Quercetin LipoMicel™

bioclinic® naturals

Highly Absorbable Quercetin

Aust L 356749

Active Ingredient

Each softgel contains:

Quercetin dihydrate	279.80 mg
Quercetin	250 mg

Recommended Dosage

Adults: 2-4 softgels per day or as directed by a health care practitioner.

Uses

- 10x higher absorption than standard quercetin, due to patent-pending LipoMicel™ delivery technology.
- Potent antioxidant activity/support.
- Effective for inflammatory conditions.
- Analgesic support for pain-associated pathologies.
- Concentrated, single ingredient formulation for targeted and flexible therapeutic dosing.
- Supports immune system balance and function.

Side Effects

Evidence of human clinical trials and a long history of use demonstrate that oral use of quercetin is generally observed to be well tolerated with side effects occurring infrequently when used at recommended dosages.[1-5] The few published reports of adverse symptoms attributed to oral quercetin have been mild nausea, stomach upset, dyspnoea, headache and tingling extremities.[1-3] High oral dosages of quercetin have been reported to be associated with kidney damage, however other reports confirmed that a daily dose of 1 g over several months did not cause any adverse effects on liver, kidney, haematology or electrolyte parameters. Also, there is no evidence of toxicity with doses up to 1 g/day.[3,4]

Cautions

If symptoms persist consult your health professional.

Interactions

Quercetin may interact with medications metabolised via CYP1A1 and CYP1A2 due to its inhibition of these hepatic enzymes, so monitoring by a health professional with concomitant use of such medications with quercetin is recommended.[1,4] Quercetin should not be taken at the same time as iron due to its significant iron-chelating effects.[1] Concurrent use of quercetin with cyclosporin inhibits its bioavailability, while quercetin increases the bioavailability of digoxin, the calcium channel blocker diltiazem, paclitaxel and pioglitazone, so concomitant use of quercetin is not recommended and caution is advised.[1,3,4]

Contraindications

- Contraindicated in individuals who are hypersensitive to quercetin.[1]
- Caution advised in individuals with thyroid disease and on thyroid medication due to preliminary evidence demonstrating quercetin's inhibition of thyroid cell growth and insulin-modulated phosphatidylinositol 3-kinase-Akt activity.[1]
- Contraindicated with concomitant use with fluoroquinolone antibiotics due to quercetin's capacity to competitively bind to bacterial DNA gyrase.[4]

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Mechanism of Action

Antioxidant

Modulates the oxidant/antioxidant balance by:

- Scavenging and reducing reactive oxygen and singlet oxygen species. [3,4,6-8]
- Decreasing levels of malondialdehyde (MDA).[9]
- Stimulating and enabling expression and activation of nuclear factor erythroid-derived 2-like/antioxidant response element (Nrf2/ARE) signalling and its induction of catalase, glutathione reductase, glutathione-S-transferase, heme oxygenase, thioredoxin reductase and superoxide dismutase.[4,6,9,10]
- Increasing total antioxidant capacity in the body.[9]
- Increasing mRNA levels of glutamylcysteine-synthetase.[10]
- Promoting activity of glutathione peroxidase, glutathione reductase and glutathione-S-transferase.[10]
- Inhibiting lipid peroxidation.[4,11]
- Binding toxic metal ions (cadmium fluoride).[3,4]
- Inhibiting iron overload-induced cellular oxidative damage.[9]
- Inhibiting damage to DNA.[3]
- Reducing oxidative stress-induced cellular and tissue damage.[4,8]
- Regulating xenobiotic metabolism via hepatic cytochrome P450 pathways.[7]
    - downregulating hepcidin expression (limiting pathogen proliferation and survival potential).[7]
    - decreasing IL-5, IL-9 and IL-13.[29]
    - maintaining integrity and stimulating repair of pulmonary epithelial barrier.[27]
    - promoting viral clearance and decreasing viral replication.[26]

Anti-inflammatory:

