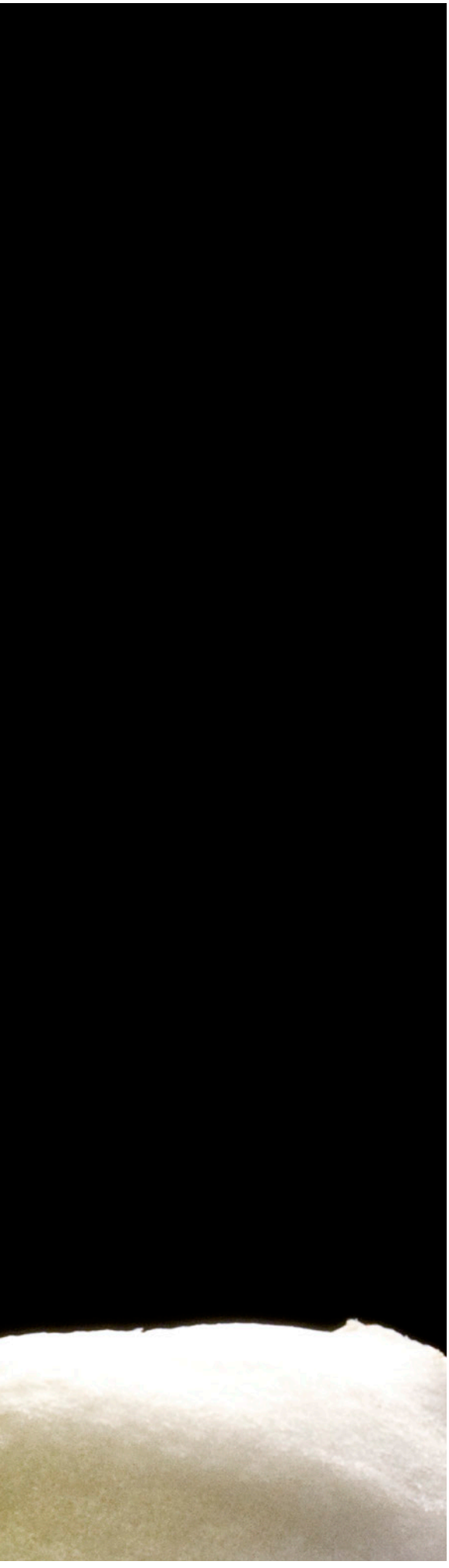
QUERCEFIT™

Quercetin, *made better.*

indena®

SCIENCE IS OUR NATURE



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1.

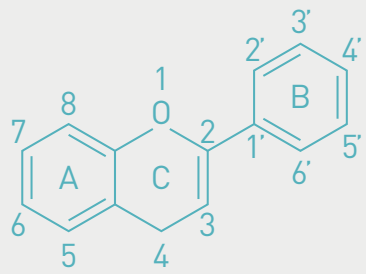
Flavonoids: a natural treasure for human wellbeing[1]

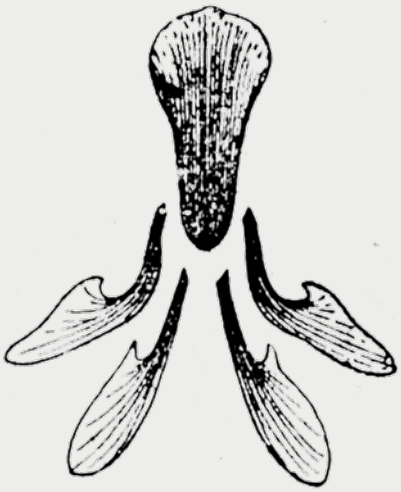
Flavonoids are an important class of natural products; particularly, they belong to a class of plant secondary metabolites having a polyphenolic structure. Flavonoids are found in fruits, vegetables, grains, bark, roots, stems, flowers, tea and wine: all products whose beneficial effects on health are well known. They are also abundantly found in foods and beverages of plant origin, such as fruits, vegetables, tea, cocoa and wine; hence they are termed as dietary flavonoids.

[1] 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/.

Flavonoids act in plants as antioxidants, antimicrobials, photoreceptors, visual attractors, feeding repellents, and for light screening.

