QUERCEFIT® (Quercetin Phytosome®)

Last Updated: 4.27.20

Quercetin - Background Information

Quercetin is a phytonutrient found in numerous plants with the majority of the 15-25mg typically ingested daily in the US coming from apples, onions and tea. More specifically, quercetin is classified as a flavonol, which is one of the six subclasses that categorize the 6000 plus known flavonoids.

Quercetin has three main effects in the human body including being a potent *antioxidant*, *anti-inflammatory* and *immune modulator*. The combination of these three biological effects allows quercetin to be a logical ingredient to support overall health as many unhealthy conditions are characterized by oxidative stress, inflammation and an unbalanced immune response including, but not limited to, respiratory health (eg, allergic rhinitis, asthma, etc), cardiovascular health (eg, hypertension, atherosclerosis, lipid abdormalities), diabetes, gut health, and the aging process itself (via the concept of *oxi-inflammaging*).

ANTIOXIDANT

The antioxidant activity of quercetin is one of its most well-known and remarkable effects of this fascinating phytonutrient. In fact, it seems to be one of the most powerful flavonoids for protecting the body against ***free radicals***; and it does so through different mechanisms of action[1,2,3,4] including:

- ***Direct* antioxidant effects** - ie, direct inactivation of free radicals such as ROS and RNS
- ***Inhibition of enzymes*** - eg, *inducible nitric oxide synthase* (iNOS), which is responsible for excessive production of NO as seen in excess inflammation) and *xanthine oxidase* (involved in metabolism of uric acid)
- ***Inhibition of lipid peroxidation*** - including inhibiting the initial oxidation of lipids
- ***Inhibition of LDL-oxidation*** - LDL is a normal constituent of the human body, while oxidized cholesterol is not, and as such is associated with an increased risk for cardiovascular disease
- ***Improved synthesis of glutathione*** - the body's most important endogenous antioxidant
- ***Metal chelation of ions*** - eg, iron, which if left unbound can initiate the oxidative process

ANTI-INFLAMMATORY

Quercetin has been found both *in vitro* and *in vivo* studies to possess strong anti-inflammatory effects[5,6,7] including:

- ***Inhibiting NF-kB*** - a key orchestrator of the inflammatory process
- ***Inhibition of cytochines*** - eg, TNF-α
- ***Inhibition of pro-inflammatory enzymes*** - such as *cyclooxygenase* (COX) and *lipoxygenase* (LOX), which produce potent inflammatory metabolites

These anti-inflammatory effects of quercetin are closely related to its strong antioxidant activity and so there appears to be a significant interplay between oxidative stress and inflammation; however, at the same time, oxidation and inflammation are also closely related to immune function.

IMMUNOMODULATOR

Quercetin can play a crucial role in **modulating immunity** through several specific actions[8,9] including:

- ***Stabilization of cell membranes*** acting as calmodulin antagonism, preventing release of allergic mediators and substances
- ***Reduction of histamine secretion*** from mast cells and basophils
- ***Reduction of release of cytokines*** (e.g. TNF-α) *and* ***interleukins*** from mast cells and basophils
- ***Inhibition of antibodies IgE***, responsible for allergic symptoms causing release of chemicals determining allergic reactions in the nose, lung, throat, and skin
- ***Inhibition of enzymes*** *cyclooxygenase* and *lipoxygenase*, leading to reduction of thromboxane, prostaglandins and leukotrienes involved in immune reactions
- ***Immune response regulation*** by targeting enzymes in white blood cells, such as kinases and phosphatases essential for cellular immune response
- ***Immuno-stimulatory*** by inducing gene expression of *interferon-γ* (IFN- γ) which stimulates natural killer (NK) cells, the body's first line of defense against viruses and cancer cells