- Modulates inflammatory response in the body.[12]
- Inhibits lipopolysaccharide-induced inflammation via inhibition of phosphatidylinositol-3-Kinase (PI3K)- (p85) tyrosine phosphorylation and toll like receptor/MyD88/PI3K complex formation.[12,13]
- Attenuates dendritic cell (DC) phenotype and function from a pro-inflammatory to tolerogenic profile and enhances induction of T-regulatory cells in DCs.[14]
- Suppresses production and signalling of inflammatory mediators (5-lipoxygenase, cyclooxygenase-2 and nuclear-factor kappa-B (NFκB)).[4,7,11-13,15]
- Inhibits translocation and transcriptional activation of nuclear-factor kappa-B (NFκB).[5]
- Interferes with the AMPK/SIRT1 pathway induction of inflammation.[16]
- Inhibits synthesis of inflammatory markers including tumour necrosis factor- α (TNF- α), interleukin (IL)- 1α, 1ß, -4, -6, -8, mitogen-activated protein kinase, nitric oxide, inducible nitric oxide synthase, interferon-y (IFN-y), leukotrienes and C-reactive protein. [4,7,9,12,13,16]
- Inhibits expression of NLR family pyrin domain containing 3 (NLRP3) inflammation-associated inflammasome proteins in local inflammatory microenvironment.[15]
- Inhibits synthesis of inflammatory cytokines and tryptase release from mast cells.[4,9]
- Suppresses eosinophilic inflammation.[8]
- Reduces inflammation-induced oedema.[3]

Analgesic:

- Attenuates/alleviates pain symptoms by:
    - modulating inflammatory responses (above).[17]
    - inhibiting nociceptive responses.[18]
    - inhibiting toll-like receptor signalling pathway.[17]
    - inhibition of neuropathic pain induced by satellite glial cells (SGCs) and their synthesis of proinflammatory cytokines (TNF- α).[18]

Immunity:

- Modulates cellular and humoral immune function.[8,12]
- Improves imbalanced T-helper type 1 and 2 cell concentration and activity and subsequent cytokine synthesis.[8,12]
- Modulates differentiation of naïve glycoprotein CD4 T-cells.[8]
- Suppresses antigen-specific immunoglobulin-E (IgE) antibody synthesis from mast cells and basophils.[8,13]
- Interacts with intracellular polyphosphoinositide signalling system which is involved in immune reactions.[7]
- Stabilises mast cells membranes.[8]
- Inhibits mast cell activation and release of histamine from basophils and mast cells.[8]
- Antiviral activity:
    - binds to viral coat protein and polymerases.[3,8]
    - enhances interferon.[3,8]
    - inhibits viral entry and replication.[3,19]
    - reduces cytokine levels (as specified above).[19]
    - decreases viral genome expression, mRNA and protein expression in infected cells.[19]
    - reduces virus-induced ROS synthesis.[19]
- Potent antimicrobial activity against gram-negative and gram-positive bacteria.[4]
- Antiprotozoal activity.[4]

Pharmaceutical Commentary

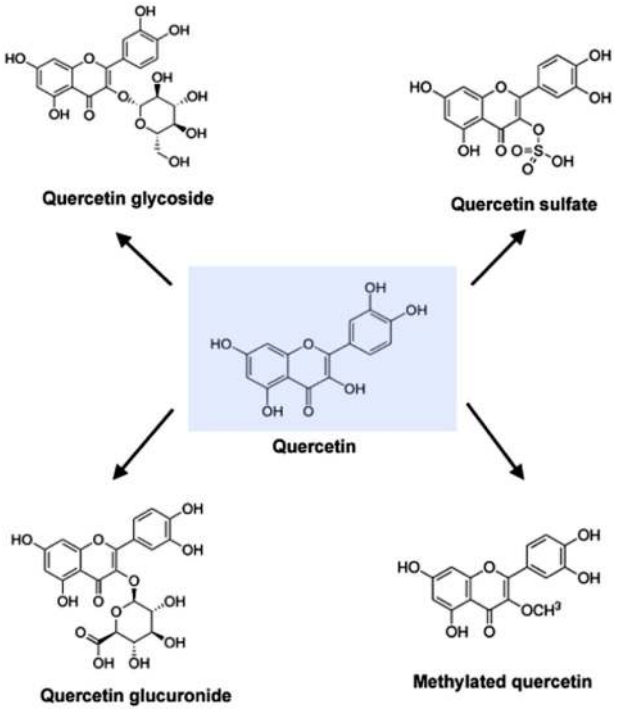
Quercetin (3,3',4',5,7-pentahydroxyflavone) is a plant-derived aglycone that is the most widely distributed bioflavonoid in foods including apples, onions, tomatoes, broccoli, green leafy vegetables, tea, red wine, grapes, berries, seeds, nuts and buckwheat.[1,20,21] Quercetin's potent antioxidant and anti-inflammatory properties are significant in the context of the recognised negative effects of excessive chronic oxidative stress and inflammation in the body.[3,4,6-8,12]

Low to moderate levels of oxidative stress and inflammation are essential for normal physiological function and health.[22-24] Excessive amounts of inflammation and oxidative stress can be induced by many endogenous and exogenous aetiological factors including infections, autoimmunity, age, obesity, diet, heavy metals, smoking, cooking, radiation, air and water pollution, low sex hormones, stress and poor sleep.[22,23] When occurring in the body in excessive amounts, inflammation and oxidative stress can significantly affect cellular and tissue structural integrity and function, and subsequently the healthy functional capacity of many organs and systems (e.g. cardiovascular, respiratory, muscles, joints, kidneys, endocrine system and gastrointestinal tract).[23-25]

Medications commonly used to alleviate inflammation are often associated with adverse side effects.[16] Consequently the use of natural substances that exhibit a broad range of mechanisms targeting the physiological consequences of excessive inflammation and oxidative stress with minimal side effects is increasing.

