QUERCEFIT®
(Quercetin Phytosome®)

Last Updated: 4.22.20

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 clearly not limited to, respiratory health (eg, allergic rhinitis, asthma, etc), cardiovascular health (eg, hypertension, atherosclerosis metabolic profile), diabetes, gut health, and overall, the aging process (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

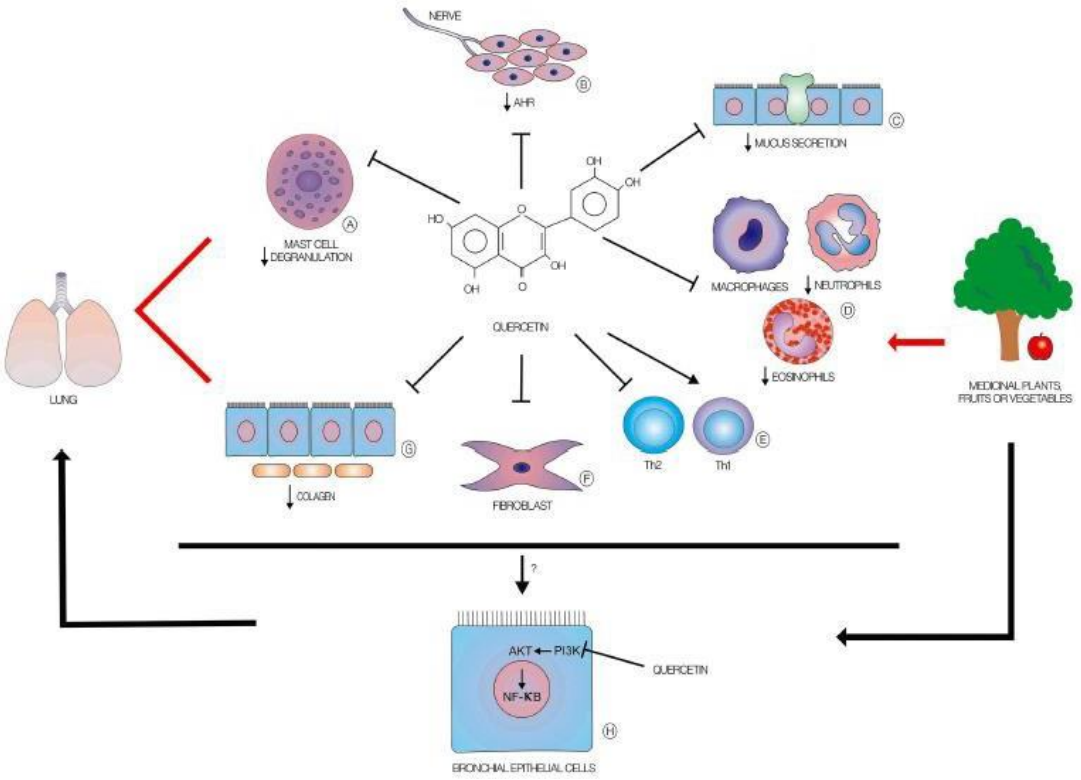


Figure 1. Possible role of quercetin in respiratory discomforts: modulation of cell degranulation (A), airway hyperreactivity (B), mucus production (C), eosinophil and neutrophil recruitment (D), Th1/Th2 cytokine production (E), anti-fibrotic activities (F) and collagen deposition (G), attenuation of 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 compared to leading antiviral drugs.[15]
    - *By acting as a zinc ionophore[16] which increases intracellular zinc which in turn increases its anti*-viral activity of this essential mineral, which is one of the mechanisms of the leading malaria drug that has been proposed to treat COVID-19 symptoms.[17]

Supplementation significantly 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.

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 reduced time to complete triathlon from 101.9 to 90.4min; an improvement that was nearly 3 times greater than the improvement seen in the control group which improved 3.9min (or 3.9%), reducing time 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; $p<0.05$)
  - ***Post-run diffuse muscular pain 43%*** (3.4 vs 6.0 in control group; $p<0.05$)
  - ***Cramps + localized pain 23%*** (3.1 vs 4.0 in control group; $p<0.05$)
  - ***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 *mild persistent* (4♀/4♂; age-36yrs) asthma attacks + rhinitis (w/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)]