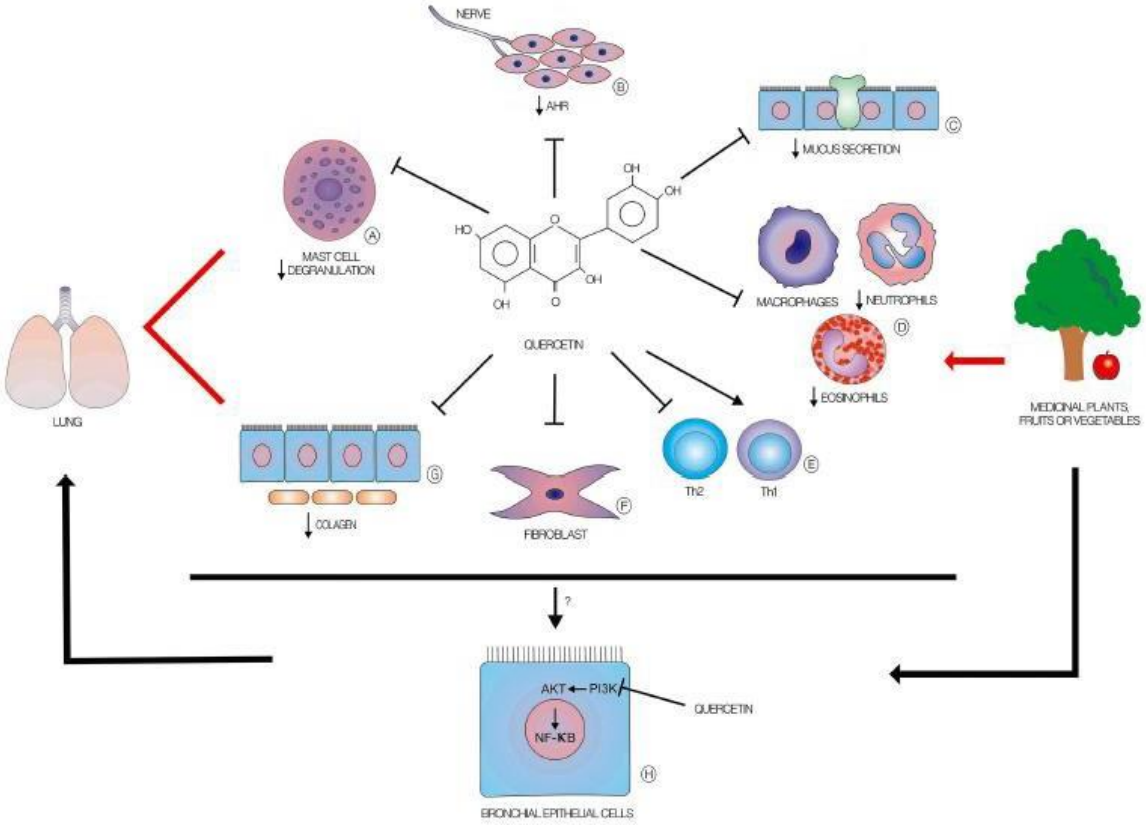


Figure 1. Possible role of quercetin in respiratory discomforts: modulation of cell degranulation (A), airway hyperreactivity (B), mucus production (C), eosinophil and neutrophil recruitment (D), Th1/Th2 cytokine production (E), anti-fibrotic activities (F) and collagen deposition (G), attenuation of NF-kB signaling pathways (H)[8]

Anti-Viral Effects

Potent anti-viral effects

In addition to the beneficial effects on the immune system, quercetin has also been shown to have *potent anti-viral effects*. *In vitro* tests, for example, have found quercetin is an effective antiviral agent against the following viruses:

