

# Quercetin

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## Description and Chemical Composition

Quercetin is categorized as a flavonol, one of the six subclasses of flavonoid compounds (Table 1). Flavonoids are a family of plant compounds that share a similar flavone backbone (a three-ringed molecule with hydroxyl [OH] groups attached). A multitude of other substitutions can occur, giving rise to the subclasses of flavonoids and the different compounds found within these subclasses. Flavonoids also occur as either glycosides (with attached sugars [glycosyl groups]) or as aglycones (without attached sugars).<sup>1</sup>

Flavonols are present in a wide variety of fruits and vegetables. In Western populations, estimated daily intake of flavonols is in the range of 20-50 mg/day.<sup>2</sup> Most of the dietary intake is as flavonol glycosides of quercetin, kaempferol, and myricetin rather than their aglycone forms (Table 2). Of this, about 13.82 mg/day is in the form of quercetin-type flavonols.<sup>2</sup>

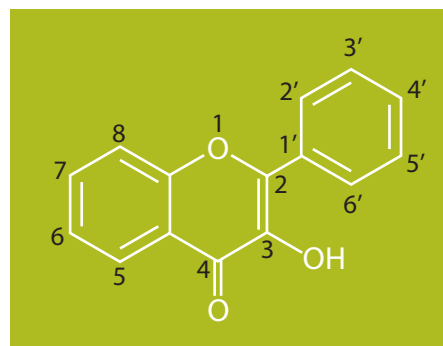
The variety of dietary flavonols is created by the differential placement of phenolic-OH groups and attached sugars. All flavonols, including quercetin, have in common a 3-hydroxyflavone backbone (Figure 1). The determination of whether a flavonol is considered to be of the quercetin type as opposed to a kaempferol or myricetin type, for example, is based on the location of phenolic-OH groups. Figure 1 shows the possible attachment positions for hydroxyl and glycosyl groups.

The International Union of Pure and Applied Chemistry (IUPAC) nomenclature for quercetin is 3,3',4',5,7-pentahydroxyflavanone (or its synonym 3,3',4',5,7-pentahydroxy-2-phenylchromen-4-one). This means that quercetin has an OH group attached at positions 3,

5, 7, 3', and 4' (Figure 2). The difference between quercetin and kaempferol is that the latter lacks the OH group at position 3'. The difference between quercetin and myricetin is that the latter has an extra OH group at position 5'.

By definition quercetin is an aglycone, lacking an attached sugar. It is a brilliant citron yellow color and is entirely insoluble in cold water, poorly soluble in hot water, but quite soluble in alcohol

**Figure 1. 3-Hydroxyflavone Backbone with Locations Numbered for Possible Attachment of Hydroxyl (OH) and Glycosyl Groups**



**Table 1. Flavonoid Subclasses and Examples**

| Subclass                          | Selected Examples                |
|-----------------------------------|----------------------------------|
| Flavones                          | Apigenin, Chrysin, Luteolin      |
| Flavonols                         | Kaempferol, Myricetin, Quercetin |
| Flavanones                        | Hesperidin, Naringenin           |
| Flavanols (also called catechins) | Epicatechin, Gallocatechin       |
| Anthocyanidins                    | Cyanidin, Malvidin, Pelargonidin |
| Isoflavones                       | Genistein, Daidzein              |

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**Table 2. Naturally Occurring Flavonol Glycosides and their Aglycones**

| Flavonol Glycoside | Aglycone Form |
|--------------------|---------------|
| Astragalin         | Kaempferol    |
| Azalein            | Azaleatin     |
| Hyperoside         | Quercetin     |
| Isoquercitin       | Quercetin     |
| Kaempferitrin      | Kaempferol    |
| Myricitrin         | Myricetin     |
| Quercitrin         | Quercetin     |
| Robinin            | Kaempferol    |
| Rutin              | Quercetin     |
| Spiraeoside        | Quercetin     |
| Xanthorhamnin      | Rhamnetin     |
| Amurensin          | Kaempferol    |
| Icariin            | Kaempferide   |
| Troxeutin          | Quercetin     |

and lipids. A quercetin glycoside is formed by attaching a glycosyl group (a sugar such as glucose, rhamnose, or rutinose) as a replacement for one of the OH groups (commonly at position 3). The attached glycosyl group can change the solubility, absorption, and *in vivo* effects. As a general rule of thumb, the presence of a glycosyl group (quercetin glycoside) results in increased water solubility compared to quercetin aglycone.<sup>1,3</sup>

The feature that distinguishes one quercetin glycoside from another is the type of glycosyl group

attached. Hyperoside (found in St. John’s wort) has a 3-O-galactoside group (an oxygen bonded to a galactoside group) at position 3 rather than an OH group. Isoquercitin (found in mangoes) has a 3-O-glucoside. Rutin (found in high amounts in buckwheat, citrus fruits, and *Ruta graveolens*) has an attached rutinose sugar at position 4. All of these are glycoside forms of quercetin (quercetin glycosides).

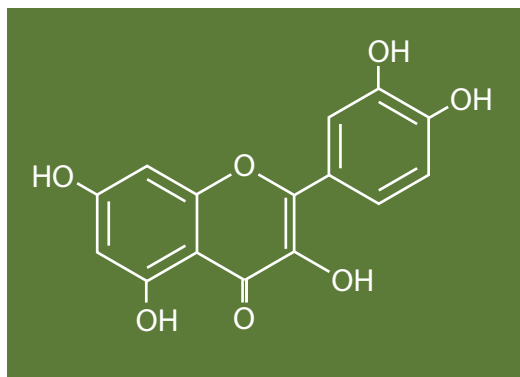
Technically, the term quercetin should be used to describe the aglycone only; however, this is not always the case in research or in the supplement industry, where quercetin is occasionally used generically to refer to quercetin-type molecules, including its glycosides.

### Dietary Sources

Quercetin-type flavonols (primarily as quercetin glycosides), the most abundant of the flavonoid molecules, are widely distributed in the plant kingdom. They are found in a variety of foods including apples, berries, Brassica vegetables, capers, grapes, onions, shallots, tea, and tomatoes, as well as many seeds, nuts, flowers, barks, and leaves. Quercetin is also found in medicinal botanicals, including *Ginkgo biloba*, *Hypericum perforatum* (St. John’s wort), and *Sambucus canadensis* (elder).<sup>4-6</sup>

Most of the dietary intake of quercetin-type flavonols is as quercetin glycosides. The most common are quercetin linked with one or two glucose molecules (quercetin glucosides) and quercetin linked with rutinose (quercetin rutinoside); tea (*Camellia sinensis*) is an example of the latter. It is considered a rich food source of quercetin in a generic sense;<sup>4</sup> however, almost all of this is actually quercetin rutinoside (rutin) and not quercetin aglycone. The aglycone form of quercetin is found in much lesser amounts in the diet. Two of the better food sources are onions and shallots, but depending upon which part of these foods is eaten, widely different amounts and forms of quercetin-type flavonols are ingested. For example, quercetin in shallot flesh is about 99.2-percent quercetin glucosides and 0.8-percent quercetin aglycone. In dry shallot skin the composition is almost the opposite – 83.3-percent quercetin aglycone and 16.7-percent quercetin glucosides.<sup>7</sup> Similar differences exist with onions. The flesh of onions contains mostly quercetin glucosides, with only trace amounts of quercetin aglycone. Like shallots, the skin and outermost layers of an onion have much more quercetin aglycone.<sup>8-10</sup>

**Figure 2. Quercetin Chemical Composition**



Growing conditions might significantly influence the amount of quercetin in food, with evidence indicating that organically grown tomatoes have significantly higher quercetin aglycone content than conventionally produced tomatoes.<sup>11</sup>

### Bioavailability and Pharmacokinetics

In a review of published information, Scholz and Williamson concluded the factors that most influence quercetin absorption are the “nature of the attached sugar, and secondly, the solubility as modified by ethanol, fat, and emulsifiers.”<sup>12</sup> This section of the monograph will discuss the basis for their conclusions, as well as other quercetin-related bioavailability and pharmacokinetic research.