Basic skeleton

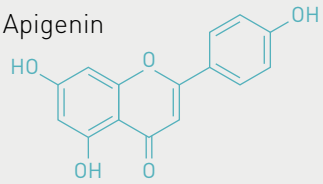




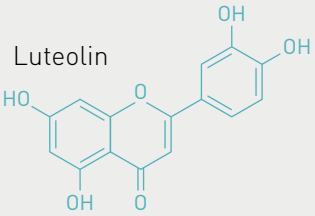
Basic skeleton structure of flavonoids and their classes
(from A. N. Panche, A. D. Diwan, S. R. Chandra, Flavonoids: an overview, Journal of Nutritional Science. 2016; 5: e47)

Flavones

Apigenin

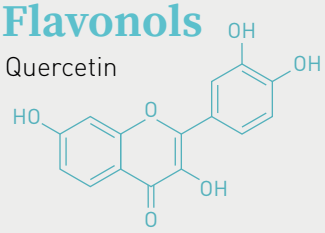


Luteolin

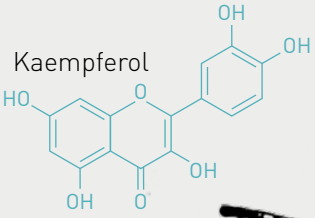


Flavonols

Quercetin

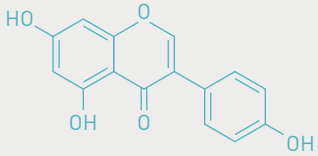


Kaempferol

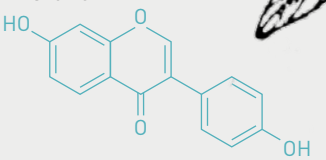


Isoflavones

Genistein

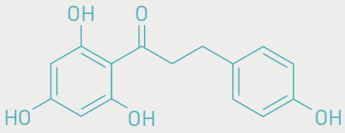


Daidzein

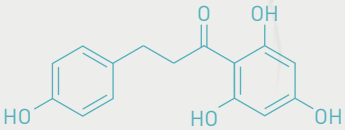


Chalcones

Chalconaringenin

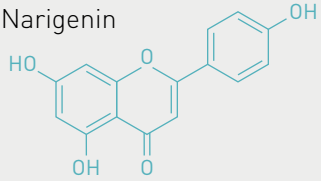


Phloretin

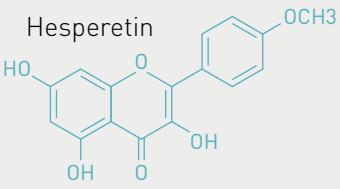


Flavonols

Narigenin

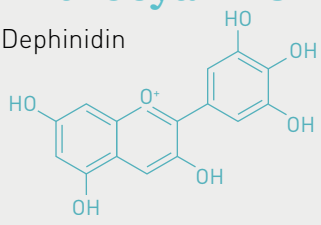


Hesperetin

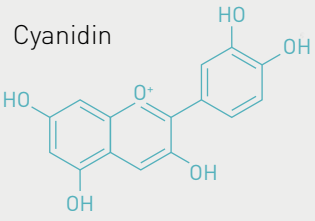


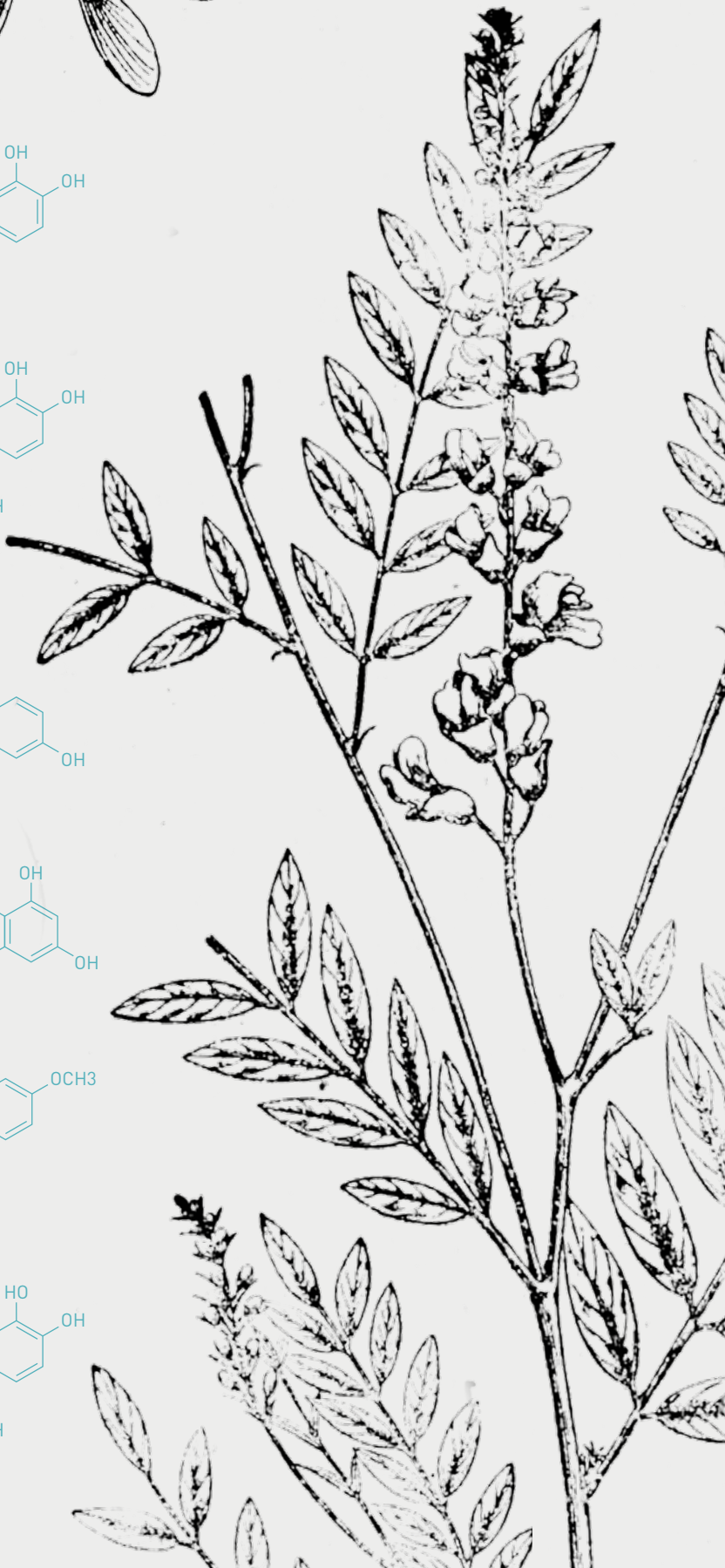
Anthocyanins

Dephinidin



Cyanidin





Many studies have suggested that flavonoids exhibit biological activities, including anti-allergenic, antiviral, anti-inflammatory and vasodilating actions. However, most interest has been devoted to the antioxidant activity of flavonoids which is due to their ability to reduce free radical formation and to scavenge free radicals.

