

QUERCETIN PHYTOSOME™:
A MULTI-TARGET ALLY FOR HEALTHY AGING

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indena
 SCIENCE IS OUR NATURE SINCE 1971

100 YEARS

0

WHAT IS AGING?

Aging, is defined as the **inevitable physiological decline** over the lifespan of an organism that weakens homeostasis and increases vulnerability to environmental challenge.

Health in older age is **not** random

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INFLAMMAGING: THE COMMON SOIL OF AGE-RELATED DISORDERS

2

2

PRO-INFLAMMATORY vs ANTI-INFLAMMATORY AGENTS: A CRITICAL BALANCE IN HEALTHY AGING

PRO-INFLAMMATORY AGENTS

ANTI-INFLAMMATORY AGENTS

3

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CAN WE IMPROVE OUR HEALTHSPAN WITH BOTANICALS?

lifespan

healthspan

Healthy aging

"Positive" Aging --- live longer and better

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QUERCETIN: A VERSATILE FLAVONOID WITH MULTIPLE BIOLOGICAL ACTIVITIES

Anti-inflammatory

Anti-allergic

Anti-hypertensive

Analgesic

Cardiovascular protection

Antitumor and Antibacterial

Sports nutrition

Immunomodulation

Neuroprotection (Cognition)

365 DAYS

5

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BOTANICALS AND ORAL BIOAVAILABILITY: AN OPEN ISSUE REQUIRING INNOVATION



Despite their acknowledged health benefits, **botanical nutraceuticals** often have poor water solubility and limited intestinal absorption which hampers the efficacy of oral bioavailability.

QUERCETIN HAS POOR BIOAVAILABILITY

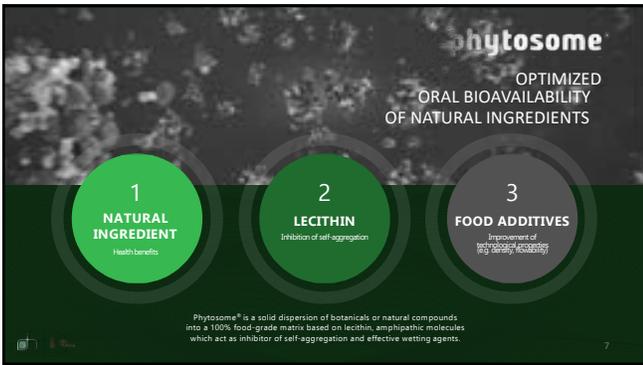
Quercetin, like many other polyphenols, is characterized by very poor oral bioavailability, which prevents efficacious plasmatic levels from being reached and undermines its remarkable multi-action health properties:

- Poor water solubility (hydrophobicity and crystallinity)
 - Poor permeability
- Extensive first pass metabolism
 - Rapid metabolism
- Bacterial degradation of the phenol moiety



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PHYTOSOME[®]

OPTIMIZED
ORAL BIOAVAILABILITY
OF NATURAL INGREDIENTS

1

**NATURAL
INGREDIENT**

Health benefits

2

LECITHIN

Inhibition of self-aggregation

3

FOOD ADDITIVES

Improvement of
technological properties
(e.g. density, wettability)

Phytosome[®] is a solid dispersion of botanicals or natural compounds into a 100% food-grade matrix based on lecithin, amphipathic molecules which act as inhibitor of self-aggregation and effective wetting agents.

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QUERCEFIT[®]

OPTIMIZED
ORAL BIOAVAILABILITY
OF NATURAL INGREDIENTS

1

QUERCETIN

2

**SUNFLOWER
LECITHIN**

3

FOOD ADDITIVES

Maltodextrin
Silicon dioxide

MANUFACTURING SOLVENT: ETHANOL
International patent application number PCT/EP2018/054533 filed on 23/02/2018

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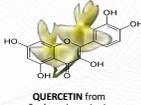
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WHAT IS **QUERCEFIT**®

Innovative food grade delivery system of quercetin, deriving from flower buds of *Sophora japonica* L., formulated with **Phytosome**® proprietary technology to optimize its biological absorption, supporting the overall wellbeing in many conditions.

Standardized in quercetin (34-42% by HPLC).

Recommended daily dosage: 250-500 mg / day



QUERCETIN from *Sophora japonica* L.