The earliest human quercetin research suggested very poor oral bioavailability after a single oral dose (~2%).<sup>13</sup> Animal and human research conducted since this time has produced a different and more comprehensive understanding of quercetin’s bioavailability and pharmacokinetics.

Quercetin glycosides are found in far greater amounts in the diet than is quercetin aglycone. When quercetin glycosides are ingested, glycosyl groups can be released during chewing, digestion, and absorption. As an example, enzymes in the mouth and intestines can hydrolyze quercetin glycosides to aglycones. Evidence also supports a contribution of mouth and gut bacteria to this enzymatic hydrolysis.<sup>14</sup> The net result, assuming the food has high quantities of quercetin glycosides (e.g., onion or shallot flesh), is greater *in vivo* exposure to quercetin aglycone than would be expected based purely on its actual content in the food.

In rats, quercetin aglycone is partly absorbed from the stomach; whereas, quercetin glycosides – isoquercitrin and rutin – are not.<sup>15</sup> Quercetin is considered lipophilic, so presumably should be able to cross enterocyte membranes via simple diffusion. In theory, this should result in better absorption than glycoside forms that reach the intestines intact.<sup>8</sup> Several human studies have been conducted to compare the bioavailability of quercetin aglycone and glycosides, as well as the bioavailability of different types of quercetin glycosides. A study of absorption in ileostomy patients revealed absorption of 24 percent of the pure aglycone and 52 percent of quercetin glycosides from onions.<sup>16</sup> In a follow-up study, ileostomy patients were fed an onion meal high in quercetin glucosides with only trace amounts of quercetin aglycone. No quercetin glucosides were detected in the ileostomy fluid. In contrast, the amounts of the aglycone

were substantial and corresponded to 19.5-35.2 percent of total ingested quercetin glucosides, which implied absorption of 64.5-80.7 percent.<sup>12</sup> These findings suggest that quercetin glucosides are efficiently hydrolyzed in the small intestine by beta-glucosidases to the aglycone form, much of which is then absorbed.

The aglycone form of quercetin appears to be better absorbed than the glycoside form when humans consume grape fruit juice.<sup>17</sup> The same is true when the effects of ingesting shallot flesh (almost entirely quercetin glucosides) and dry shallot skin (mostly quercetin aglycone) were compared in nine volunteers. Maximum plasma quercetin concentrations were almost four-fold greater after shallot dry skin consumption.<sup>9</sup> In another human study comparing quercetin aglycone and quercetin rutinoid, while the mean area under the plasma concentration-time curve and maximum plasma concentration of the two were similar, the time to reach maximum plasma concentration was significantly shorter after the quercetin aglycone treatment; the absorption of quercetin from the aglycone was also more predictable with a small interindividual variation.<sup>18</sup> These studies suggest that, in humans, quercetin aglycone might be more bioavailable, or least more *reliably* bioavailable, than its glycosides.

Quercetin glycosides might be differently absorbed based on the type of sugar attached. Available evidence is that quercetin glucosides (like those found predominantly in onion or shallot flesh) are far better absorbed than quercetin rutinoides (the major quercetin glycoside in tea).<sup>3,19</sup>

Quercetin from dietary sources is bioavailable. A high-vegetable, -berry, and -other fruit diet for six weeks nearly doubled plasma quercetin, while subjects placed on a diet low in vegetables, berries, and other fruit, exhibited a 30-percent decrease in plasma quercetin.<sup>20</sup> Consuming 100 g/day of bilberries, black currants, and lingonberries for two months increased plasma quercetin levels up to 50 percent.<sup>20</sup> Consuming sufficient bilberries, black currants, and lingonberries to provide a total of 12.3 mg/day of quercetin increased quercetin between 32-51 percent.<sup>21</sup> An average intake of 160 g/day of bilberries, lingonberries, black currants, and chokeberries for eight weeks increased plasma quercetin significantly compared to baseline and to the control group.<sup>22</sup> While strawberries are a food source of quercetin glycosides, unlike these other berries, no impact on plasma quercetin was detected in volunteers who consumed 300 g of

fresh strawberries and stored strawberries.<sup>23</sup> A meal rich in plant foods designed to deliver 87 mg of quercetin increased plasma quercetin concentration from pre-meal levels ranging from 28-142 nM to a mean of 373 nM three hours post-ingestion.<sup>24</sup> A meal of fried onions (225 g) increased plasma quercetin from a baseline of 28.4 ng/mL to 248.4 ng/mL two hours post-ingestion; levels did not decrease to baseline until 24 hours after the onion meal.<sup>25</sup> Human studies report plasma quercetin levels increase after ingestion of black currant juice,<sup>20</sup> red grape juice,<sup>26</sup> wine, and vegetable juice.<sup>27</sup> The increase from juice<sup>26</sup> ingestion appears to be very low when compared to the increase reported after ingestion of onions.<sup>25</sup> Quercetin is absorbed after drinking black and green tea, with increasing infusion time appearing to increase the amount absorbed. Adding milk to tea had no effect on quercetin bioavailability.<sup>28,29</sup>

Studies have also assessed the bioavailability of quercetin as a dietary supplement. Two-week supplementation increased plasma levels of quercetin 178-, 359-, and 570 percent for daily doses of 50-, 100-, and 500 mg, respectively.<sup>30</sup> Supplementation with 1,000 mg/day for six weeks increased mean fasting plasma quercetin concentrations from 71 to 269 nmol/L.<sup>31</sup> In a 12-week study a daily dose of 500 and 1,000 mg/day resulted in a net increase of overnight-fasted plasma quercetin of 332 and 516 mcg/L, respectively.<sup>32</sup> In another study with healthy volunteers, a 14 carbon (<sup>14</sup>C)-labeled dose of quercetin was provided orally. Oral absorption ranged from 36.4-53.0 percent and the biological half-life was 20-72 hours.<sup>33</sup> Two of these studies also reported that the increase in plasma quercetin was highly variable among individuals.<sup>30,32</sup> These studies indicate that oral doses of quercetin can dramatically increase plasma levels, suggesting far better bioavailability than was originally thought.

The low bioavailability originally reported for quercetin has led to attempts to improve absorption. A quercetin lipid complex might improve bioavailability.<sup>34</sup> On the other hand, a water-soluble, pro-drug of quercetin – 3'(N-carboxymethyl) carbonyl-3,4',5,7-tetrahydroxyflavone – was not orally bioavailable.<sup>35</sup> There currently is not sufficient evidence to draw conclusions as to which delivery vehicle or form of quercetin is the most bioavailable, nor is there any human comparative clinical evidence available to determine whether these modified forms of quercetin offer a therapeutic advantage.