[2] Havsteen B (2002) The biochemistry and medical significance of the flavonoids. Pharmacol Ther 96, 67–202.

[3] Dewick PM (2001) The shikimate pathway: aromatic amino acids and phenylpropanoids In Medicinal Natural Products: a Biosynthetic Approach, 2nd ed., pp. 137–186 [Dewick PM, editor]. Chichester: John Wiley.

Hence, flavonoids are associated with a broad spectrum of positive effects on human health, thanks to their antioxidative, anti-inflammatory, anti-mutagenic and anti-carcinogenic properties coupled with their capacity to modulate key cellular enzyme functions.

Flavonoids are used by vegetables for their growth and defence against plaques.[2] They belong to a class of low-molecular-weight phenolic compounds that are widely distributed in the plant kingdom and constitute one of the most characteristic classes of compounds in higher plants.
Many flavonoids are easily recognized as flower pigments in most angiosperm families. However, their occurrence is not restricted to flowers but are found in all parts of plants.[3]

Flavonoids have several subgroups, which include chalcones, flavones, flavonols and isoflavones. These subgroups have unique major sources. For example, onions and tea are major dietary sources of flavonols and flavones.

Currently there are **6000 flavonoids** that contribute to the colorful pigments of fruits, herbs, vegetables and medicinal plants.

2.