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

Duration: **30d** (during the spring, when symptoms were more common and 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 improvement (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 improvements 32%+38% in respective control groups)
- ***Reduced rhinitis 45% in both groups*** (compared to reductions of 25% and 13% in respective control groups; p<0.05 between high-dose and control group)
- ***Improved lung function***
  - ***By improving 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 improvements of 10% +13% in respective control groups)
  - ***By reducing PEF variability 30% in the low-dose group and 56% in the high-dose group*** (p<0.05 vs baseline; compared to NS reductions of 29% +28% in respective control groups)
- ***Reduced oxidative stress 10% in the low-dose group and 16% in the high-dose group*** (vs just 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 improvement of 23% in control group)
- ***Reduced nighttime symptoms 48% in the high-dose group*** (p<0.05 vs baseline; compared to NS improvement of 24% in control group)
- ***Improved lung function***
  - ***By improving peak expiratory flow*** *(PEF)]* ***7% in the high-dose group*** (p<0.05 vs baseline; compared to NS improvement of 1% in control group)
  - ***By reducing PEF variability 24% in the high-dose group*** (p<0.05 vs baseline; compared to NS reduction 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)

References

[1] Rice-Evans CA, Miller NJ, Bolwell PG et al. *The relative antioxidant activities of plant-derived polyphenolic flavonoids.* **Free Radic Res** 1995;22:375-83.

[2] Lakhanpal P, Rai DK. *Quercetin: a versatile flavonoid.* **Internet J Med Update** 2007;2:22-37.

[3] Meyer AS, Heinonen M, Frankel EN. *Antioxidant interactions of catechin, cyanidin, caffeic acid, quercetin, and ellagic acid on human LDL oxidation.* **Food Chem** 1998;61:71-5.

[4] Xu D, Hu MJ, Wang YQ, Cui YL. *Antioxidant activities of quercetin and its complexes for medicinal application.* **Molecules** 2019;24:1123.

[5] Li Y, Yao J, Han C et al. *Quercetin, inflammation and immunity.* **Nutrients** 2016;8:167.

[6] Boots AW, Haenen GR, Bast A. *Health effects of quercetin: from antioxidant to nutraceutical.* **Eur J Pharmacol** 2008;585:325-37.

[7] Liu CM, Sun YZ, Sun JM et al. *Protective role of quercetin against lead-induced inflammatory response in rat kidney through the ROS-mediated MAPKs and NF-κB pathway.* **Biochim Biophys Acta** 2012;1820: 1693-1703.

[8] Mlcek J, Jurikova T, Skrovankova S, Sochor J. *Quercetin and its anti-allergic immune response.* **Molecules** 2016;21:623.

[9] Fortunato LR, Alves CDF, Teizeira MM, Rogerio AP. *Quercetin: a flavonoid with the potential to treat asthma.* **Brazilian J Pharm Sci** 2012;48:589-99.

[10] Bachmetov L, Gal-Tanamy M, Shapira A et al. *Suppression of hepatitis C virus by the flavonoid quercetin is mediated by inhibition of NS3 protease activity.* **J Viral Hepat** 2012;19:e81-8.

[11] Ganesan S, Faris AN, Comstock AT et al. *Quercetin inhibits rhinovirus replication in vitro and in vivo.* **Antiviral Res** 2012;94:258-71.

[12] Wu W, Li R, Li X et al. *Quercetin as an antiviral agent inhibits influenza A virus (IAV) entry.* **Viruses** 2015;8:6.

[13] Jo S, Kim S, Shin DH, Kim MS. Inhibition of SARS-CoV 3CL protease by flavonoids. **J Enzyme Inhib Med Chem** 2020;35:145-51.

[14] Khaerunnisa S, Kurniawan H, Awaluddin R et al. *Potential inhibitor of COVID-19 main protease (M^{pro}) from several medicinal plant compounds by molecular docking study.* **Preprints.org** March 13, 2020.

[15] Smith M, Smith JC. *Repurposing therapeutics for COVID-19: supercomputer-based docking to the SARS-CoV-2 viral spike protein and viral spike protein-human ACE2 interface.* **ChemRxiv** 2020.

[16] Dabbagh-Bazarbachi H, Clergeaud G, Guesada IM et al. *Zinc ionophore activity of quercetin and epigallocatechin-gallate: from Hepa 1-6 cells to a liposome model.* **J Agric Food Chem** 2014;62:8085-93.

[17] Xue J, Moyer A, Peng B et al. Choroquine is a zinc ionophore. **PLoS One** 2014;9:109180.

[18] Nieman DC, Henson DA, Gross SJ et al. *Quercetin reduces illness but not immune perturbations after intensive exercise.* **Med Sci Sports Exerc** 2007;39:1561-9.

[19] Riva A, Ronchi M, Petrangolini G et al. *Improved oral absorption of quercetin from Quercetin Phytosome®, a new delivery system based on food grade lecithin.* **Eur J Drug Metab Pharmacokinet** 2019;44:169-77.

[20] Riva A, Vitale JA, Belcaro G et al. *Quercetin phytosome® in triathlon athletes: a pilot registry study.* **Minerva Med** 2018;109:285-9.

[21] Cesarone MR, Belcaro G, Hu S et al. *Supplementary prevention and management of asthma with quercetin phytosome: a pilot registry.* **Minerva Med** 2019;110:524-9.