Several animal studies have assessed whether dietary factors might influence bioavailability. Quercetin might be better absorbed when consumed with apple pectin<sup>36,37</sup> and non-digestible oligosaccharides,<sup>38</sup> possibly because of compositional and quantitative changes in intestinal flora.<sup>37,38</sup> A diet with at least a modest amount of fat or lecithin increased the absorption of quercetin.<sup>39</sup> Quercetin also appears to be better absorbed when consumed with a meal that has higher fat content (compared to a very low-fat meal). Elimination of quercetin was also significantly delayed when it was consumed with a higher fat meal.<sup>40</sup>

Bioavailability and pharmacokinetic studies generally measure plasma quercetin levels. Some evidence suggests that this might be contributing to an underestimate of bioavailability, and that a significant amount of an oral dose of quercetin might be in the red blood cells (RBC) that are centrifuged off to isolate plasma.<sup>41,42</sup>

Quercetin and quercetin glycosides from food or dietary supplements are extensively metabolized by enzymatic hydrolysis, microbial action, and conjugation reactions. During this extensive metabolism, glycosyl groups are removed and the majority of quercetin aglycone is glucuronated, sulfated, or methylated. It is these quercetin metabolites that appear to comprise a significant amount of quercetin in the plasma, RBCs, and tissues of animals and humans.<sup>39,42-45</sup> While there is agreement on the types of conjugation reactions quercetin undergoes *in vivo*, there currently is no consistent agreement as to which conjugation metabolites and the amount of quercetin aglycone that appear in human circulation. Human studies have variously reported only quercetin glucuronides and no free quercetin,<sup>46</sup> both quercetin glucuronides and sulfates,<sup>47</sup> and these latter two along with significant amount of unconjugated (free) quercetin aglycone.<sup>18,27</sup>

Relatively little research has been conducted on tissue distribution of quercetin following an oral dose, and no research has investigated this issue in humans. In rats quercetin and its metabolites are widely distributed in tissues, with the highest concentrations in lungs and the lowest in brain, white fat, and spleen.<sup>48</sup> In pigs, the liver, kidney, and small intestines contain high concentrations, but the brain, heart, and spleen have low concentrations.<sup>48,49</sup> There is also evidence of quercetin flavonoids accumulating in the central nervous system, with peak levels being reached with repeated dosing over eight days.<sup>50</sup> *In vitro*



experimental evidence indicates rapid uptake of quercetin by cells, resulting in significant intracellular accumulation. There is also significant uptake by isolated mitochondria, suggesting quercetin might be stored there and released into the cytosol when needed.<sup>51</sup> *In vivo* evidence indicates that quercetin feeding influences the cardiac mitochondria reduced glutathione (GSH) and oxidized glutathione (GSSG) ratio.<sup>52</sup> Taken as a whole, the limited research suggests that quercetin and its metabolites tend to accumulate in the organs involved in its metabolism and excretion, and that perhaps mitochondria might be an area of quercetin concentration within cells.

While the range reported has varied slightly (e.g., from 3-7% in one study and 3.3-5.7% in another), human studies are in agreement that the percent of quercetin metabolites excreted in urine following an oral dose is small.<sup>27,33,47</sup> The profile of metabolites excreted in urine, while also comprised of glucuronide and sulfate conjugates, appears to differ significantly from those found in the plasma. Many of the major urinary components, including quercetin-3'-glucuronide, two quercetin glucoside sulphates, and a methylquercetin diglucuronide, are either absent or present in only trace amounts in the bloodstream, suggesting there is further phase II metabolism of quercetin metabolites after they arrive in the blood.<sup>47,53</sup> Fecal recovery appears to be in the range of 1.6-4.6 percent of an oral dose. In one study, the majority of the quercetin that was unaccounted for in urinary and fecal excretion was recovered as exhaled carbon dioxide (CO<sub>2</sub>), suggesting that a high amount of absorbed quercetin is extensively metabolized and eventually eliminated by the lungs.<sup>33</sup>

### Clinical Indications/Mechanisms

Quercetin appears to have many potential beneficial effects on human health. In some instances (e.g., blood pressure lowering) clinical studies have been conducted. In other areas (e.g., cancer) all or most of the current research is pre-clinical.

### Antioxidant

An extensive amount of *in vitro* and *in vivo* animal research has focused on the antioxidant potential of quercetin.<sup>52,54-69</sup> Animal evidence suggests quercetin's antioxidant effects afford protection of the brain, heart, and other tissues against ischemia-reperfusion injury, toxic compounds, and other factors that can induce oxidative stress.

Like other antioxidant compounds, quercetin might have pro-oxidant activity, at least under some circumstances. Long-term feeding of quercetin (20 mg/day) to Sprague-Dawley rats increased serum and liver alpha-tocopherol concentrations and significantly decreased malondialdehyde concentrations, but also significantly decreased GSH concentrations and glutathione reductase activity.<sup>70</sup> In a mice feeding study, daily intake of 1 mg/day of quercetin increased the GSH:GSSG ratio in hepatic tissue, had no effect on GSH:GSSG ratio in plasma or cardiac tissue, and reduced the GSH:GSSG ratio in cardiac mitochondria.<sup>52</sup> These preliminary animal results suggest that quercetin might have complex tissue-specific effects on aspects of antioxidant defense systems.

Most human studies have not detected significant effects of quercetin on the antioxidant indices measured. A test meal of fried onions increased plasma quercetin levels significantly from baseline. This increase was accompanied by a slight increase in the total antioxidant activity of the plasma, but there was no significant change in the susceptibility of the plasma or isolated low density lipoprotein (LDL) to oxidation over the 48-hour period following consumption of the fried onions.<sup>25</sup> Two weeks of quercetin supplementation in healthy subjects at doses up to 150 mg per day did not affect plasma alpha- or gamma-tocopherols, oxidized LDL, or plasma antioxidant capacity. This lack of effect occurred despite the significant increase in plasma quercetin levels.<sup>30</sup> In a 12-week study, doses of 500 or 1,000 mg/day of quercetin significantly increased plasma quercetin levels, but, when compared to a placebo group, had no effect on plasma F(2)-isoprostanes, oxidized LDL, GSH, ferric reducing ability of plasma (FRAP), or oxygen radical absorbance capacity (ORAC) in male and female subjects.<sup>71</sup> Four weeks of a 730 mg/day quercetin dose had no effect on plasma or urine indices of oxidative stress in persons with prehypertension and stage 1 hypertension.<sup>72</sup> A dose of 1,000 mg/day of quercetin taken for six weeks failed to prevent exercise-induced increases in oxidative stress in a study of 40 athletes.<sup>73</sup> However, in two studies of overweight and obese subjects with metabolic syndrome traits, a daily dose of 150 mg/day of quercetin for six weeks decreased plasma concentrations of atherogenic oxidized LDL.<sup>31,74</sup>

