



INDENA QUERCEFIT™: EFFECTIVE SUPPORT FOR RESPIRATORY HEALTH, WHEN ALLERGIES ARE RIFE

Quercefit™ is the Indena's unique Phytosome® formulation of quercetin deriving from flower buds of the natural plant *Sophora japonica* L..

Quercetin is potentially very effective for maintaining healthy conditions but, like many botanical extracts and natural compounds, is provided with poor water solubility. As a consequence, it is barely bio-absorbable, and that decreases its potential effectiveness. For optimal bioabsorption, natural products must have a good balance between hydrophilicity for dissolving into the gastro-intestinal fluids and lipophilicity to cross cell's lipidic biomembranes.

Indena's "biomimetic approach", adopted since years, allows the company to produce the new bioavailable quercetin on the market. Biomimetics is the science that studies Nature and natural phenomena to understand the principles of underlying mechanisms, to obtain ideas from nature, imitating its design, plans and processes and to apply concepts that benefit Science, engineering, and medicine, to solve human problems. NATURE AS MEASURE™ represents the very notion of biomimetics and its philosophical origins.

The search for a bio-mimetic approach

to optimize bioabsorption of natural compounds in the full respect of their natural profile, has been pioneered by Indena with the development of Phytosome®, the proprietary 100% food-grade delivery system which is the result of a wide experience and deep knowledge in product and process research. Phytosome® represents a natural approach to obtain a solid dispersion of poorly oral bioavailable compounds that can promote phytochemicals solubility and bioabsorption through improved wetting, reduced agglomeration and changes in the physical state of the active ingredients (such as modifications in the crystalline status or production of either partially or totally amorphous stable forms).

Back to Quercefit™, standardized in ≥36.0% and ≤42.0% of quercetin, five human studies have been focused on it. According to a published human pharmacokinetic study comparing the Indena formulation to unformulated quercetin, it proved to be up to 20-fold more bioavailable, in line with the levels of a diet rich in vegetables and fruits, preserving its profile of natural ingredient.¹

Twelve healthy volunteers of both sexes, aged 18-50 years, were administered orally with a dose of unformulated quercetin (500 mg) and two different doses of Quercefit™ (250 and 500



mg). Blood samples were collected at twelve time intervals (0h to 24h) after administration, and quercetin levels in plasma were measured by HPLC/MS/MS. Quercefit™ demonstrated a significant improvement of oral absorption of quercetin and allowed to reach optimized quercetin plasma levels in line with a vegetables and fruits nutritional approach (such as onions and apples).

Quercetin: the queen of flavonoids

Quercetin is categorized as a flavonol, one of the six subclasses of flavonoid compounds. Flavonoids are an important class of natural products: particularly, they belong to a class of plant secondary metabolites having a polyphenolic structure.

Flavonoids are a natural help for human wellbeing² for their antioxidant activity which is due to their ability to reduce free radical formation and to scavenge free radicals.

In Western populations, estimated daily intake of flavonols is in the range of 20-50 mg/day. Of this, about 13.82 mg/day is in the form of quercetin-type flavonols.³ Quercetin-type flavonols 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.

An extensive scientific literature demonstrates that quercetin has multiple biological activities: it has antioxidant, antiaging, anti-inflammatory and antiviral properties.^{4,5,6} Furthermore, it is important to highlight its potential use for maintaining well-being in situations of fatigue or stress.^{7,8}

As for the antioxidant effect, quercetin acts through a direct inactivation of free radicals, the inhibition of lipid peroxidation (oxidants such as free radicals attack lipids contained in cellular membranes, lipoproteins, etc.) blocking the oxidative stress cascade from the beginning; it also acts as inhibitor of enzymes, such as NO-synthase producing free radicals.

Moreover, quercetin reduces the activation and synthesis of crucial players in inflammatory process, such as NF-kB transcription factor, enzymes like cyclooxygenase (COX) and lipoxygenase (LOX) which catalyze the conversion of arachidonic acid to its metabolites, pro-inflammatory cytokines (e.g. TNF-α) and interleukins, mediators of immunity and inflammation.

Quercetin is also able to act as a modulator for immune cells, such as lymphocytes; the release of interferon-γ (IFN-γ); the activity of eosinophils, through inhibition of eosinophils peroxidase; the stabilization of cell membranes, managing release of histamine from mast cells, cause of sneezing, itchy eyes, scratchy throat and itchy skin; the inhibition of antibody IgE responsible for allergic symptoms causing release of chemicals which determine allergic reactions in the nose, lung, throat, and skin.

These positive evidences support the promising use of quercetin for respiratory health. Additionally, quercetin has shown in-vitro activity against multiple viral targets and very recently it arises as a promising ingredient against Covid-19.⁹ Also a new in vitro study conducted by the Institute of Nanotechnology of the National Research Council (Cnr-Nanotec) of Cosenza in Italy with a group of researchers from Zaragoza and Madrid, whose results have been published in the International Journal of Biological Macromolecules.¹⁰ confirms that quercetin can interact with COVID-19 virus replication.