Quercetin, the queen of flavonoids[4]

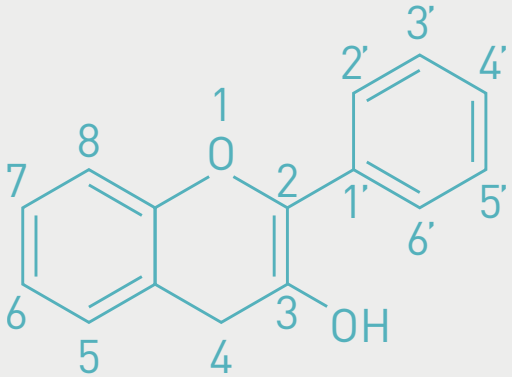
Quercetin is categorized as a flavonol, one of the six subclasses of flavonoid compounds. In Western populations, estimated daily intake of flavonols is in the range ofn20-50 mg/day. Of this, about 13.82 mg/day is in the form of quercetin-type flavonols.[5]

The variety of dietary flavonols is created by the differential placement of phenolic-OH groups and attached sugars. All flavonols, including quercetin, have in common a 3-hydroxyflavone backbone. The determination of whether a flavonol is considered to be of the quercetin type as opposed to a kaempferol or myricetin type, for example, is based on the location of phenolic-OH groups.

[4] Gregory S. Kelly, ND, Quercetin, Alternative Medicine Review, Volume 16, Number 2, 2011.

[5] Cao J, Zhang Y, Chen W, Zhao X. The relationship between fasting plasma concentrations of selected flavonoids and their ordinary dietary intake. Br J 14. Nutr 2010;103:249-255.

Figure 1 shows the possible attachment positions for **hydroxyl and glycosyl groups**



The International Union of Pure and Applied Chemistry (IUPAC) nomenclature for quercetin is 3,3',4',5,7 -pentahy-droxyflavanone (or its synonym 3,3',4',5,7-pentahydroxy-2-phenylchro- men-4-one).
This means that quercetin has an OH group attached at positions 3, 5, 7, 3', and 4'.

> **By definition quercetin is an aglycone, lacking an attached sugar. It is a brilliant citron yellow color and is entirely insoluble in cold water, poorly soluble in hot water, but quite soluble in alcohol and lipids.**

Quercetin-type flavonols (primarily as quercetin glycosides), the most abundant of the flavonoid molecules, 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.

Growing conditions might significantly influence the amount of quercetin in food, with evidence indicating that organically grown tomatoes have significantly higher quercetin aglycone content than conventionally produced tomatoes.[6]

As suggested by scientific publications, quercetin has antioxidant, antiaging, anti-aggregation and vasodilation properties.[7-9] Scientific literature highlights its potential use for maintaining well-being in situations of fatigue or stress.[10-11]

[6] Mitchell AE, Hong YJ, Koh E, et al. Ten-year comparison of the influence of organic and conventional crop management practices on the content of flavonoids in tomatoes. J Agric Food Chem 2007;55:6154-6159.

[7] Chondrogianni N, Kapeta S, Chinou I, Vassilatou K, Papassideri I, Gonos ES. (2010) Anti-ageing and rejuvenating efects of quercetin. Exp Gerontol. 45(10):763–71.

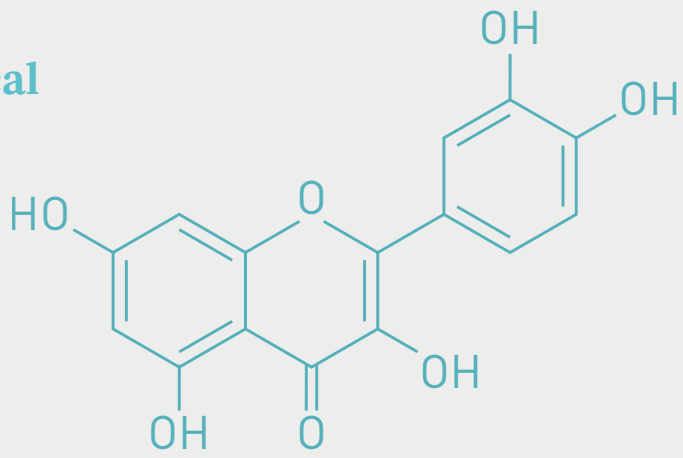
[8] Chopra M, Fitzsimons PE, Strain JJ, Thurnham DI, Howard AN. (2000) Nonalcoholic red wine extract and quercetin inhibit LDL oxidation without affecting plasma antioxidant vitamin and carotenoid concentrations. Clin Chem. 46(8 Pt 1):1162–70.

[9] 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.

[10] 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.

[1] D'Andrea G. (2015) Quercetin: a favonol with multifaceted therapeutic applications? Fitoterapia. 106:256–71.

Quercetin chemical composition



3.

Quercefit™: the most bioavailable quercetin

Like many botanical extracts and natural compounds, quercetin, while being potentially very effective for maintaining healthy conditions, on the other hand 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. To face such a challenge, Indena has adopted since years a "biomimetic approach".