+



INDENA TECHNOLOGY TO IMPROVE BIOAVAILABILITY

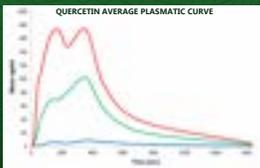
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HEALTH-FOOD INGREDIENT

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QUERCEFIT SOLVES THE ISSUE OF POOR ABSORPTION: IMPROVEMENT OF QUERCETIN ABSORPTION UP TO 20 TIMES



| INGREDIENT | DOSAGE | AUC IMPROVEMENT |
|------------------------|--------|-----------------|
| QUERCEFIT | 500 mg | 20 X |
| QUERCEFIT | 250 mg | 10 X |
| UNFORMULATED QUERCETIN | 500 mg | 1 X |

Risk A, Sano M, Marzulli C et al. Improved Oral Absorption of Quercetin from Quercetin Phytosome, a New Delivery System Based on Food Grade Lectin™. Eur J Drug Metab Pharmacol (2018) 100:100-106. doi:10.1016/j.ejdr.2018.02.001

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QUERCEFIT : NO DRUG-INTERACTION AND HIGH TOLERABILITY

POLYPHARMACY IS COMMONLY DEFINED AS THE CONSUMPTION OF A MULTIPLE NUMBER OF MEDICATIONS, AND IS CONSIDERED A RISK FACTOR FOR FALL THROUGH ADVERSE EFFECTS OF DRUG-DRUG OR DRUG- DISEASE INTERACTIONS.

| DRUG THERAPY | ADMINISTRATION TIME | UNALTERED PARAMETERS |
|--|---------------------|---|
| ANTIPLATELET AGENTS (acetylsalicylic acid, ticlopidine, clopidogrel) 10 individuals | 10 days | BT (Bleeding Time) |
| ANTICOAGULANT AGENTS (warfarin, dabigatran) 10 individuals | 20 days | INR (International Normalized Ratio) Platelets Levels |
| ANTIDIABETIC THERAPY (metformin) 10 individuals | 20 days | Glycaemia Glycated Hemoglobin |

QUERCEFIT®
SHOWED NO INTERACTIONS
WITH COMMONLY-PRESCRIBED
MEDICATIONS, CONFIRMING ITS
FAVORABLE SAFETY PROFILE

Risk A, et al. "Interaction Study between antiplatelet agents, anticoagulants, diabetic therapy and a novel delivery form of quercetin" Minerva cardiolangiologica (2018)

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WHAT IS THE UNDERLYING CONDITION OF AGE-RELATED DISEASE? **INFLAMMATION**

The quercetin complex has a protective effect against tissue damage induced by a cytokine storm.

Quercetin's ability to inhibit pro-inflammatory activities can be utilized against a number of conditions caused by inflammation, especially those that contribute to aging.

© 2012 H.B. Rothman, D.S. Anderson, R.L. Shaker, B.A.M. Al-Dabbas et al. The Anti-Cytokine Storm Activity of Quercetin, Zinc, and Vitamin C Complex. Adv. Virol. 2012, vol. 3, 2012, 117-120.

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APPLICATIONS OF **QUERCEFIT**

EVIDENCE-BASED SCIENCE

SPRING/SUMMER

ALLERGY AND RESPIRATORY HEALTH

FALL/WINTER

IMMUNITY AND ANTI-VIRAL ACTIVITY

HEALTHY AGING: SENOLYTIC

SPORTS NUTRITION

EYE HEALTH

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IMMUNITY AND ANTI-VIRAL ACTIVITY

YEAR-ROUND IMMUNE SUPPORT
APPLICATION: FALL/WINTER

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QUERCETIN'S MULTIPLE VIRAL TARGETS

JAPANESE ENCEPHALITIS VIRUS (JEV): a low antiviral activity of quercetin with IC_{50} = 212.1 μ g/mL was enough to reduce JEV, a virus responsible for the mosquito-borne disease Japanese encephalitis, activity *in vitro*.

MOUSE HEPATITIS VIRUS (MHV) AND DENGUE VIRUS (DENV): a low antiviral activity of quercetin with IC_{50} = 125.00 μ g/mL and IC_{50} = 176.76 μ g/mL was effective at inhibiting both MHV and DENV, respectively, *in vitro*.