## Allergy, Asthma, and Atopic Disease

*In vitro* quercetin inhibits histamine release by mast cells and basophils,<sup>75,76</sup> suggesting an anti-allergy effect. Animal evidence indicates that quercetin might have therapeutic potential for allergic airway disease. Several studies conducted in guinea pigs have reported that quercetin, provided orally or administered via inhalation, has anti-asthmatic activity.<sup>77-79</sup> In murine models of allergic airway inflammation and asthma, quercetin had pronounced anti-inflammatory effects,<sup>80</sup> reduced eosinophil and neutrophil counts and infiltration in lung tissue,<sup>81</sup> and inhibited asthmatic reactions.<sup>82</sup>

One *in vitro* and one *in vivo* animal study suggest that quercetin might counter aspects of anaphylactic reactions. Quercetin inhibits anaphylactic contraction of guinea pig ileum smooth muscle *in vitro*.<sup>83</sup> In Wistar rats experimentally sensitized to have an anaphylactic reaction to peanut, treatment with quercetin (50 mg/kg for four weeks) suppressed immunoglobulin E responses, reduced plasma histamine against peanut proteins, and protected against peanut-induced anaphylactic reactions.<sup>84</sup>

Human epidemiological research reports an inverse association between intakes of quercetin and asthma incidence.<sup>85</sup> Human intervention studies investigating quercetin for asthma and atopic disease are currently lacking. However, two studies have investigated the effects of an enzymatically-modified isoquercitrin (a quercetin glycoside) on allergic symptoms. Subjects took 100-200 mg of the active treatment or a placebo for eight weeks, starting four weeks prior to the onset of pollen release. In these studies, this specific quercetin glycoside provided a statistically significant relief of ocular symptoms, but no statistically significant relief of nasal symptoms caused by pollen.<sup>86,87</sup>

A pilot study reported that quercetin might reduce niacin-induced "flushing." In this study, four subjects received 1 g of immediate-release niacin either alone or after taking a dietary supplement that contained 150 mg quercetin, along with chondroitin, glucosamine, and olive kernel oil. Subjects reported lower erythema and burning sensation when the quercetin-containing dietary supplement was taken. Presumably this occurred in part because quercetin inhibited niacin-induced human mast cell prostaglandin D2 release.<sup>88</sup>

## Cancer

An abundance of *in vitro* and *in vivo* animal experiments have attempted to elucidate quercetin's effect in cancer. *In vitro* evidence indicates that quercetin has a variety of anticancer mechanisms, including antioxidant, antiproliferative, pro-apoptotic, cell signaling effects, and growth factor suppression, as well as potential synergism with some chemotherapeutic agents.<sup>89-125</sup> Quercetin has also been shown to inhibit the growth of cancer *in vivo* in animal experiments designed to promote tumor formation.<sup>126-135</sup> While most of the animal studies have shown a beneficial effect (especially in preventing colon tumorigenesis), a high dose of quercetin did not prevent UVB-induced carcinogenesis.<sup>136</sup> A modified quercetin (quercetin chalcone) and a pH-modified citrus pectin were reported to reduce the growth of solid primary tumors.<sup>137</sup>

*In vitro* findings suggest that quercetin might have a role in reversing drug resistance and re-sensitizing cancer cells to some chemotherapeutic agents.<sup>138-144</sup> Quercetin might also possibly potentiate the effectiveness of some chemotherapeutic agents.<sup>118,119,145-157</sup>

Four cohort studies and six case-control studies have examined associations of flavonoid intake with cancer risk. There is consistent evidence from these studies that flavonoids, especially quercetin, may reduce the risk of lung cancer.<sup>158</sup> A case-control study reported a reduced risk of developing colon but not rectal cancer with increasing non-tea quercetin intake.<sup>159</sup> Evidence from the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study reported an association between dietary quercetin intake and lower risk of renal cell cancer in male smokers.<sup>160</sup> Among the participants randomized to placebo (but not those taking supplemental alpha-tocopherol and/or beta-carotene), dietary quercetin intake was associated with decreased pancreatic cancer risk.<sup>161</sup> A diet high in quercetin, kaempferol, and myricetin – tea, fruit, cabbage, and wine – was associated with lower pancreatic cancer risk in smokers in a U.S.-based population.<sup>162</sup>

Familial adenomatous polyposis (FAP) is an autosomal-dominant disorder characterized by the development of hundreds of colorectal adenomas and eventual colorectal cancer. Five FAP patients with prior colectomy (four with retained rectum and one with an ileal anal pouch) received oral curcumin 480 mg and quercetin 20 mg three times a day. All five patients had a decreased polyp number (60.4% decrease) and size (50.9% decrease) from baseline after a mean of six months of treatment.<sup>163</sup>

In a phase I clinical trial, undertaken to establish safe dosing levels of intravenous (IV) quercetin, a single patient with ovarian cancer refractory to cisplatin had a significant decrease in CA 125 (from 295 to 55 units/mL) following two courses of quercetin (420 mg/m<sup>2</sup>). In another patient with hepatoma, serum alpha-fetoprotein levels decreased.<sup>164</sup>

In total, existing preclinical and animal evidence is supportive of quercetin as a prospective anticancer candidate for human clinical studies.

### Cardiovascular Disease

Quercetin supplementation attenuates the development of cardiac hypertrophy induced by pressure overload in rats.<sup>165</sup> However, a quercetin-supplemented diet did not delay the onset or lessen the severity of cardiovascular complications that develop in spontaneously hypertensive rats.<sup>166</sup>

Several epidemiological studies have reported an inverse association between quercetin intakes and coronary heart disease. In the Zutphen Elderly Study, the risk of heart disease mortality decreased significantly as flavonoid intake increased, with the flavonoid-containing foods most commonly eaten in this study containing high amounts of quercetin compounds (e.g., tea, onions, apples).<sup>167</sup> In a cohort of the same study, dietary flavonoids (mainly quercetin) were inversely associated with stroke incidence.<sup>168</sup> In the Finnish Mobile Clinic Health Examination Survey, low flavonoid intake was associated with higher risks of coronary disease. Intakes of onions and apples, the main dietary sources of flavonoids as well as rich sources of quercetin compounds, had similar associations.<sup>169</sup>

In humans, quercetin inhibits platelet aggregation and thrombus formation.<sup>170</sup> Quercetin appears to be effective in improving blood pressure and might have an effect on cholesterol in humans. This information is summarized in more detail in the subsections on “Hypertension” and “Metabolic Syndrome Traits and Obesity.”

### Diabetes and Diabetic Complications

Aldose reductase, the enzyme that catalyzes the conversion of glucose to sorbitol, is especially important in the eye and plays an essential role in the formation of diabetic cataracts. Quercetin is an *in vitro* inhibitor of lens aldose reductase<sup>171,172</sup> and effectively blocks polyol accumulation in intact rat lenses incubated in medium containing high concentration of sugars.<sup>173</sup> In the rodent *Octodon degus*, oral administration of quercitrin (a quercetin glycoside) led to a significant decrease in lens

sorbitol accumulation and significantly delayed the onset of diabetes-induced cataracts.<sup>173</sup>

Quercetin has been reported to lower plasma glucose, normalize glucose tolerance tests, preserve pancreatic  $\beta$ -cell integrity and function, and help protect against diabetes-induced declines in cognition, mood, and renal function in rat models of diabetes.<sup>174-180</sup> These studies have been short-term, lasting 30 days or less. Quercetin also appears to be beneficial in diabetic neuropathy and neuropathic pain in streptozotocin (STZ)-induced diabetic rats.<sup>181,182</sup>

One 28-week animal experiment, using a STZ-induced diabetes rat model, raised potential concerns about long-term administration of quercetin in diabetes. While the incidences of cataract, injured glomerules, and renal cell carcinoma were high in this study, the most severely affected involved one of the groups administered quercetin. The authors speculated that this might be, at least in part, a consequence of quercetin acting as a pro-oxidant as diabetes progresses.<sup>183</sup> While not conclusive, this study suggests that the stage of diabetes might be an important consideration in the decision to supplement in diabetes and that more research is required to determine whether long-term supplementation with quercetin is safe in humans with diabetes.