QUERCEFIT™

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 may benefit Science, engineering, and medicine, to solve human problems.

The term "biomimetics" originates from the Greek words "bios" (life) and "mimesis" (to imitate), yet its definition is not as simple as just those two words. More specifically, biomimetics is a creative form of technology that uses or imitates nature to keep healthy levels in human lives. In biomimetics, Nature is the measure and the standard for judging appropriateness, sustainability and also the formal, strategic and ethical correctness of technological products and process innovations. The central idea is that nature, by necessity, has already solved many of the problems we are dealing with.

Phytosome™
THE BIOMIMETIC DELIVERY SYSTEM

NATURE AS MEASURE™ represents the very notion of biomimetics in literature and its philosophical origins. The search for a bio-mimetic approach to optimize actives bioabsorption of natural compounds in the full respect of their natural profile, has been pioneered by Indena with the development of Phytosome® delivery system.

Indena has developed some of the most innovative products and technologies on the market to optimize the bioabsorption of selected botanicals. Phytosome®, Indena's proprietary 100% food-grade biomimetic delivery system, is the result of a wide experience and deep knowledge in product and process research.
In its innovative and genuine inspiration by Nature, Phytosome® allows to maintain the original chaos of natural products according to the biomimetic principle of Nature as Measure™, without involving new chemical derivatives or new chemical entities, pharmaceutical excipients or structural modification of the ingredients, rather maintaining their tolerability over time and safety. In a continuous evolution and innovation of R&D value chain, every Phytosome® is specifically designed to optimize the bioabsorption of the selected botanical.

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).

Quercefit™: specifications

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

34-42% quercetin by HPLC

suggested dose: 250 mg once or twice a day

yellow powder for use in nutritional supplements

compliant with main worldwide markets food regulations (BELFRIT, US, EU)

high tolerability in individuals assuming antiplatelet agents, anticoagulants or living with diabetes

4.

Main applications

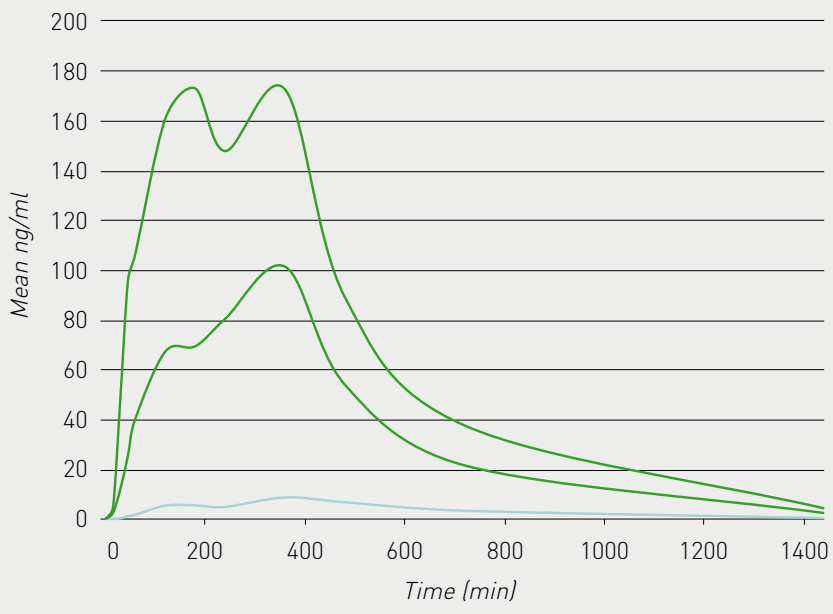
New recent studies suggest positive results in terms of bioavailability, efficacy in sports, discomforts and high tolerability for Quercefit™.

[12] 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.

Five human studies have been focused on Quercefit™, standardized in ≥36.0% and ≤42.0% of quercetin.

According to a published human pharmacokinetic study comparing the Indena formulation to unformulated quercetin, **it proved to be up to 20-fold more bioavailable and able to be used at lower dosages, preserving its profile of natural ingredient**.[12]

Twelve healthy volunteers of both sexes, aged 18-50 years, were administered orally with a dose of quercetin (500 mg) and two different doses of Quercefit™ (250 and 500 mg). Pharmacokinetic samples were collected at twelve time intervals (0h to 24h) after administration, and quercetin levels in plasma were measured by HPLC/MS/MS.