ANTIVIRAL

HEPATITIS C VIRUS (HCV): The NS3 protease is largely involved in the production and replication of HCV. Quercetin was found to inhibit NS3 activity in a dose-dependent manner *in vitro*.

INFLUENZA A: Quercetin was shown to impede virus cell entry, by targeting the HA2 subunit responsible for viral-cell fusion.

RHINOVIRUS: Addition of quercetin *in vitro* reduced pro-inflammatory cytokine expression, inhibited virus replication, and improved lung function.

Mazuch, Azevedo, et al. "Pharmacological applications of quercetin and its derivatives." *Tropical Journal of Pharmaceutical Research* 13.9 (2014): 1443-1446.
 Abd-Elhameed, et al. "Inhibition of Hepatitis C Virus by the Flavonoid Quercetin is Associated to Inhibition of NS3 Protease Activity." *Journal of Pharmaceutical Sciences* 93 (2012): 454-458.
 Chiu, et al. "Inhibition of antiviral activities of hepatitis viruses: Thymine, acyclovir, quercetin and camostat in mouse coronavirus and dengue virus infection." *Asian Pacific Journal of Tropical Biomedicine* 3 (2013): 1-7.
 Wu, Weizhen, et al. "Quercetin as an antiviral agent inhibits hepatitis A virus (HAV) entry." *Virus* 8 (2016): 8.
 Gokhale, Rajendra, et al. "Quercetin inhibits infectious hepatitis in mice and in man." *Antonie van Leeuwenhoek* 68.2 (2012): 209-211.

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ACTIVITIES OF QUERCETIN IN COVID-19

INHIBITION OF VIRAL PROTEASES

Proteases play essential roles in viral replication and assembly. Quercetin was evaluated as the main protease inhibitor based on COVID-19. Quercetin was found to be the most effective inhibitor of the main protease activity in SARS-CoV-2 cells. Quercetin was found to be the most active in the COVID-19 viral active site.

INHIBITION OF VIRAL SPIKE-PROTEIN

Quercetin was identified between the two binding sites of the SARS-CoV-2 spike protein ACE2 receptor interaction. This potentially binding site to block the recognition of host cells and/or disrupt their virus interactions.

REGULATION OF HUMAN GENES ENCODING VIRUS TARGETS

Quercetin was found to alter the expression of 88 of 183 (48%) of human genes encoding protein targets of SARS-CoV-2, that potentially interacting with the Nucleocapsid (N) protein of SARS-CoV-2 viral proteins in human cells.

POWERFUL ANTINFLAMMATORY ACTIVITY

Functional similarity was reported between deacetylase and quercetin, with both being potentially quercetin (Pqq) inhibitors. Pqq, a reversible histonease, helps in the reduction of histone levels. In an inflammatory condition, increased histone levels have been observed to inhibit the expression and activity. As Pqq inhibitors, both deacetylase and quercetin are expected to provide similar or "synergistic" like combination in COVID-19 patients.

Chen, et al. "Inhibition of COVID-19 Main Protease (Mpro) from SARS-CoV-2 by Quercetin." *Journal of Pharmaceutical Sciences* 101 (2020): 1-10.
 Wang, et al. "Quercetin Inhibits SARS-CoV-2 Replication and Assembly." *Journal of Pharmaceutical Sciences* 101 (2020): 1-10.
 Wang, et al. "Quercetin Inhibits SARS-CoV-2 Replication and Assembly." *Journal of Pharmaceutical Sciences* 101 (2020): 1-10.

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VIRAL CLEARANCE VS. IMMUNE RESPONSE: EXAMPLE FROM COVID-19

However, immune response is already enhanced and rapidly increasing, even as viral load decreases. This can lead to a state of **chronic inflammation**.

Viral load rapidly increases and then steadily drops

VIRAL CLEARANCE IS NOT ENOUGH.