The only human study using quercetin in diabetes was conducted in 34 men and women with type 1 or 2 diabetes and diabetic neuropathy. Subjects applied a topical compound that contained quercetin, ascorbyl palmitate, and vitamin D<sub>3</sub> or placebo three times daily for four weeks to each foot. A reduction in the severity of numbness, jolting pain, and irritation was reported, as well as an improvement in quality-of-life measures with active treatment.<sup>184</sup>

### Gastroprotective and Oral Mucosa Effects

Animal studies report a protective effect of quercetin against ethanol-induced gastric ulceration<sup>185-188</sup> and experimental reflux oesophagitis.<sup>189</sup>

Quercetin weakly inhibits the growth of *Helicobacter pylori in vitro*.<sup>190,191</sup> Treatment of *H. pylori*-infected guinea pigs for 15 days with a dose of 200 mg/kg of quercetin decreased *H. pylori* infection in the gastric mucosa and reduced the inflammatory response.<sup>192</sup>

Topical quercetin application directly on minor mouth aphthous ulcers three times daily relieved pain and produced complete healing in 35 percent of subjects in 2-4 days, 90 percent in 4-7 days, and 100 percent in 7-10 days.<sup>193</sup>

## Hypertension

A variety of studies have been conducted in animal models of hypertension. In these studies quercetin has consistently demonstrated a blood pressure (BP) lowering effect.<sup>166,194-207</sup> A review of the animal evidence concluded that quercetin induces a progressive, dose-dependent, and sustained reduction in BP in a variety of rat models of hypertension and metabolic syndrome.<sup>208</sup>

Quercetin also appears to have BP lowering effects in hypertensive, but not normotensive, individuals. A single dose of 150 mg quercetin had no effect on resting systolic or diastolic BP, pulse pressure, or resting pulse rate in normotensive females.<sup>209</sup> In another study conducted in healthy men and women, 28 days of supplementation with a daily dose of 1,000 mg quercetin had no effect on blood pressure or resting heart rate.<sup>210</sup> In a study of men and women with prehypertension and stage 1 hypertension, a daily dose of 730 mg of quercetin for 28 days lowered systolic and diastolic BP by an average of 7 mmHg and 5 mmHg, respectively, in the subjects with stage 1 hypertension; however, BP was not altered in the prehypertensive subjects.<sup>72</sup> A supplement containing 100 mg/day quercetin along with 128 mg of other mixed flavonoids (composition not specified) or placebo was given to male smokers for 10 weeks. Subjects with hypertension were excluded from the study. Prior to the intervention all subjects were asked to restrict their intake of food sources rich in quercetin – apples, berries, fruit juices, onions, tea, wine, etc. While BP decreased slightly in both groups, and the decrease was statistically significant from baseline in the quercetin group, no statistically significant differences in systolic or diastolic BP were observed between the quercetin and placebo groups.<sup>211</sup> In overweight or obese subjects with metabolic syndrome traits, six weeks of 150 mg/day quercetin decreased systolic blood pressure by 2.6 mmHg in the entire study group, 2.9 mmHg in the subgroup of hypertensive subjects, and 3.7 mmHg in the subgroup of younger adults ages 25-50.<sup>31</sup> In overweight and obese individuals with metabolic syndrome traits, the apolipoprotein (apo) E phenotype appears to moderate the effects of quercetin on BP. Daily supplementation with 150 mg/day quercetin for six weeks decreased systolic BP by 3.4 mmHg in the group with an epsilon3/epsilon3 genotype (apoE3); however, no effect was detected in the group with an epsilon4 allele (apoE4).<sup>74</sup>

Human evidence suggests that the antihypertensive effect of quercetin might involve improved

endothelial function, since a single 200-mg dose of quercetin augmented nitric oxide status and reduced endothelin-1 concentrations.<sup>212</sup>

## Immunity and Infections

Quercetin has *in vitro* antiviral activity against reverse transcriptase of HIV and other retroviruses, *Herpes simplex* virus type 1, polio-virus type 1, parainfluenza virus type 3, respiratory syncytial virus (RSV),<sup>213</sup> and hepatitis C.<sup>214</sup> Quercetin has *in vitro* antibacterial activity against five microorganisms – *Actinobacillus actinomycetemcomitans*, *Actinomyces viscosus*, *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Actinomyces naeslundii* wvl – associated with onset and progression of periodontal disease.<sup>215,216</sup> It also has *in vitro* and *in vivo* activity against *H. pylori*.<sup>190-192</sup>

In murine studies, quercetin has been shown to lower liver bacterial titers, prevent liver damage, and prolong survival of *Salmonella typhimurium* aroA-infected mice,<sup>217</sup> protect against intraperitoneal encephalomyocarditis<sup>218</sup> and MengoM virus infections,<sup>219,220</sup> and decrease susceptibility to respiratory infection by influenza virus following stressful exercise.<sup>221</sup> Quercetin also appears to protect the lungs of mice from influenza-induced oxidative stress.<sup>222</sup>

Quercetin exerts immune and inflammation modulating activity in several murine models of autoimmunity. In experimental allergic encephalomyelitis (EAE) – a T-helper 1 (Th1) cell-mediated inflammatory demyelinating autoimmune disease model of multiple sclerosis (MS) – quercetin ameliorated EAE by blocking interleukin-12 (IL-12) signaling and Th1 differentiation.<sup>223</sup> In experimental autoimmune myocarditis (EAM) – a T-cell mediated disorder that is an animal model of human giant cell myocarditis and post-myocarditis dilated cardiomyopathy – quercetin ameliorated EAM in Dark Agouti rats by interfering with production of proinflammatory (tumor necrosis factor-alpha [TNF- $\alpha$ ] and IL-17) and/or anti-inflammatory (IL-10) cytokines.<sup>224</sup>

Despite positive results in *in vitro* and *in vivo* animal studies, human evidence is mixed as to whether chronic quercetin supplementation has a significant effect on immune system performance. In a randomized, double-blinded, placebo-controlled trial, 1,002 subjects took 500 or 1,000 mg/day quercetin or a placebo for 12 weeks. For the group as a whole, quercetin supplementation had no significant influence on rates of upper respiratory tract infections (URTI) compared to placebo. In a subgroup of subjects age 40 or older who



self-rated themselves as physically fit, 1,000 mg/day quercetin resulted in a statistically significant reduction in total sick days and symptom severity associated with URTI.<sup>225</sup> Female subjects were supplemented with 500 or 1,000 mg/day quercetin or placebo for 12 weeks. While quercetin supplementation significantly increased plasma quercetin levels, it had no influence on measures of immune function.<sup>226</sup> Quercetin (100 mg/day) did not alter exercise-induced changes in several measures of immune function following three days of intense exercise in trained athletes, but it significantly reduced URTI incidence (1 of 20 subjects in active versus 9 of 20 in placebo group) during the two-week post-exercise period.<sup>227</sup> A similar lack of effect on strenuous exercise-induced immune system perturbation was found in subjects who took 1,000 mg/day of quercetin for three weeks before, during, and continuing for two weeks after the 160-km Western States Endurance Run. In this study, however, there were no differences in the post-race illness rates between quercetin and placebo groups.<sup>228</sup>