AUC IMPROVEMENT

Quercefit™ 500mg	20x
Quercefit™ 250mg	10x
Quercetin 500mg	1x

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 (2018). https://doi.org/10.1007/s13318-018-0517-3

Sports performance/recovery

Quercefit™ demonstrated a significant oral absorption of quercetin, both in terms of AUC, T_{max} and with a maximum concentration of 223.10 ± 16.32 ng/ml at the highest dose, significantly improved compared to unformulated quercetin (10.93 ± 2.22 ng/ml , p <0.0001) and the lowest dose (126.35 ± 14.79 ng/ml, p <0.005), thus also suggesting a dose-related absorption profile.
Most importantly, Quercefit™ allows to reach optimized quercetin plasma levels in line with a diet rich in vegetables and fruits (such as onions and apples).

Furthermore, the effectiveness of 250 mg (twice a day) of the ingredient emerged in a controlled human study on amateur healthy athletes practicing triathlon according to "Sprint" format (100 minutes for swimming 750 m + cycling 20 km + running 5 km).[13]
Quercefit™ has statistically maintained (P <0.05) the physical resistance, measured as time to complete the race, the performance and optimized recovery, minimizing stresses such as muscle discomfort and post-training cramps.
The oxidative stress measured was also statistically lower (p <0.05 compared to the control group).
No undesirable effects were observed, showing excellent tolerability to repeated supplementation.
This study suggests that oral supplementation with Quercefit™ can optimize sports performance and physical recovery.

This study suggests that oral supplementation with Quercefit™ can optimize sports performance and physical recovery.

[13] Riva A. et al. Quercetin Phytosome® in triathlon athletes: a pilot registry study Minerva Medica 2018 August;109(4):285-9.

[14] http://www.salute.gov.it/portale/salute/p1_5.jsp?lingua=italiano&id=158&area=Malattie_del_sistema_immunitario

Did you know?

Allergy is the most common immune disease, characterized by an inflammatory reaction towards harmless agents which are present in the external environment: components of inspired air (pollen, mold, dust of the domestic or working environment), components of food or drugs, poison of stinging insects. These substances are called "allergens" due to their common characteristic of inducing allergies.

Allergic inflammatory pathologies have an important impact on people's quality of life and relevant health costs: recent epidemiological studies conducted in Italy indicate that 25% of the population aged between 18 and 44 suffer from allergic rhinitis and 5% suffer from asthma.[14]

The spread of allergic diseases is increasing in Europe and, also due to climate change, is no longer limited to specific seasons or environments.

Respiratory allergies are the most common form of allergies in Europe and the world. **Respiratory allergies are mainly characterized by lacrimation, sneezing, sometimes coughing and asthma: symptoms that affect breath functionality, which can be objectively measured testing the PEF – Peak Expiratory Flow, the maximal rate that a person can exhale during a short maximal expiratory effort after a full inspiration.**