INGREDIENTS FORMULATED TO MODULATE INFLAMMATION ARE NECESSARY TO ACHIEVE A HEALTHY STATE.

https://www.worldscientific.com/doi/abs/10.1142/9789811204444_ch011

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QUERCEFIT IMMUNITY AND ANTI-VIRAL ACTIVITY STUDIES – STUDIES IN COVID-19

1)

2)

© 2020, Research, et al. "Positive Therapeutic Effects of Adjunct Quercetin Supplementation Against Early Stage COVID-19 Infection: A Prospective, Randomized, Controlled, and Open-Label Study." International Journal of General Medicine 14(2020): 2008.
© 2020, Research, et al. "Therapeutic Effect of Quercetin in the Early Stage of COVID-19 Infection: A Randomized, Controlled, and Open-Label Study." International Journal of General Medicine 14(2021): 2007-2012.

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1st STUDY

STUDY DESIGN:
Prospective, randomized, controlled, open-label.
Registered on [clinicaltrials.gov](#) identified as no. NCT04578158.

STUDY POPULATION:
n. 152 subjects, >18 years old of either gender, with confirmed infection of SARS-CoV-2 and mild/moderate typical symptoms manageable at home including fever, dyspnea (with oxygen saturation >93%), dry cough, sore throat, cold, rhinorrhea and conjunctivitis.

STANDARD CARE (SC):
Home therapy, possibly including analgesic, anti-fevers, oral steroids, antibiotics as established by hospital guidelines. Normal diet. Abstinence from supplements containing lactoferrin, zinc, vitamin C and vitamin D.

PRIMARY ENDPOINTS:

- Need and length of hospitalization
- Need of non-invasive oxygen therapy
- Progression to intensive care unit
- Death

SECONDARY ENDPOINTS:

- Adherence to supplementation
- Tolerability of supplementation
- Side effects of supplementation

© 2020, Research, et al. "Positive Therapeutic Effects of Adjunct Quercetin Supplementation Against Early Stage COVID-19 Infection: A Prospective, Randomized, Controlled, and Open-Label Study." International Journal of General Medicine 14(2020): 2008.

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QUERCEFIT MET PRIMARY ENDPOINTS

AS AN ADD-ON TO STANDARD CARE, QUERCEFIT HAS POSITIVE EFFECTS ON:

NEED FOR HOSPITALIZATION

-68%

(as number of individuals hospitalized compared with standard care)

LENGTH OF HOSPITALIZATION

-77%

(as number of days of hospitalization compared with standard care)

NEED FOR NON-INVASIVE OXYGEN THERAPY

-93%

(as number of individuals needing oxygen compared with standard care)

PROGRESSION TO INTENSIVE CARE UNIT

0

(as number of individuals in ICU, vs 8 in control group)

NUMBER OF DEATHS

0

(as number of dead individuals, vs 3 in control group)

© 2020, Research, et al. "Positive Therapeutic Effects of Adjunct Quercetin Supplementation Against Early Stage COVID-19 Infection: A Prospective, Randomized, Controlled, and Open-Label Study." International Journal of General Medicine 14(2020): 2008.

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QUERCEFIT

**HEALTHY AGING:
SENOLYTIC**

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WHAT IS SENEESCENCE?

SENEESCENCE IS A CELLULAR STRESS RESPONSE CHARACTERIZED BY A PROLONGED AND GENERALLY IRREVERSIBLE CELL CYCLE ARREST:

Senescence can be triggered by stressful exogenous insults (e.g. oxidative stress, exogenous toxic compounds, virus-infections, disease state, etc.) and certain physiologic processes (e.g. aging process).

It triggers profound phenotypic changes such as:

- cell macromolecular damage (e.g. DNA, enzymes)
- altered metabolism
- production of a bioactive secretome, referred to as the Senescence-Associated Secretory Phenotype (SASP), including pro-inflammatory cytokines, chemokines, pro-coagulatory factors

RESEARCH TO-DATE SUPPORTS THE USE OF QUERCETIN AS A SENOLYTIC AGENT

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WHY QUERCETIN FOR SENEESCENCE?

Removing senescent cells is required to increase the likelihood of **lifespan extension**.

The combination of **dasatinib and quercetin (D+Q)** was established as the world's first senolytic drug in 2015.

D+Q was effective in **eliminating** senescent mouse embryonic fibroblasts.

Ingredients being explored to help with the removal of senescent cells include **quercetin**, grape seed extract, fisetin...