- **Hepatitis C virus** - by inhibiting viral production and replication[10]
- **Rhinovirus** – by inhibiting viral replication of the virus that causes a majority of common colds, as well as reducing pro-inflammatory cytokines, while improving lung function when given *in vivo*.[11]
- **Influenza A viruses** (including at least two H1N1s + H3N2) - by preventing viral cell entry[12]
- **SARS-Coronavirus** - by inhibiting proteases, which are essential for the replication of the virus (as determined by molecular docking analysis).[13]
- **New Coronavirus COVID-19**
    - *By inhibiting the main protease (M^{pro}) found in COVID-19* (6LU7) and doing so as effectively as the most potent antiviral drug against COVID-19.[14]
    - *By inhibiting the binding of the virus to human cells*; more specifically, quercetin was found to be one of the top 5 most active inhibitors of the binding of the viral spike protein (S-protein) on the virus to specific receptors on human cells, such as the Angiotensin-Converting Enzyme 2 (ACE2) receptor, even when such comparisons included the leading antiviral drugs.[15]
    - *By acting as a zinc ionophore*[16] which increases intracellular levels of free zinc, which in turn increases its anti-viral activity of this essential mineral, which is also one of the mechanisms of the leading malaria drug that has been proposed to treat COVID-19 symptoms.[17]

Quercetin supplementation reduces upper respiratory tract infections nearly 90%

- Based on the above, it is not surprising that quercetin supplementation was shown to significantly reduce upper respiratory tract infections (URTI) nearly 90% (ie, 1/20 athletes got sick compared to 8/20 in the placebo group; an 89% reduction; p=0.004).[18]
- The dose of quercetin given to the trained cyclists in this double-blind, placebo controlled (DBPC) and randomized clinical trial was 1000mg/d (500mg bid w/bkfst + dinner) which was given for 3wks; 4 d prior to, during 3d of intense training, and then for 2wks thereafter.

QUERCEFIT®

- QUERCEFIT® is a high-quality and standardized food-grade ingredient developed by Indena utilizing their proprietary Phytosome® technology to overcome quercetin's low oral bioavailability.
- QUERCEFIT® contain ~40% quercetin + ~40% sunflower lecithin + ~20% food-grade excipients.

↑ Bioavailability 50-Fold

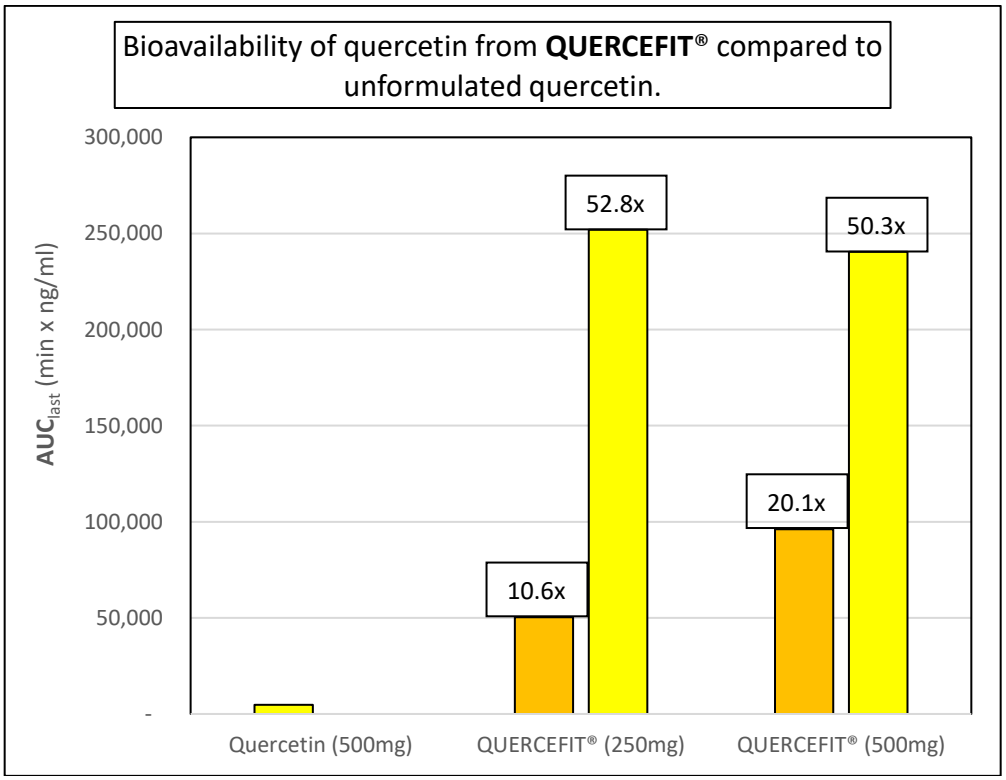
A human pharmacokinetic study was recently conducted to test the bioavailability of quercetin from **QUERCEFIT®** compared to regular quercetin. Impressively, this very well-controlled (3-way randomized crossover design) clinical trial found that on a per mg quercetin basis, **QUERCEFIT®** improved the bioavailability of quercetin 50-fold.[19]