### Inflammation, Injury, and Pain

*In vitro*, quercetin inhibits production of inflammation-producing enzymes (cyclooxygenase [COX] and lipoxygenase [LOX]).<sup>229,230</sup> It also inhibits TNF- $\alpha$ ,<sup>231</sup> nitric oxide production, and nitric oxide synthase (NOS) expression.<sup>232</sup>

*In vivo* animal experiments also support an anti-inflammatory effect. Quercetin ameliorates the inflammatory response induced by carrageenan<sup>233</sup> and a high-fat diet.<sup>234</sup> Quercetin reduced visceral adipose tissue TNF- $\alpha$  and nitric oxide production and downregulated NOS expression in obese Zucker rats.<sup>235</sup> In chronic rat adjuvant-induced arthritis, quercetin decreased clinical signs of arthritis compared to untreated controls.<sup>236</sup>

In rats, post-trauma administration of quercetin improves recovery of motor function after acute traumatic spinal cord injury. Intraperitoneal (IP) doses of 5-100 micromoles quercetin/kg body weight resulted in half or more of the animals walking, although with deficit.<sup>237</sup> This ability to promote recovery from spinal cord injury appears to be highly dependent on the dose and frequency of dosing. In this study a lower IP dose was ineffective. In another study, compared to an untreated control group of animals (none of which recovered motor function sufficient to walk), quercetin administration twice daily for three or 10 days resulted in about 50 percent of the animals recovering sufficient motor function to walk.

However, when quercetin was injected three times daily none of the nine animals recovered the ability to walk.<sup>238</sup>

Quercetin has antinociceptive (pain-relieving) effects in animal experiments. It appears to exert these effects by influencing the L-arginine-nitric oxide, serotonin, GABAergic, and opioid systems, as well as inhibiting pronociceptive cytokine production and the free radical generation that accompanies inflammatory pain.<sup>182,239,240</sup>

Human studies have been mixed as to whether quercetin has anti-inflammatory effects. Two weeks of quercetin supplementation in healthy subjects at doses up to 150 mg/day did not affect TNF- $\alpha$ . This lack of effect occurred despite a significant increase in plasma quercetin levels.<sup>30</sup> A dose of 1,000 mg/day quercetin for six weeks failed to prevent exercise-induced increases in C-reactive protein (CRP) in 40 athletes.<sup>73</sup> In a study of overweight and obese subjects with metabolic syndrome traits, quercetin (150 mg/day) had no effect on TNF- $\alpha$  or CRP when compared with placebo.<sup>31</sup> In a similar study, quercetin (150 mg/day) for six weeks had no effect on CRP, but TNF- $\alpha$  was decreased.<sup>74</sup> A daily dose of 100 mg/day quercetin along with 128 mg of other mixed flavonoids (composition not specified) failed to change levels of interleukin-6 or soluble vascular cell adhesion molecule-1 (sVCAM-1) after 10 weeks of supplementation in male smokers.<sup>211</sup>

### Prostatitis/Interstitial Cystitis

Several studies report benefits of quercetin alone or in combination with other nutrients for symptom management in several chronic inflammatory conditions. Thirty men with category IIIa and IIIb chronic pelvic pain syndrome (chronic prostatitis) were randomized to receive 500 mg quercetin or placebo twice daily for one month in a double-blind, placebo-controlled trial. In patients taking quercetin, symptom scores significantly improved from baseline. In a follow-up unblinded, open-label study, 17 additional men received one month of a supplement containing quercetin in combination with bromelain and papain. Eighty-two percent had at least a 25-percent improvement in symptom score.<sup>241</sup> Genetic polymorphisms, which can alter cytokine gene expression and the response to quercetin, were studied in men with chronic pelvic pain syndrome. Seventeen of the 28 men had a positive response to quercetin. All 11 of the men who failed to respond to quercetin had a genotype associated with low TNF- $\alpha$  production. A genotype associated with low IL-10 production was also

associated with treatment failure.<sup>242</sup> Twenty-two patients (five men and 17 women) with interstitial cystitis (IC) were given 500 mg quercetin twice daily for four weeks in an open-label trial. Significant improvements in symptoms were observed.<sup>243</sup> Significant improvement in symptoms was reported in 37 female patients with IC who were supplemented with a combination of quercetin, chondroitin sulfate, and sodium hyaluronate for six months.<sup>244</sup>

### Arthritis

Although quercetin does not appear to be beneficial in rheumatoid arthritis (RA), in combination with other nutrients it might reduce symptoms of osteoarthritis (OA). Twenty patients with rheumatoid arthritis were randomized to receive three capsules daily of quercetin (166 mg/capsule) plus vitamin C (133 mg/capsule), alpha-lipoic acid (300 mg/capsule), or placebo for four weeks with a two-week washout period before the subject started the next supplementation. No significant differences were found in the serum concentrations of pro-inflammatory cytokines or CRP. Scores of disease severity did not differ among treatment periods.<sup>245</sup> Glucosamine, chondroitin, and quercetin glucoside were given to 46 persons with OA and 22 persons with RA for three months. Significant improvements in pain symptoms, daily activities (walking and climbing up and down stairs), visual analogue scale, and changes in the synovial fluid properties were observed in OA subjects. No beneficial effects were observed in RA subjects.<sup>246</sup>

### Metabolic Syndrome Traits and Obesity

Mixed results have been reported with quercetin and aspects of metabolic syndrome in animal studies. In old mice fed a high-cholesterol diet, quercetin reduced cholesterol levels and down-regulated cholesterol 24-hydroxylase.<sup>61</sup> A quercetin dose of 2 or 10 mg/kg body weight, added to the diet of obese Zucker rats for 10 weeks, improved total cholesterol, triglycerides, and insulin levels and decreased inflammatory molecules produced by visceral adipose tissue.<sup>234</sup> In a 20-week study, quercetin (0.5% of the diet) helped prevent diet-induced increases in visceral and hepatic fat, cholesterol, triglycerides, blood glucose, insulin, and inflammatory adipokines in mice fed a diet high in fat, cholesterol, and sugar.<sup>247</sup> Quercetin was reported to be effective in reducing high-fat induced elevations in cholesterol and triglyceride levels in rabbits over 12 weeks. The decrease in

cholesterol levels was associated with reduced formation of atherosclerotic plaques in the aorta and carotid artery.<sup>248</sup> But in male Wistar rats, a diet supplemented with 0.5-percent quercetin for two weeks increased LDL and decreased high-density lipoprotein (HDL) levels.<sup>249</sup> Quercetin (1.2% of the diet) for eight weeks was not effective in preventing hepatic insulin resistance caused by a high-fat diet in mice.<sup>250</sup>