Quercetin has potent antioxidant and anti-inflammatory properties, however because in its natural form it has a low solubility and bioavailability profile, maximising its therapeutic potential requires use of specific technology to enhance its absorption.[20,21,26]

Figure 1: Molecular structure of quercetin, quercetin glycoside, quercetin glucuronide, quercetin sulfate and methylated quercetin.[12]



LipoMicel™ Matrix

LipoMicel™ Matrix is a unique, patent-pending technology that overcomes quercetin's naturally low bioavailability profile by creating a liquid micelle matrix that disperses quercetin into tiny microdroplets. This superior delivery system results in enhanced absorption that is 10 times higher than occurs with standard forms of quercetin.[34]

Antioxidant

Quercetin has significant antioxidant activity with a total antioxidant capacity 3.5 times higher than curcumin.[1] This is one of quercetin's key biological properties fundamental to its potent therapeutic effects, with several mechanisms demonstrated.[1] Specifically, quercetin has been shown to scavenge and neutralise free radicals including reactive oxygen species (peroxynitrite, hydroxyl radicals, hydrogen peroxide) potentiate the antioxidant activity of other antioxidants (e.g. vitamin C), chelate metals, improve erythrocyte and plasma redox status (reduced/oxidised glutathione ratio and reduced thiobarbituric acid reactive substance [TBARS] levels) and activate the nuclear erythroid 2-related factor 2-antioxidant response element (Nrf2-ARE) pathway.[1,20, 27-29]

The beneficial effects of these mechanisms have been observed in clinical trials in humans exhibiting elevated oxidative stress.[20,30]

A double intervention trial investigated the effect of quercetin supplementation on oxidative stress and inflammatory markers in non-smoking individuals (age 45 ± 10, 12 male and 6 female) with respiratory oxidative stress and inflammation and associated symptoms (dyspnoea, coughing, chest pain).[30]

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Following a two-day washout period where subjects were advised not to consume quercetin-concentrated foods or supplements, subjects in the active treatment group (n=12) were given 4 x 500 mg quercetin orally while the other group were given placebo (n=6) over a 24-hour period (during lunch, dinner and before bed). In blood samples taken from all subjects before and after supplementation, assessments performed included measuring total plasma quercetin (sum of quercetin aglycone and quercetin glucuronides/sulfates), total plasma antioxidant status (trolox equivalent antioxidant capacity [TEAC]), plasma levels of ascorbic acid, uric acid and glutathione) and inflammatory markers (basal and LPS-induced levels of TNFα/IL-10 and IL-8/IL-10). Quercetin supplementation resulted in significant reductions in oxidative stress (malondialdehyde [MDA]) and inflammation (TNFα/IL-10 and IL-8/IL-10). The authors noted that these effects correlated with individual baseline levels of oxidative stress and inflammation and quercetin plasma levels in the individual. These results demonstrate that quercetin supplementation over 24-hours reduces markers of oxidative stress and inflammation in individuals with elevated respiratory oxidation and inflammation.

Quercetin also reduced oxidative stress in amateur triathletes (30-40 years of age) during a 14-day training period for a 'sprint' distance event (750m swim, 20km cycling and 5km run).[20] Over the 14-day study period, subjects were given either placebo (n=25) or quercetin (n=23) 250 mg twice daily. All subjects underwent an oxidative stress assessment (d-RMS test) and Visual Analog Scale (VAS) to measure performance and post-training pain and cramps, conducted at baseline and at day 14 after completing a 'sprint' distance (on day 1 and 14). Compared with placebo, quercetin resulted in significant decreases in plasma free radicals ($p<0.05$). These results suggest a beneficial effect of oral quercetin on oxidative stress parameters of individuals training for triathlons.

