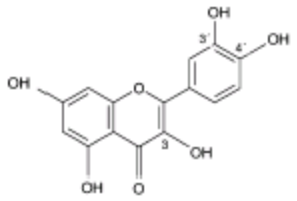
Quercetin Monograph

Scientific Name: 3,3',4',5,7-Penthydroxyflavone[1]
Common Names: Citrus Bioflavonoids, Meletin, Sophretin[1]



Quercetin

Active Ingredients: Quercetin is a polyphenolic bioflavonoid or flavonoid, more specifically classified as a flavonol. The bioflavonoids are thought to be responsible for the therapeutic effects of Quercetin.[2] Bioflavonoids are found in many plants and are commonly found in plants that are used as medicinal herbs like *Hypericum perforatum* (St. Johns Wort) and *Sambucus nigra L* (Elder flower).[2] Quercetin is highly abundant in food and beverage sources that are part of the human diet such as broccoli, lettuce, apples, tomatoes, onions, wine, tea, and coffee.[3]

Mechanisms of Action:

1. **Antioxidant:**
    - Quercetin's phenol groups have hydrogen-donating capacity and exhibits antioxidant effects by scavenging electrophilic, oxygen free radicals as well as blocking the formation of copper and iron induced free radicals,[2] and inhibits lipid peroxidation in vtiro.[3]
2. **Anti-inflammatory:**
    - Inhibits production of leukotrienes and prostaglandins, inhibits lymphocytes, and suppresses macrophage phagocytosis.[3]
3. **Antiplatelet:**
    - a complicated process involving inhibition of the eicosanoid pathway and reducing cyclicAMP.[3]
4. **Antineoplastic:**
    - Inhibits cell cycle at G1 and S phase in vitro, inhibits phosphorylation of protein kinase C (PKC) and tyrosine kinase, which ultimately blocks cellular signal transduction leading to decreased tumor growth. Inhibits the *ras* cascade, which is important for cellular proliferation and induces apoptosis[2,4] Binds to type II estrogen receptors to stimulate growth inhibition/proliferation.[2,3]
5. **Antiviral:**
    - Binds to viral coat and may inhibit nucleic acid synthesis, competitive inhibitor of reverse transcriptase.[3]
6. **Antihistamine:**

- Inhibits the release of histamine and basophils from mast cells in lung and intestinal tissues.[1,3]

Indications:
Allergies, asthma, atherosclerosis, chronic prostatitis (non-bacterial), heart disease, diabetes, gout, inflammation, schizophrenia in combination with other antioxidants, viral infections (herpes), and various types of cancer (breast, leukemia, colon, ovary, endometrial, gastric and non-small-cell lung cancers).[1,2,3]

Efficacy: Most of the evidence in humans resides with quercetin being used in chronic prostatitis and cancer. All other indications originate from in vitro data and epidemiological studies. More in vivo (human) studies need to be conducted to determine the efficacy of quercetin in allergies, asthma, atherosclerosis, diabetes, gout, schizophrenia, and viral infections. If used for these indications, caution is advised due to the lack of data for efficacy, safety, and long-term effects.

1. Chronic Prostatitis
Evidence: In vitro and animal studies have shown quercetin to improve symptoms of chronic nonbacterial prostatitis in mice (BPH).[3,1]
Human data:

- **Study design and methods:** A preliminary prospective, double-blinded, placebo-controlled trial funded by the NIH analyzed the effects of quercetin 500 mg po BID for 1 month in 30 men diagnosed with category IIIa and IIIb non-bacterial chronic prostatitis. An additional follow-up unblended, open-label study with 17 men received Prosta-Q® for 1 month, quercetin plus bromelain and papain which augments its absorption. The objectives of the study were symptom relief and quality of life at the start and end of the study.
- **Results:**
  - Upon completion of the study the mean symptom score improved from 21 to 13 ($p=0.003$) in the treatment group. Patients taking quercetin experienced less pain (10 to 6.2) and improved quality-of-life (8 to 4.9) which were significant differences. No significant difference was found for urinary symptoms (voiding dysfunction). One patient taking quercetin experienced mild tingling in the extremities and another patient experienced a headache, which resolved on its own. The tingling resolved upon discontinuation of quercetin.
  - Patients receiving Prosta-Q experienced an improved symptom score mean of 44%, whereas patients taking just quercetin saw a mean improvement of 35%.
- **Conclusion:** Overall this was a well-designed trial, however due to the small sample size a larger RCT is recommended and ideal formulations, dosage, and long-term effects have not been determined. Quercetin's place in therapy may be additive or in place of alpha-blockers and NSAIDS in men with refractory

chronic prostatitis category III with negative cultures and antibiotic therapy has failed to relieve symptoms.