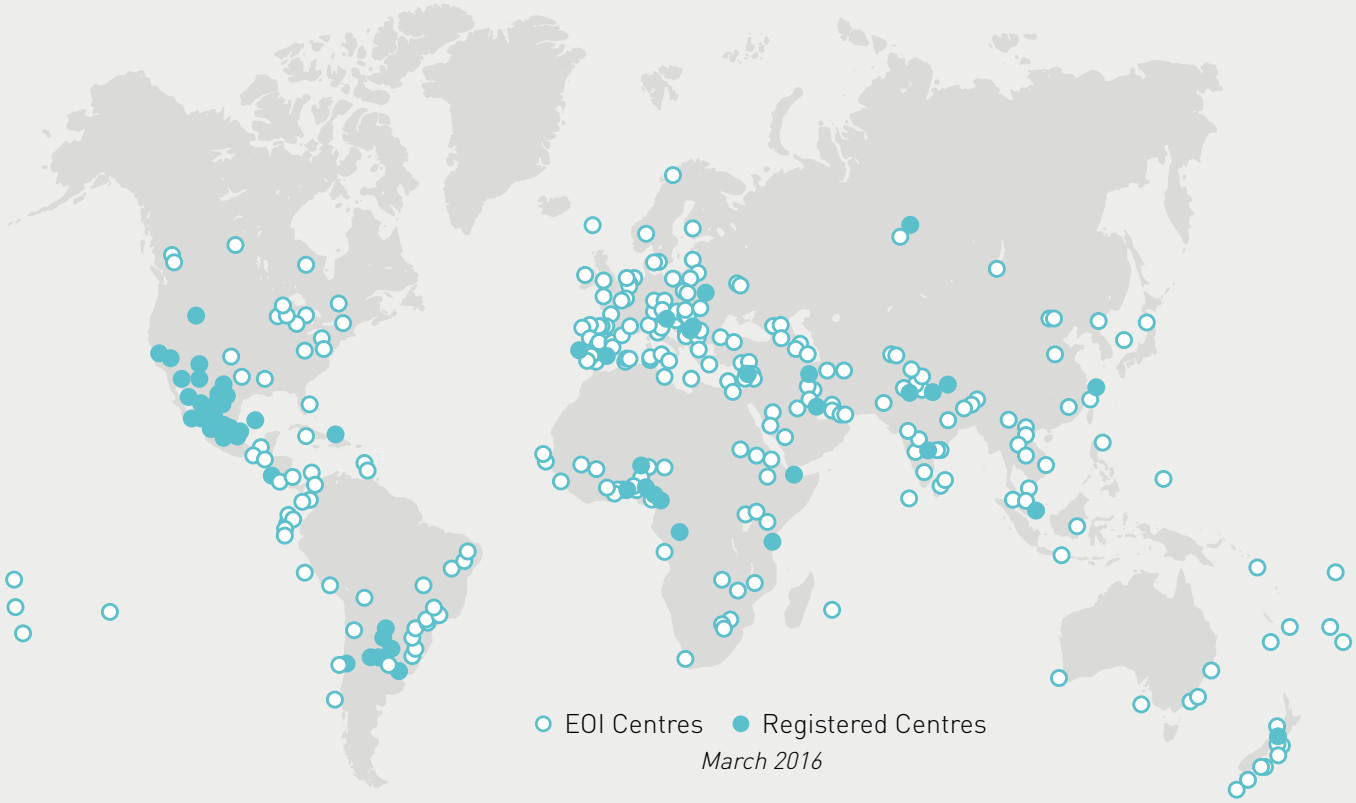
Science makes different remedies available to manage symptoms of allergies and solve allergic discomforts, from drugs to nutritional supplements.

Allergic rhinitis affects **60%**
of the European population.

From 15% to 20% of these patients
suffer from a severe form of the disease.

It is estimated that allergic asthma affects
5%-12% of the European population.[15]

Global Asthma Network Centres



[15] http://www.salute.gov.it/portale/salute/p1_5.jsp

Allergic discomforts

The optimized bioavailability of quercetin formulated with Indena's Phytosome® delivery system has recently allowed Quercefit™ to achieve very interesting results also for the maintenance of well-being by sensitive or intolerant subjects, as demonstrated by two human studies.[16,17]

A recent human study on supplementary management of discomforts during allergy seasons, , evaluated the benefits of Quercefit™ in synergy with the standard management (SM) in otherwise healthy subjects experiencing discomforts during allergy seasons and taking only the standard management (SM).[16]

After 30 days of supplementation, using either 1 or 2 tabs/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™ demonstrated a reduction of day (up to 50%) and night (up to 70%) intermittent discomfort frequency, and a significant improvement of the breath function (Peak Expiratory Flow) in mild persistent discomforts.

The supplementary use of Quercefit™ synergistically improved the use of the best available remedy, while optimizing additional discomfort conditions and keeping a low oxidative stress with a very good safety profile.

In a second human study focussing on local skin discomforts, Quercefit™ has been administrated for just 3 days, followed by a histamin local skin stimulus.

Compared to the control, only the healthy volounteers administered with Quercefit™ shown a statistically significant dose-dependent control of all main local conditions and a skin conditions amelioration with capillary filtration reduction.[17]

> **These recent human studies show a potential beneficial effect of Quercefit™ in controlling the most common discomforts linked to allergy era and individual intolerances.**

Lastly, to further confirm the positive safety profile of Quercefit™, a preliminary human study was conducted in order to investigate any interaction of this complementary and natural approach with common standard synthetic drugs, preventing any possible harmful effect.[18]