Immunity, Inflammation and Pain

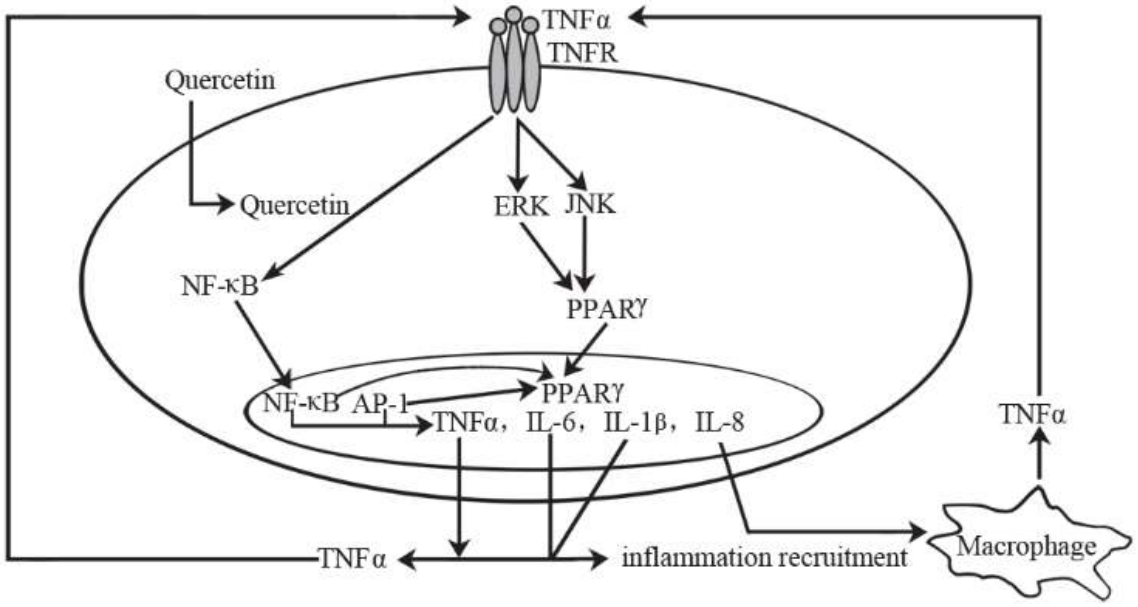
Quercetin also has significant immunomodulatory, anti-inflammatory and analgesic actions which contribute to its therapeutic effects.[14,26,31] These actions of quercetin are linked via multiple mechanisms which include inhibition of pro-inflammatory mediators such as nuclear-factor kappa B, tumour necrosis factor alpha (in whole blood, macrophages, lung and glial cells), interleukins (IL-12), tryptase, prostaglandins; inhibiting histamine release from mast cells; suppressing inflammation-inducing enzyme activity (cyclooxygenase (COX) and lipoxygenase (LOX)) and hepatic C-reactive protein release; decreasing immunoglobulin-E antibody release from B cells; and modulating dendritic cells towards a tolerogenic phenotype functional expression.[1,14,21,31,32]

These anti-inflammatory and analgesic effects were confirmed in two separate systematic reviews and meta-analyses reviewing the efficacy of quercetin on inflammatory biomarkers.[11,12] Quercetin was found to significantly reduce circulating C-reactive protein levels in diagnosed inflammatory disease states when levels were elevated (>3 mg/L) when used at a daily dose of at least 500 mg.[11,16]

Quercetin's analgesic properties were also demonstrated in a randomised, double-blind, placebo-controlled clinical trial in women with joint inflammation and pain.[33] Over 8-weeks, women were given either quercetin (500 mg/day) or placebo. Assessments performed at baseline and after 8-weeks included a Physical Activity Questionnaire, clinical pain symptoms (early morning pain stiffness, after-activity pain, swollen joint counts [SJC]), high-sensitivity TNF- α and erythrocyte sedimentation rate (ESR) measurements. At the end of the treatment period, quercetin showed significant improvements in pain symptoms and inflammation compared to placebo ($p<0.05$).

This evidence confirms the immunomodulatory, anti-inflammatory and analgesic properties of oral quercetin.

Figure 2: Quercetin and Inflammation[12]



Working model on how quercetin blocks tumor necrosis factor-α (TNFα)-mediated inflammation. Quercetin prevents TNF-α from directly activating extracellular signal-related kinase (ERK), c-Jun NH2-terminal kinase (JNK), c-Jun, and nuclear factor-κB (NF-κB), which are potent inducers of inflammatory gene expression and protein secretion. In addition, quercetin may indirectly prevent inflammation by increasing peroxisome proliferator-activated receptor c (PPARy) activity, thereby antagonising NF-κB or activator protein-1(AP-1) transcriptional activation of inflammatory genes. Together, these block TNF-α-mediated induction of inflammatory cascades.

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