More specifically, 100mg and 200mg of quercetin from either 250mg or 500mg QUERCEFIT® were found to be 10 and 20x more bioavailable than 500mg quercetin, respectively (see pK data below).

Since **QUERCEFIT®** is ~40% quercetin, the 10 and 20 times greater bioavailablity equates to 50-fold greater bioavailability (see chart below):

- Gold bars are comparisons on a mg/mg finished formulation basis (ie, comparing bioavailability of 500mg Quercetin to 250mg **QUERCEFIT®** and 500mg **QUERCEFIT®**)
- Yellow bars compare bioavailablity on a mg/mg quercetin basis.

Parameter	**Quercetin** (500mg)	**QUERCEFIT®** (250mg)	**QUERCEFIT®** (500mg)
AUC_{last} (min x ng/ml)	**4775**±1191	**50,402**±6418	**96,164**±9291
C_{max} (ng/ml)	**11**±2	**126**±15	**223**±13
T_{max} (min)	**290**±31	**229**±37	**203**±36



↑ Athletic Performance 11.3% in just 2 wks

Athletic performance:[20]

N: 48 Amateur Triathletes

Groups: **Control** - 25 (9♀/16♂; age-33yrs); **QUERCEFIT®** - 23 (7♀/16♂; age-33yrs)

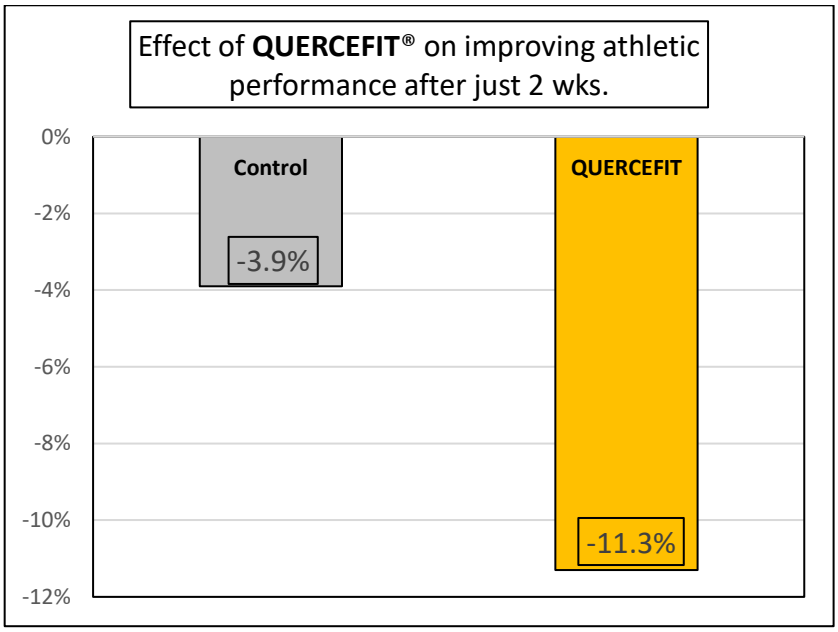
Dose: **500mg QUERCEFIT®** (dd bid; ie, 250mg at breakfast + 250mg at dinner)

Duration: **14d** (during which time the triathletes completed 8 triathlon training sessions (ie, 750m swim + 20km ride + 5km run)

Location: Italy

Results:

- ***QUERCEFIT® significantly reduced triathalon times by 11.5min*** *(or 11.3%)* ***in just 2 wks***
  - **QUERCEFIT®** supplementation significantly reduced time to complete triathlon from 101.9 to 90.4min; an improvement of 11.3% that was nearly 3 times greater (2.9x) than the improvement seen in the control group which improved 3.9min (or 3.9%), reducing time to completion from 100.6 to 96.6 min.
  - The greater improvement seen in the **QUERCEFIT®** group was significantly better than the improvement seen in the control group ($p<0.05$).