Respiratory health and allergic discomforts: the demonstrated efficacy of Quercefit™

Respiratory area is one of the fields in which the health benefits of Quercefit™ have been recently explored.

Two human studies^{11,12} showed very in-

teresting results achieved by Quercefit™ for the maintenance of well-being by sensitive or intolerant subjects.

After 30 days of supplementation, using either 250 or 500 mg/day of Quercefit™, the subjects wellbeing and their seasonal discomforts were evaluated according to the GINA (Global INitiative for Asthma) classification system also considering the need of additional support. In such subjects Quercefit™ was shown to keep normal parameters related to diurnal and nocturnal respiration with particular regard to breath function (Peak Expiratory Flow) in mild persistent discomforts. The supplementary use of Quercefit™ along with the best available remedy, while optimizing general comfort management, and keeping a low oxidative stress, demonstrated to have a very good safety profile.¹¹

In a second human study focusing on local skin discomforts, Quercefit™ has been administrated for just 3 days, followed by a histamine local skin stimulus. Compared to the control, only the healthy volunteers supplemented with Quercefit™ showed a statistically significant dose-dependent control of all main local skin conditions along with capillary filtration reduction.¹²

According to available data, Quercefit™ allows to exploit quercetin health benefits in respiratory and lung discomforts.

Quercefit™: efficacy and safety

In addition to being highly effective in respiratory health, Quercefit™ has been shown to have an excellent safety profile.

A human study was conducted with Quercefit™ in order to investigate any interaction of this natural approach with common standard pharmacological treatments, controlling any possible harmful effect.¹³

The results might suggest that Quercefit™ does not alter the activity of the most common antiplatelet agents (acetylsalicylic acid, ticlopidine or clopidogrel, after 10 days of supplementation), has no impact in stable patients treated with warfarin or dabigatran after 20 days of supplementation and might not influence the metabolic control of diabetic

subjects taking metformin.

Efficacy and safety of Quercefit™ make the natural power of quercetin actually available for human health. ●

References

1. Riva A. et al. Improved Oral Absorption of Quercetin from Quercetin Phytosome®, a New Delivery System Based on Food Grade Lecithin. Eur J Drug Metab Pharmacokinet. 2018 Oct 16;doi: 10.1007/s13318-018-0517-3.
2. A. N. Panche, A. D. Diwan, S. R. Chandra, Flavonoids: an overview, Journal of Nutritional Science. 2016; 5: e47. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5465813/>
3. Cao J, Zhang Y, Chen W, Zhao X. The relationship between fasting plasma concentrations of selected flavonoids and their ordinary dietary intake. Br J Nutr 2010;103:249-255.
4. A - Chondrogianni N, Kapeta S, Chinou I, Vassilatou K, Papassideri I, Gonos ES. (2010) Anti-ageing and rejuvenating effects of quercetin. Exp Gerontol. 45(10):763-71.
5. Chopra M, Fitzsimons PE, Strain JJ, Thurnham DI, Howard AN. (2000) Nonalcoholic red wine extract and quercetin inhibit LDL oxidation without affecting plasma antioxidant vitamin and carotenoid concentrations. Clin Chem. 46(8 Pt 1):1162-70.
6. Erlund I, Kosonen T, Alfthan G, Mäenpää J, Perttunen K, Kenraali J, et al. (2000) Pharmacokinetics of quercetin from quercetin aglycone and rutin in healthy volunteers. Eur J Clin Pharmacol. 56(8):545-53.
7. Wang W, Sun C, Mao L, Ma P, Liu F, Yang J, et al. (2016) The biological activities, chemical stability, metabolism and delivery systems of quercetin: a review. Trends Food Sci Technol. 56:21-38.
8. D'Andrea G. (2015) Quercetin: a flavonol with multifaceted therapeutic applications? Fitoterapia. 106:256-71. 10-11.
9. Khaerunnisa, Siti, et al. "Potential Inhibitor of COVID-19 Main Protease (Mpro) From Several Medicinal Plant Compounds by Molecular Docking Study." (2020).
10. Abian, Ortega-Alarcon et al. "Structural stability of SARS-CoV-2 3CLpro and identification of quercetin as an inhibitor by experimental screening", International Journal of Biological Macromolecules, Volume 164, 1 December 2020, Pages 1693-1703 (available at <https://www.sciencedirect.com/science/article/pii/S0141813020339970#1>)
12. Cesarone, M. R., et al. Minerva medica (2019).
13. Belcaro G. et al Esperienze dermatologiche (2020)
14. Riva A, Corti A, Belcaro G, Cesarone MR, Dugall M, Vinci- guerra G, Feragalli B, Zuccarini M, Eggenhoffner R, Giacomelli L. (2019) Interaction study between antiplatelet agents, anticoagulants, diabetic therapy and a novel delivery form of quercetin. Minerva Cardioangiol. 67(1):79-83.