects**: Quercetin is a dietary antioxidant flavonoid (31668). Quercetin, like other flavonoids, has a high propensity for electron transfers and is a free radical scavenger (70329). It may also be able to suppress the physiological reactions with heavy metals ions that are known to generate free radicals (35485). Phenolic hydroxyl groups at the B-ring and the 3-position may be responsible for its free radical-scavenging activity (70330). *In vitro* and *in vivo* studies have shown that quercetin prevents the oxidation of low-density lipoproteins (67086, 70305). Although red wine contains quercetin, bioavailability studies suggest that one glass of red wine provides fewer available flavonols than an onion; thus, the usefulness of this source of quercetin is questionable (8976). There is also evidence that dietary quercetin intake substantially affects oxidative DNA damage in leucocytes (66763). Contrary to animal-based studies, there was no quercetin-evoked reduction in markers of oxidative stress in three human studies (16424, 70328, 70332). Consumption of onions (a source of quercetin glucosides) failed to enhance the antioxidant activity of the plasma fraction against LDL oxidation; however, quercetin metabolites were detected in the human atherosclerotic aorta where they exhibited antioxidant activity when oxidative stress was loaded in the vascular system (66930).
- **Antiviral effects**: Quercetin appears to exert antiviral effects against reverse transcriptase of HIV and other retroviruses (54936). It may reduce the infectivity and cellular replication of the herpes simplex virus, polio virus, parainfluenza virus and the respiratory syncytial virus.
- **Cardiovascular effects**: Epidemiological studies report that quercetin supplementation is associated with a reduced risk of coronary heart disease/stroke and reduces blood pressure in hypertensive humans and rodents (16424). In a randomized, controlled trial performed in healthy men, quercetin augmented nitric oxide status and reduced endothelin-1 concentrations, indicating improved endothelial function (70334). In a cohort study, mortality from coronary heart disease ($p=0.15$), as well as incidence of myocardial infarction ($p=0.08$), were not significantly related to flavonoid intake (7726). However, quercetin consumption exhibited an inhibitory effect on developmentof aortic atherosclerotic lesions and on atherogenic modificationsof LDL injury by inhibiting lipoprotein oxidation or directly protecting cells from oxidized low-density lipoproteins (70325, 70350, 66758). The effects may be mediated by the metabolites of quercetin (9444). In human study, a fat-enriched breakfast with red wine supplementation (which contains quercetin) inhibited NF-kappaB activation in peripheral blood mononuclear cells, which may explain red wine's supposed reduction in cardiovascular mortality (70307). It is important to note, however, that red wine intake induced a certain increase in serum lipids, particularly VLDL, which did not increase after the fat ingestion alone. There is evidence that quercetin metabolites were detected in human atherosclerotic aorta exclusively where they incorporated into atherosclerotic regions and acted as complementary antioxidants when oxidative stress was applied to the vascular system (66930).
- **Gastrointestinal effects**: In a randomized, double-blind, clinical study performed to evaluate the safety and efficacy of an orally administered phytodrug (QG-5) developed from guava leaves, standardized in its content of quercetin, QG-5 decreased the duration of abdominal pain in patients with acute diarrheic disease (70318). Quercetin supplementation alone was not studied.
- **Glycemic response**: Consumption of a low-calorie cranberry juice containing quercetin-3-galactoside was associated with a favorable glycemic response and may be beneficial for persons with impaired glucose tolerance (46442). Normal-calorie cranberry juice resulted in significantly higher blood glucose concentrations 30 minutes postprandially, although the differences were no longer significant after 180 minutes. Plasma insulin of normal-calorie cranberry juice was significantly higher 60 minutes postprandially, but not significantly different 120 minutes postprandially.
- **Hepatic effects**: Quercetin inhibits xanthine oxidase and the proliferation of hepatic stellate cells (70315, 70314).
- **Lipid peroxidation properties**: Oxidative damage to lipids *in vivo* may be involved in the development of atherosclerosis and

cancer. Onions and black tea are foods rich in flavonoids, predominantly the flavonoid quercetin, which is a potent *in vitro* inhibitor of membrane lipid peroxidation and LDL oxidation (66773). Alcohol-free red wine extract and one of its components, quercetin, can inhibit LDL oxidation after *in vivo* supplementation; such "inhibition" is unrelated to changes in antioxidant vitamin and carotenoid concentrations (70305). Flavonoid consumption in onions and tea had no significant effect on plasma F2-isoprostane concentrations and MDA-LDL autoantibody titer in this study and thus does not seem to inhibit lipid peroxidation in humans (66773). In two human studies, quercetin supplementation (either alone or as onions) did not affect levels of oxidized LDL (70332, 66930).