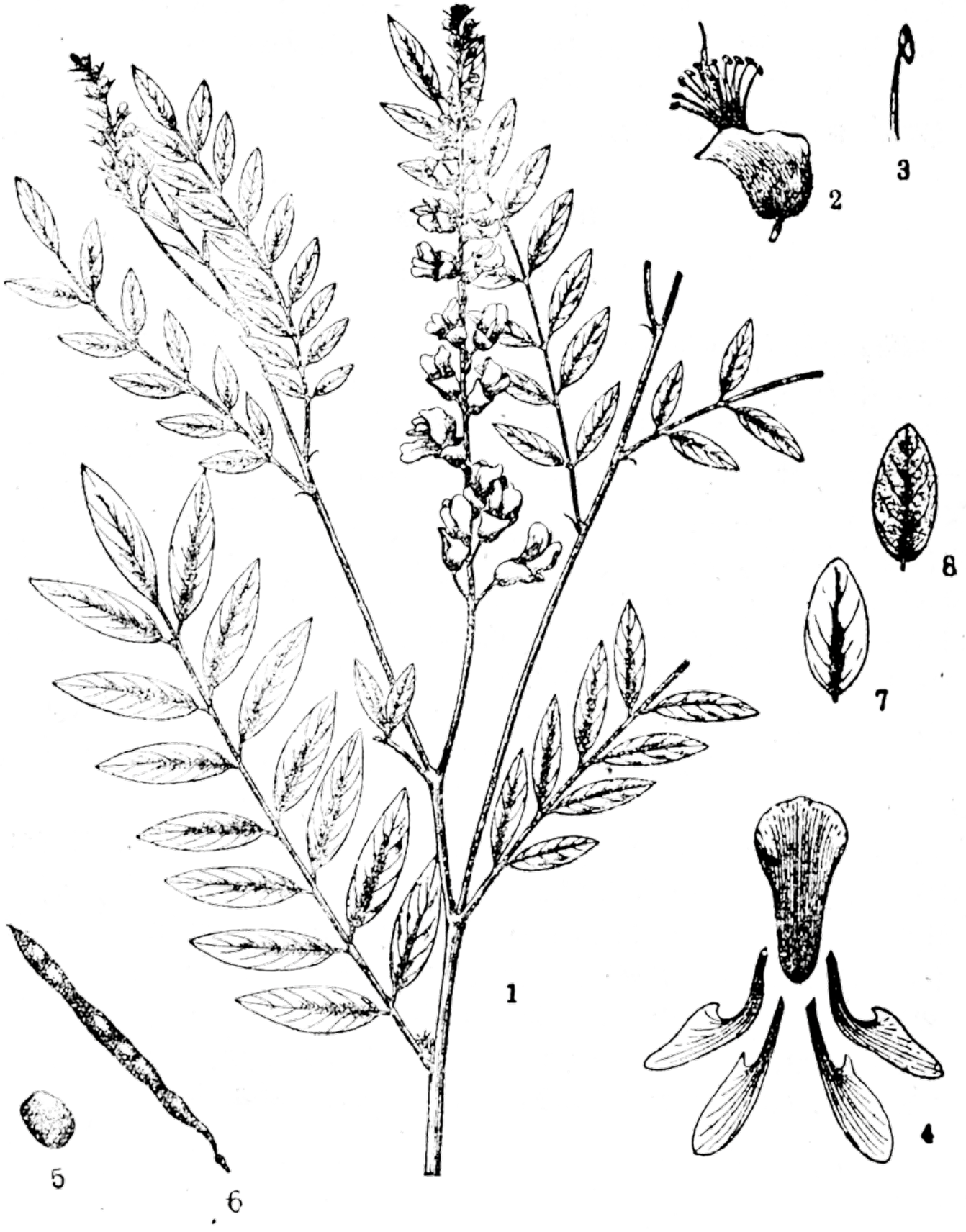
The preliminary results suggest that Quercefit™ might not alter the activity of the most common antiplatelet agents (acetylsalicylic acid, ticlopidine or clopidogrel, after 10 days of supplementation), has no impact in stable patients treated with warfarin or dabigatran after 20 days of supplementation and might not influence the metabolic control of diabetic patients taking metformin. [19]

[16] Cesarone, M. R., et al. Minerva medica (2019)

[17] Manuscript submitted

[18] Riva A, Corti A, Belcaro G, Cesarone MR, Dugall M, Vinciguerra 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.

[19] Riva A et al, Interaction study between antiplatelet agents, anticoagulants, diabetic therapy and a novel delivery form of quercetin. Minerva Cardioangiol. 2018 Sep 13. doi: 10.23736/S0026-4725.18.04795-3.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