- ***QUERCEFIT® also significantly improved:***
  - **Training efficacy 21%** [8.6 vs 7.1 in control group; 0-10 Visual Analogue Scale (VAS); $p<0.05$)]
  - **Post-run diffuse muscular pain 43%** (3.4 vs 6.0 in control group; VAS; $p<0.05$)
  - **Cramps + localized pain 23%** (3.1 vs 4.0 in control group; VAS; $p<0.05$)
  - **Time to full recovery** (18.1 vs 20.4 hrs in control group; $p<0.05$)
  - **Oxidative stress 9%** (392 vs 431 in control group; plasma Carr units; $p<0.05$)

↓ Asthma + Rhinitis/↑ Lung Function in 30d

Asthma:[21]

N: 58 Healthy subjects w/mild-moderate with either *intermittent* or asthma attacks + rhinitis (with all subjects continuing to take standard medications)

Groups: **Control** – **28**; **QUERCEFIT®** - **30** [**10** in *low-dose* group (6♀/4♂; age-36yrs) + **20** in *high-dose* group; (10♀/10♂; age-35yrs)] *Mild persistent* were on high-dose (4♀/4♂; age-36yrs)

Dose: ***Low-dose* - 250mg** (once daily); ***High-dose* - 500mg** (once daily)

Duration: **30d** (during the spring, when symptoms were more common and more frequent)

Location: Italy

Results - **in *intermittent* subjects**, **QUERCEFIT®** supplementation significantly...

- ***Reduced daytime symptoms 37%* in the low-dose group and *51%* in the high-dose group** (p<0.05 vs baseline; compared to non-significant (NS) ↓ of 24% + 30% in respective control groups)
- ***Reduced nighttime symptoms 60%* in the low-dose group and *70%* in the high-dose group** (p<0.05 vs baseline; compared to NS ↓ 32% + 38% in respective control groups)
- ***Reduced rhinitis 45%* in both groups** (compared to ↓ of 25% + 13% in respective control groups; p<0.05 between high-dose and control group)
- ***Improved lung function***
  - ↑ **Peak expiratory flow** (PEF)] **12% in the low-dose group and 15% in the high-dose group** (p<0.05 vs baseline; compared to NS ↑ of 10% + 13% in respective control groups)
  - ↓ **PEF variability 30% in the low-dose group and 56% in the high-dose group** (p<0.05 vs baseline; compared to NS ↓ of 29% + 28% in respective control groups)
- ***Reduced oxidative stress* *10% in the low-do se group and 16% in the high-dose group*** (vs ↓ of 3% in control groups; p<0.05 between high-dose and control groups)

Results - **in *mild persistent* subjects**, **QUERCEFIT®** supplementation significantly...

- ***Reduced daytime symptoms 50% in the high-dose group*** (p<0.05 vs baseline; compared to NS ↓ of 23% in control group)
- ***Reduced nighttime symptoms 48% in the high-dose group*** (p<0.05 vs baseline; compared to NS ↓ of 24% in control group)
- ***Improved lung function***
  - ↑ **Peak expiratory flow** (PEF)] **7% in the high-dose group** (p<0.05 vs baseline; compared to NS ↑of 1% in control group)
  - ↓ **PEF variability 24% in the high-dose group** (p<0.05 vs baseline; compared to NS ↓ of 15% in control group)

Results - ***overall***, **QUERCEFIT®** supplementation significantly...

- ***Reduced rescue medication nearly 50%*** (ie, 15% vs 28.56% in control groups; p<0.05)
- ***Reduced drop-out rate*** as drop out rate was 4.3 times greater in control groups vs **QUERCEFIT®** groups (28.6% vs 6.65%, respectively; p<0.023)

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