- **Platelet aggregating properties**: *In vitro* studies have suggested that flavonoids like quercetin have antiaggregatory effects, yet one *in vivo* study was unable to verify this, hypothetically due to the inability to establish therapeutic levels *in vivo*. Effects of dietary flavonols and flavones on cardiovascular risk are possibly not mediated by hemostatic variables (1999). In bioavailability studies, plasma quercetin concentrations peaked at 4.66mcM (± 0.77) and 9.72mcM (± 1.38) 30 min after ingestion of 150mg and 300mg doses of quercetin-4'-O-beta-D-glucoside, respectively, demonstrating that quercetin was bioavailable, with plasma concentrations attained in the range known to affect platelet function *in vitro*. Platelet aggregation was inhibited 30 and 120 min after ingestion of both doses of quercetin-4'-O-beta-D-glucoside. Correspondingly, collagen-stimulated tyrosine phosphorylation of total platelet proteins was inhibited. This was accompanied by reduced tyrosine phosphorylation of the tyrosine kinase Syk and phospholipase Cgamma2, components of the platelet glycoprotein VI collagen receptor signaling pathway (16419).
- **Rheumatoid arthritis**: Rheumatoid patients subjectively benefited from a vegan diet rich in antioxidants, lactobacilli and fiber, resulting in a much higher intake of polyphenolic compounds like quercetin, and this was also seen in objective measures (70308).
- **Schizophrenia**: A complex of antioxidants, including quercetin, as well as enterosorbent, had a positive effect on the clinical course of the condition in 63.2% of group I patients who managed, among other therapeutic benefits, to achieve a stable remission. They have also demonstrated a concomitant improvement or normalization of indices for lipid peroxidation (70357).

Pharmacokinetics

- **Absorption**: Quercetin is absorbed in sufficient concentration from a diet containing 10.9 to 51.6mg to cause an overall increase in plasma antioxidant capacity (487, 7726, 67086, 9443). It is hydrolyzed in the small intestine and absorbed as an aglycone. Absorbed quercetin is conjugated in the liver and secreted in bile into the intestinal lumen (70302). Quercetin does not appear to be well absorbed by the gut or gastrointestinal tract (70317, 67111). Quercetin chalcone (a modified version of quercetin) appears be better absorbed. Quercetin was administered at 4g oral and 100mg intravenous doses to six volunteers, in order to examine pharmacokinetics (70317). Quercetin glucoside is actively absorbed from the small intestine, whereas quercetin rutinoside is absorbed from the colon after deglycosylation (67111). The site of absorption seems to be different for quercetin-4'-O-glucoside and quercetin-3-O-rutinoside (37291). In pharmacokinetic study, peak concentration of quercetin (C_{max}) in plasma was 20 times higher and was reached (T_{max}) more than ten times faster after intake of the glucoside (C_{max} = 3.5±0.6mcM mean ± SE); T_{max} < 0.5 h) than after the rutinoside (C_{max} = 0.18±0.04mcM; T_{max} = 6.0±1.2 h). The bioavailability of the rutinoside was only 20% of that of the glucoside. Absorption of other food components might also be enhanced by attachment of a glucose group (70353). In another study, absorption of quercetin, defined as oral intake minus ileostomy excretion and corrected for 14% degradation within the ileostomy bag, was 52 ± 15% for quercetin glucosides from onions, 17 ± 15% for quercetin rutinoside, and 24 ± 9% for quercetin aglycone. Mean excretion of quercetin or its conjugates in urine was 0.5% of the amount absorbed; quercetin excretion in urine was negatively correlated with excretion in ileostomy effluent (r = -0.78, N=27). The authors conclude that humans absorb appreciable amounts of quercetin and that absorption is enhanced by conjugation with glucose (67086).
- Following oral administration of QC12, study authors were unable to detect QC12 or quercetin in plasma. After intravenous administration, we detected peak plasma concentrations of QC12 of 108.7 ± 41.67mcM. A two-compartment model with mean t(1/2)alpha of 0.31 ± 0.27 hours and mean t(1/2)beta of 0.86 ± 0.78 hours best described the concentration-time curves for QC12. The mean AUC was 44.54 ± 13.0 mcM.hour and mean volume of distribution (Vd) of 10.0 ± 6.2L. Quercetin was found in all patients following intravenous infusion of QC12, with peak levels of quercetin 19.9 ± 11.8mcM. The relative bioavailability of quercetin was estimated to be 20%-25% quercetin released from QC12. QC12 is not orally bioavailable. Authors conclude that this water-soluble pro-drug warrants further clinical investigation; starting with a formal Phase I, IV, dose-escalation study (70310).
- Tea providing 49mg quercetin and 27mg kampferol daily and onions providing 13mg quercetin and no kampferol were studied. Flavonols from both foods were clearly absorbed. However, the excretion of unmodified quercetin was 0.5% of intake after tea and 1.1% after onions. Thus, the absorption of quercetin from tea was half of that from onions (36597).
- **Distribution**: Dietary flavonols appear in plasma and urine as potential biomarkers in concentrations related quantitatively to intake (66751, 16419, 70319). Quercetin is commonly present as a glycoside and is converted to glucuronide/sulfate conjugates during intestinal absorption and only conjugated metabolites are therefore found in circulating blood (70330). In plasma, it is extensively protein-bound (9442, 70351, 487). Following 220g of onions daily providing 114mg quercetin daily, mean plasma quercetin concentrations increased (1999). In another study, the plasma quercetin concentration after the consumption of wine was lower than that after onions ($p<0.05$) and not different from that after tea (8976). Other authors reported that quercetin metabolites from onion circulating in the human blood stream were mostly localized in plasma albumin fraction, but not LDL fraction (66930). Onion consumption failed to enhance the antioxidant activity of plasma fraction against LDL oxidation, indicating that the level of quercetin metabolites bound to albumin is insufficient to exert the antioxidative effect *in vivo*. Quercetin metabolites accumulated in the human atherosclerotic aorta exclusively, implying that quercetin metabolites are incorporated into the atherosclerotic region and act as complementary antioxidants, when oxidative stress is loaded in the vascular system. It is likely that plasma albumin is a carrier for translocation of quercetin metabolites to vascular target.
- Following intravenous administration, half-lives were determined to be 8.8 ± 1.2 minutes for the alpha phase and 2.4 ± 0.2