In normal and hyperuricemic rats, quercetin treatment for 14 days significantly reduced serum uric acid levels. It also significantly inhibited hepatic xanthine oxidase/xanthine dehydrogenase activity.<sup>251</sup>

Human studies have also been mixed. Two weeks of supplementation with doses of quercetin ranging from 50-150 mg/day had no effect on serum uric acid, lipids/lipoproteins, body composition, or resting energy expenditure.<sup>30</sup> Healthy men and women with cholesterol levels ranging from 156-278 mg/dL received either 1,000 mg/day quercetin or placebo for 28 days. Active treatment increased plasma quercetin concentrations approximately 23-fold compared with placebo, but supplementation did not modify total cholesterol, LDL, HDL, or triglyceride levels. Quercetin also did not modify blood pressure, resting heart rate, or thrombotic risk factors (platelet aggregation and platelet thromboxane B2 production).<sup>210</sup> In a large community study, subjects (n=1,002) received either (1) 500 mg quercetin, 125 mg vitamin C, and 5 mg niacin, (2) 1,000 mg quercetin, 250 mg vitamin C, and 10 mg niacin, or (3) placebo daily for 12 weeks. A small decrease in blood pressure was reported for both active treatment groups. The higher dose quercetin, vitamin C, and niacin group also had a small decrease in HDL levels.<sup>252</sup> A supplement containing 100 mg/day quercetin along with 128 mg of other mixed flavonoids (composition not specified) or placebo was given to male smokers for 10 weeks. Prior to the intervention all subjects were asked to restrict their intake of food sources rich in quercetin – apples, berries, fruit juices, onions, tea, wine, etc. While there were statistically significant decreases from baseline for total cholesterol, LDL, and serum glucose, as well as increases in HDL, within the quercetin group, no statistically significant differences were detected between the quercetin and placebo groups. Triglycerides, body mass index and waist circumference were also unchanged by active treatment.<sup>211</sup> Quercetin supplementation (150 mg/day) decreased blood pressure slightly in overweight and obese subjects with metabolic syndrome traits;

however, it also decreased HDL-cholesterol concentrations while having no effect on total cholesterol or triglycerides.<sup>31</sup> The effect on aspects of metabolic syndrome might be influenced by apolipoprotein (apo) E genotype. A dose of 150 mg/day for six weeks decreased systolic blood pressure by 3.4 mmHg in the apoE3 group, but had no effect in the apoE4 group. Quercetin decreased HDL and apoA1 and increased the LDL:HDL cholesterol ratio in the apoE4 subgroup, but the apoE3 subgroup experienced no significant changes in these variables.<sup>74</sup>

### Mood Disorders

Quercetin has shown anxiolytic- and antidepressant-like effects in animal experiments; however, no studies have investigated whether quercetin has similar effects in humans.

Quercetin dose-dependently increases social interaction time, decreases immobility time, and minimizes changes in behavior in animal experiments, such as the swim test or forced immobilization, designed to create anxiety and behavioral despair.<sup>175,177,253-255</sup> In diabetic rats this effect was comparable to that of the antidepressants fluoxetine and imipramine.<sup>174</sup> It also helps protect against changes in behavior caused by alcohol withdrawal.<sup>256</sup>

Several potential mechanisms might explain the ability of quercetin to improve mood. *In vitro* and *in vivo* evidence indicates that quercetin can inhibit monoamine oxidase A.<sup>257-259</sup> *In vivo* quercetin can decrease stress-induced brain corticotropin-releasing factor (CRF) expression (CRF has been implicated in anxiety and depression).<sup>253,260</sup> It also attenuates stress-induced increases of plasma corticosterone and adrenocorticotropic hormone.<sup>260</sup>

### Sleep

Intraperitoneal administration of quercetin (200 mg/kg) significantly increased non-rapid eye movement (non-REM) sleep during dark periods in rats, while it significantly decreased REM sleep. The impact on sleep architecture was presumably related to a quercetin-induced activation of GABA(A) receptors.<sup>261</sup> No studies on sleep have been conducted in humans.

### Sports Nutrition

In addition to studies that have investigated whether quercetin supplementation can prevent post-exercise immune system perturbations and susceptibility to infections (discussed in subsection

on “Immunity and Infections”), studies have also sought to determine whether quercetin has any ergogenic potential. Existing evidence is mixed on whether quercetin has an effect in untrained persons and not supportive of an ergogenic effect in trained athletes.

Untrained, young adult males received either quercetin (1,000 mg/day) or placebo for two weeks. Following quercetin supplementation there was an improvement in the net change in distance achieved during a 12-minute exercise trial.<sup>262</sup> In a study of 12 untrained healthy volunteers, 500 mg quercetin or a placebo was dissolved in Tang, which volunteers drank twice daily for seven days. Modest increases in maximal oxygen uptake ( $VO_{2max}$ ) (3.9%) and substantial increases in ride time to fatigue (13.2%) were observed with quercetin supplementation.<sup>263</sup> However, in another study of 11 untrained subjects, 1,000 mg/day quercetin for six days had no effect on  $VO_{2max}$ .<sup>263</sup> In 30 recreationally-active but not endurance-trained young men, 7-16 days of quercetin (1,000 mg/day) did not produce a difference in  $VO_{2peak}$ , perception of effort during submaximal exercise, total work done during the 10-minute maximal effort cycling trial, or voluntary and electrically evoked strength loss compared to placebo.<sup>264</sup>

Forty cyclists randomly received either quercetin (1,000 mg/day) or placebo for three weeks during normal training. No ergogenic effect of quercetin was detected in any variable measured, including muscle glycogen content, power output, cadence, respiratory exchange ratio, blood glucose, heart rate, or volume of oxygen consumption over time.<sup>265</sup> In persons participating in the 160-km Western States Endurance Run, there was no difference in race times between persons supplementing with 1,000 mg/day quercetin or placebo for three weeks prior to the event.<sup>227,266</sup> There was also no observed effect on self-perceived ratings of exertion.<sup>267</sup> Quercetin ingestion also failed to attenuate ultra-marathon induced muscle damage, inflammation, or increases in plasma cytokine or hormone levels.<sup>268</sup>

Adding quercetin to antioxidant vitamin supplementation for six weeks appeared to have ergogenic effects in 11 elite male cyclists. Compared to antioxidant vitamin supplementation without added quercetin, time to complete the 30 km time trial was improved by 3.1 percent while taking quercetin. Average and relative power was also higher while taking quercetin, and no differences were detected in heart rates or percent  $VO_{2max}$ .<sup>269</sup>