2. Cancer

Evidence:

Epidemiological evidence does not support the hypothesis that foods high in quercetin reduce one's risk of cancer.[3]

In vitro and animal studies have demonstrated that flavonoids may inhibit cancer cell growth by binding to type II receptors, which are overexpressed in a wide range of tumor tissues (breast, prostate, ovarian, skin, colon, and lung). Other in vitro and animal studies have demonstrated that quercetin may act synergistically with antineoplastic agents by inducing apoptosis.[5]

Human data:[7]

- **Study design**: A phase 1 clinical trial analyzed the pharmacokinetics and effects in 51 cancer patients with refractory disease to standard therapies. The cancer types involved included large bowel (14), ovarian (10), pancreas (7), melanoma (6), stomach (5), NSCLC (2), hepatoma (3) and renal (2).
- **Methods:** The starting dose used was 60 mg/m2 by IV infusion over 30 seconds. The doses were escalated in 3-week intervals until dose-limiting side effects were encountered. Quercetin was delivered in DMSO to make it more water-soluble.
- **Results:**
  - Pharmacokinetics: 2 compartment model
    - Elimination half-life: 3.8-86 min
    - Clearance: 0.23-0.84 l/min/m2
  - Side effects: Nephrotoxicity was seen at 1700 mg/m2 in all 3 patients treated and was preventable with pre and post-hydration of 1 liter NS. Grade 3 emesis occurred in patients at 1700 mg/m2 and did not respond to anti-emetics. Doses above 940 mg/m2 were infused over 5 minutes instead of 30 s due to infusion related pain. Most patients experienced mild flushing after infusion lasting about 3 minutes. The maximum tolerated dose was determined to be 1400 mg/m2.
  - Anticancer activity: 1 hepatocellular cancer patient experienced a sustained fall in AFP and alkaline phosphatase after the first dose, 1 patient with stage 4 ovarian cancer with liver mets experienced a decrease in CA levels at 420 mg/m2 and was then combined with carboplatin and the CA marker decreased enough as to suggest response to treatment.

Conclusion: Since this was a phase I trial not designed to determine the efficacy of quercetin in cancer, the antitumor results are not conclusive. However, we can conclude that quercetin is comparably safe (compared to chemotherapy toxicity profiles) under doses of 1400 mg/m2 and may have anti-tumor activity. Further RCT are needed before a definitive recommendation can be made. The role of quercetin in cancer may be in patients refractory to the standard of care or as adjunctive treatment for possible synergy with chemotherapy.

Dosing and Administration:
Cancer: 1400 mg/m2 IV bolus weekly or in three week intervals[2,3,7]

Prostatitis: 500 mg po BID for 4 weeks or Prosta-Q: 1 tablet po BID for 4 weeks.[6]

Other: 400-500 mg po TID or 250 mg po TID if use water soluble chalcone form.[3]

Contraindications:
Hypersensitivity to quercetin's components (flavonoids present in many natural foods).

Adverse Reactions:
IV: flushing, sweating, nausea, vomiting, and injection site pain after infusion. Nephrotoxicity may occur with IV infusions >945 mg/m2.[1,3,7]
Oral: tingling of extremities, headache.[1,3,6]

Drug Interactions:[6]
Quinolones-competitive inhibition via DNA gyrase site on bacteria.

Safety:
- Liver Impairment: Metabolism: Quercetin is broken down in the small intestine to glucuronide byproducts and the metabolites may undergo further hepatic metabolism.[4,5] Caution is advised in patients with severe liver dysfunction.
- Caution in renal impairment[7]
- Protein binding: mainly albumin. Use caution with narrow therapeutic range drugs like warfarin or digoxin, which are highly protein bound as well.[6]
- Pregnancy and Lactation: Lack of data available. Quercetin should not be used during pregnancy or lactation.[1]
- Anti-platelet activity: Inconclusive data. Monitor for signs and symptoms of bleeding.[3]
- When recommending this product keep in mind;
    - Oral absorption varies among individuals and as with most herbal supplements there is a lack of product/manufacturing heterogeneity or consistency.

References:

[1] Jellin JM, Batz F, Hitchens K. Pharmacist's Letter/Prescriber's Letter. Natural Medicines Comprehensive Database. Therapeutic Research Faculty, Stockton, CA. 2003. p. 1100-1101.

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[3] Spoerke D, Rouse J.(Eds): AltMedDex® System. MicroMedex, Inc., Englewood, Colorado (Edition expires [03/2003]).

[4] Manach C, Regerat F, Texier O, et al. Bioavailability, metabolism and physiological impact of 4-oxo-flavonoids. Nutrition Research 1996;16:517-534.

[5] Cipak L, Rauko P, Miadokova E, Cipakova I, Ladislav N,. Effects of Flavonoids on Cisplatin-induced Apoptisis of HL-60 and L1210 Leukemia Cells. Leukemia Research 2003;27:65-72.

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7 Ferry DR, et al. Phase I clinical trial of the flavonoid quercetin: Pharmacokinetics and the evidence for in vivo tyrosine kinase inhibition. Clinical Cancer Research 1996;2(4):659-668.