hours for the beta phase. Protein binding was greater than 98%; the apparent volume of distribution was small at 0.34 ± 0.03 1/kg in one study. Of the intravenous dose 7.4 ± 1.2% was excreted in urine as a conjugated metabolite, and 0.65 ± 0.1% was excreted unchanged. After oral administration, no measurable plasma concentrations could be detected, nor was quercetin found in urine, either unchanged or in a metabolized form. These results exclude absorption of more than 1% of drug. Recovery in feces after the oral dose was 53 ± 5%, which suggests extensive degradation, probably by microorganisms, in the gut. Quercetin pharmacokinetics were described by a first-order two-compartment model with a median t(1/2)alpha of six minutes and median t(1/2)beta of 43 minutes. The median estimated clearance was 0.28 liter/min/m^2, and median volume of distribution at steady state was 3.7L/m^2 (9564).

- **Metabolism**: Carbon dioxide is the major metabolite of quercetin in humans (70313). Different food production methods may result in differences in the content of secondary metabolites, such as polyphenolic compounds (70320). Quercetin exists as its glucoside form in onion and is metabolized into several glucuronides and/or sulfate conjugates with or without methylation during its intestinal absorption (66930).
- **Elimination**: Quercetin is eliminated in the urine (36597, 67086, 37291, 8976, 70321), and urine excretion is enhanced following increased intake of mixed fruits and vegetables containing quercetin (70324).
- **Bioavailability**: Berries are believed to be a good source of bioavailable quercetin (black currants, lingonberries and bilberries) (17632). It is noted in one review that quercetin bioavailability has been underestimated in the past and can be improved by food matrix components or particular delivery forms (70333). Conversion of quercetin glycosides into glucosides is a possible strategy to enhance bioavailability of quercetin from foods (70303). Quercetin may be more bioavailable in women than in men (70311). Bioavailability of Venoruton derivatives (mono-3'-HQ and mono-4'-HQ) tend to be proportional to the dose (70354). Additional bioavailability studies have been published (70347).
- The overall kinetic behavior of quercetin differed remarkably after ingestion of quercetin aglycone or rutin in one study. The mean area under the plasma concentration-time curve from 0 hours to 32 hours [AUC(0-32)] and maximum plasma concentration (C_{max}) values of the two treatments were similar. However, time to reach C_{max} (t_{max}) was significantly shorter after the quercetin aglycone treatment than after the rutin treatment (1.9, 2.7 and 4.8 versus 6.5, 7.4 and 7.5 hours, for doses one, two and three, respectively). Also, the absorption of quercetin from quercetin aglycone was predictable and inter-individual variation was small. In contrast, after ingestion of rutin, inter-individual variations in AUC (0-32) and C_{max} values were considerable and seemed to be associated with gender and use of oral contraceptives. Quercetin and rutin were found in plasma as glucuronides and/or sulfates of quercetin and as unconjugated quercetin aglycone, but no rutin was detected. In clinical trials, studying the effects of quercetin from rutin, bioavailability must be taken into consideration and plasma quercetin concentrations monitored. Whether results apply to other glycosidic drugs as well, especially other rutosides, should be investigated (9442).