**Table 3. The Effect of Quercetin on Drug Bioavailability**

| Drug Name    | Quercetin Dosing                                    | Interaction  | Notes  |
|--------------|---|--|--|
| Cyclosporin  | Co-administration                                   | Decreased bioavailability  | Presumably secondary to an interaction with both CYP3A4 and P-glycoprotein (Rat and Pig Study)                   |
| Digoxin      | Co-administration                                   | Increased bioavailability  | Potentially lethal interaction with high doses of quercetin, secondary to P-glycoprotein interaction (Pig Study) |
| Diltiazem    | Co-administration                                   | None   | Mechanism not reported (Rabbit Study)  |
| Diltiazem    | Pretreatment prior to diltiazem                     | Increased bioavailability  | Mechanism not reported (Rabbit Study)  |
| Etoposide    | Co-administration                                   | Increased bioavailability  | Presumably secondary to an interaction with both CYP3A4 and P-glycoprotein (Rat Study)                           |
| Fexofenadine | Supplementation with 1500 mg/d quercetin for 1 week | Increased bioavailability  | Potentially secondary to P-glycoprotein interaction (Human Study)  |
| Irinotecan   | Pretreatment prior to irinotecan                    | Increased bioavailability  | Potentially secondary to P-glycoprotein interaction (Rat Study)  |
| Moxidectin   | Pretreatment prior to moxidectin                    | Increased bioavailability  | Potentially P-glycoprotein and CYP3A4 interaction (Lamb Study)   |
| Nifedipine   | Co-administration with 400 mg of quercetin          | No effect on bioavailability   | (Human Study)  |
| Paclitaxel   | Pretreatment prior to paclitaxel                    | Increased bioavailability  | Mechanism not reported (Rat Study)   |
| Pioglitazone | Pretreatment prior to pioglitazone                  | Increased bioavailability  | Potentially secondary to CYP3A4 inhibition (Rat Study)   |
| Saquinavir   | Supplementation with 1500 mg/d quercetin for 1 week | No effect on bioavailability   | (Human Study)  |
| Simvastatin  | Co-administration                                   | No effect on bioavailability   | (Pig Study)  |
| Simvastatin  | Pretreatment for 1 week                             | Decreased bioavailability  | Potentially secondary to CYP3A4 inhibition (Pig Study)   |
| Tamoxifen    | Co-administration                                   | Increased bioavailability  | Mechanism not reported (Rat Study)   |
| Verapamil    | Co-administration                                   | No effect on bioavailability   | (Rabbit Study)   |
| Verapamil    | Pretreatment prior to verapamil                     | Increased bioavailability  | Potentially secondary to CYP3A4 inhibition (Rabbit Study)  |
| Vincristine  | Co-administration                                   | Decreased bioavailability at low dose & increased bioavailability at high dose | Potentially secondary to P-glycoprotein interaction ( <i>In Vitro</i> & Mouse Study)                             |

### Drug Interactions

Quercetin appears to be an *in vivo* inhibitor of CYP3A4,<sup>270-274</sup> to decrease CYP1A2,<sup>275</sup> and increase CYP2A6, N-acetyltransferase, and xanthine oxidase activity.<sup>275</sup> Quercetin also is an *in vivo* inhibitor of P-glycoprotein (Pgp) – a drug efflux

transporter that can play a significant role in the intestinal and biliary transport and elimination of some drugs and their metabolites.<sup>270,271,273,276-280</sup> Because of these interactions, quercetin has the potential to alter serum levels of any drugs metabolized by these enzymes.



Daily administration of rutin (quercetin rutinoside) reduced the anticoagulant effect of racemic warfarin.<sup>281</sup> Potential interactions between quercetin (the aglycone form) and anticoagulants have not been investigated.

Interactions between quercetin and a variety of drugs have been studied primarily because of its interactions with CYP3A4 and Pgp. Animal or human evidence suggests that quercetin might decrease the bioavailability of cyclosporin<sup>270</sup> and simvastatin,<sup>282</sup> and increase the bioavailability of digoxin,<sup>280</sup> doxorubicin,<sup>273</sup> etoposide,<sup>283</sup> fexofenadine,<sup>277</sup> irinotecan,<sup>276</sup> moxidectin,<sup>284</sup> paclitaxel,<sup>285</sup> pioglitazone,<sup>274</sup> tamoxifen,<sup>286</sup> and verapamil.<sup>287</sup> These findings and the possible mechanisms are listed in Table 3.

Animal evidence also suggests that a quercetin-drug interaction might be moderated by the timing and/or chronicity of quercetin dosing. For example, simultaneous co-ingestion of a single dose of quercetin with simvastatin had a negligible effect on plasma simvastatin concentrations. However, daily quercetin intake for one week prior to simvastatin significantly decreased area under the concentration time curve of simvastatin.<sup>282</sup> Simultaneous co-administration of quercetin and verapamil had no effect on verapamil pharmacokinetics; however, pretreatment with quercetin 30 minutes before verapamil administration significantly increased its bioavailability.<sup>287</sup> These studies suggest that quercetin might be more likely to have an interaction with a medication if it is being taken chronically or if it is taken 30 minutes or more prior to the medication.

Dose might also influence drug-nutrient interactions. A study conducted in pigs reported a lethal interaction between digoxin – a substrate of P-glycoprotein with very narrow therapeutic range – and quercetin. Co-administration of quercetin (50 mg/kg) with digoxin (0.02 mg/kg) resulted in sudden death of two of three pigs within 30 minutes after digoxin administration. Although co-administration with a slightly lower dose of quercetin (40 mg/kg) significantly elevated the C<sub>max</sub> of digoxin by 413 percent, it did not have lethal effects.<sup>280</sup>

Quercetin might also influence the bioavailability of some dietary supplements. It appears to improve the bioavailability of epigallocatechin gallate (EGCG)<sup>288</sup> and possibly other flavonoids.<sup>289</sup>

Preliminary evidence suggests that quercetin might have synergistic effects with some drugs. Quercetin can reverse the development of morphine tolerance and dependence in mice.<sup>290</sup>

Pretreatment with quercetin reduced or reversed haloperidol-,<sup>291</sup> perphenazine-, and reserpine-induced catalepsy in animals.<sup>258</sup> It also might potentiate the effects of L-dopa and carbidopa.<sup>258</sup> A quercetin-containing supplement decreased niacin “flushing.”<sup>287</sup> As discussed in the subsection “Cancer,” quercetin might have synergistic interactions with some chemotherapeutic medications and might play a role in multi-drug resistance; however, the evidence for this is preclinical.

## Side Effects and Toxicity Data

Based on the Ames test, quercetin is regarded as mutagenic; however, most *in vivo* animal studies indicate that quercetin is not carcinogenic. In 1999, the International Agency for Research on Cancer (IARC) concluded that quercetin should not be classified as carcinogenic to humans.<sup>292-294</sup>

There is no definitive evidence regarding a teratogenic effect of quercetin on embryonic development; however, *in vitro* evidence suggests both that quercetin might have mild negative effects on embryo development and protective effects against toxic substances.<sup>295</sup> In DNA repair-deficient mice, prenatal exposure to quercetin produced a slight increase in the incidence of malignancies in offspring.<sup>296</sup>

In a four-week rat study, the ratios of the liver and kidney weights to the body weight were significantly increased in rats fed more than 314 mg and 157 mg quercetin/kg body weight/day, respectively. At doses above 157 mg quercetin/kg body weight/day a pro-oxidant effect was also noted.<sup>297</sup>

In human studies, quercetin has generally been well tolerated. Doses up to 1,000 mg/day for several months have produced no adverse effects on blood parameters of liver and kidney function, hematology, or serum electrolytes.

Currently, the biggest toxicity concern is co-administration of high quercetin doses with digoxin, because of the lethal effect the combination had in one pig study. Until more information is available on safe dosage levels, quercetin is probably best avoided by persons taking digoxin.<sup>280</sup>

## Dosage

Doses as low as 150 mg/day significantly increase plasma quercetin concentrations and demonstrate a biological effect in humans. The most common dosing in studies has been 1,000 mg/day, generally in two divided doses.

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