- A previous study in ileostomy patients indicated that dietary glucosides of the flavonoid quercetin are hydrolyzed efficiently in the intestinal lumen, followed by absorption of a large fraction of the quercetin aglycone. To determine the fate of quercetin, researchers administered 1.85MBq (50 microCi) of (14)C-quercetin both orally (100mg, 330mcM) and intravenously (intravenous; 0.3mg, 1mcM) to healthy volunteers. Serial plasma samples, urines and stools were collected for 72 hours. Total radioactivity was determined by liquid scintillation spectrometry directly in plasma and urine, and after repeated methanol extraction of stool homogenate samples. The oral absorption, based on total radioactivity, was surprisingly high, ranging from 36.4 to 53.0%. The biological half-life was very long, ranging from 20 to 72 hours. The urinary recovery of total radioactivity ranged from 18.4 to 26.8% after the intravenous dose and from 3.3 to 5.7% after the oral dose. The corresponding fecal recoveries were only 1.5-5.0% and 1.6-4.6%, respectively. Thus, the total recovery of the (14)C-quercetin doses, in particular after oral administration, was very low. In search for the unaccounted for fraction of the (14)C-quercetin dose, they performed (14)CO(2) recovery studies in three volunteers (three intravenous and three oral doses). At timed intervals, (14)CO(2) in expired air was trapped in hyamine hydroxide/thymolphthalein and analyzed for radioactivity. As much as 23.0-81.1% of the quercetin dose was recovered as (14)CO(2) in the expired air from these volunteers, after both oral and intravenous doses. The disposition of quercetin in humans is thus highly complex, requiring further studies (70313).
- Concentration and time curves were determined for hypericin, pseudohypericin, hyperforin, the flavonoid aglycone quercetin, and its methylated form isorhamnetin for 48 h after single dosing and for 24 h on day 14 at the end of two weeks of continuous daily dosing. After single-dose intake, the key pharmacokinetic parameters were determined as follows: Quercetin and isohamnetin showed two peaks of maximum plasma concentration separated by about 4 h. Quercetin: AUC(0-infinity) = 318,7 h x ng/mL, Cmax (1) = 47.7ng/mL, t_{max} (1) = 1.17 hours, C_{max} (2) = 43.8ng/mL, t_{max} (2) = 5.47 hours, $t_{1/2}$ = 4.16 hours. The trial preparation was well tolerated (70326).
- When provided along with dietary sources, quercetin aglycone is more bioavailable than its glucosides in humans (66935). The lipophilic character of quercetin suggests that it can cross enterocyte membranes via simple diffusion. In a randomized crossover study, nine volunteers took a single dose of either shallot flesh (99.2% quercetin glucosides and 0.8% quercetin aglycone) or dry shallot skin (83.3% quercetin aglycone and 16.7% quercetin glucosides), providing 1.4mg quercetin per kg of body weight. The maximum plasma quercetin concentration of 1.02 ± 0.13micromol/L was reached at 2.33 ± 0.50 hours after shallot flesh consumption compared with 3.95 ± 0.62micromol/L at 2.78 ± 0.15 hours after dry skin consumption. The area under the concentration-time curve after dry skin consumption was 47.23 ± 7.53micromol x h(-1) x L(-1) and was significantly higher than that after shallot flesh intake (22.23 ± 2.32micromol x h(-1) x L(-1)). In a different study, the areas under the plasma concentration-time curves ranged from 76.1mumol.min.L(-1) to 305.8mumol.min.L(-1) (50mg and 150mg dosages, respectively) (70332). Median maximum plasma concentrations of quercetin (431nmol/L) were observed 360 minutes after intake of 150mg quercetin (70332).

Classifications

Cytochrome P450 2D6 (CYP2D6) Inhibitors

Evidence Table / Discussion

See detailed Evidence Summary

References

See Monograph References

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