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QUERCETIN AS A SENOLYTIC IN A COVID-19 (VIRUS) MODEL

RESPIRATORY MUCOSA OF NASOPHARYNGEAL SPECIMENS FROM COVID-19 PATIENTS AND NON COVID-19 INDIVIDUALS (% of positive cells)



Investigations of COVID-19 patients showed the presence of:

- High number of senescent cells in their airway mucosa
- High levels of SASP (e.g. pro-inflammatory cytokines, chemokines, pro-coagulatory factors) in blood

Quercetin flavonoid in combination with dasatinib allowed a **substantial reduction of senescent cells** in the respiratory tracts of COVID-19-infected animals and a **drastic reduction of SASP cytokines** in their blood serum.

Quercetin addresses the **highest number of cellular targets** compared with other senolytic agents.

Lee, S., Xu, C., Stoppel, J. and Klein-Heckbradt, A. *Viruses* 2021, 13(10), 1988. <https://doi.org/10.3390/v13101988>

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THE SENOLYTIC POTENTIAL OF QUERCEFIT

Nature Magazine (September 2021)
"Virus-induced senescence (VIS) is a trigger and therapeutic target for COVID-19"

As viral load increases, senescent cells increase

VIRUS

SENESCENT CELLS

As senescent cells increase, the opportunity for viruses to propagate increases

Science Magazine (July 2021)
"Senescent cell depletion reduces mortality in mice from coronavirus infection"

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QUERCEFIT

ONGOING CLINICAL TRIAL: TARGETING CELLULAR SENESCENCE WITH SENOLYTICS FOR SKELETAL HEALTH IN OLDER HUMANS

To determine if senolytic drugs reduce senescent cell burden and reduce bone resorption markers/increase bone formation markers in elderly women.

Randomized, open-label, parallel assignment

120 participants

Dasatinib + Quercefit® vs. Fisetin vs. Untreated Control

Duration: 20 weeks
Dosing: Dasatinib (100mg) for 2 days + Quercefit® (1000mg) for 3 days; Intermittent schedule repeating every 28 days
Fisetin (~20 mg/kg/day) for 3 days; Intermittent schedule repeating every 28 days
Five total dosing periods throughout the entire intervention

C-terminal telopeptide of type I collagen (CTX) and propeptide of type I collagen (P1NP)

Collaboration with Mayo Clinic

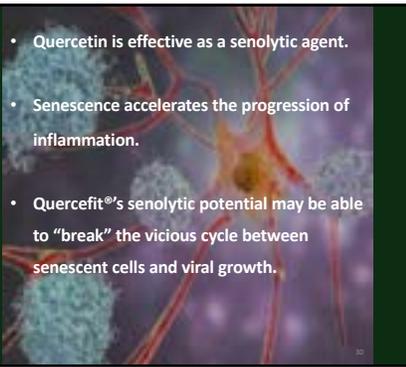
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QUERCEFIT
 In HEALTHY AGING:
 SENOLYTIC
KEY TAKEAWAYS

A RECENT STUDY IN A
 HIGH-IMPACT JOURNAL
 SHOWED:

- Quercetin is effective as a senolytic agent.
- Senescence accelerates the progression of inflammation.
- Quercetin's senolytic potential may be able to "break" the vicious cycle between senescent cells and viral growth.



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APPLICATIONS OF **QUERCEFIT**

EVIDENCE-BASED SCIENCE

SPRING/SUMMER FALL/WINTER

ALLERGY AND RESPIRATORY HEALTH IMMUNITY AND ANTI-VIRAL ACTIVITY HEALTHY AGING: SENOLYTIC SPORTS NUTRITION EYE HEALTH

A MULTI-TARGET ALLY FOR HEALTHY AGING



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NOT JUST **QUERCEFIT**
 OTHER INGREDIENTS FOR HEALTHY AGING

MERIVA CURCUMIN POLYPHENOLS

SARCOPENIA OSTEOGENIA

Age of participants: > 65 years Age of participants (standard management): 70.82 ± 1 Age of participants (standard management + Meriva®): 71.02 ± 1

miti xol

KNEE OSTEOARTHRITIS

Age of participants: mean age: 62.46 ± 8.45

FRANZBLAU, et al. "A novel phytopharmacological approach of curcumin (Meriva 30) preserves muscular mass in healthy aging subjects." Eur Rev Med Pharmacol 51:25-4 (2016): 762-766.
 IMAI, et al. "Effects of curcumin-based supplementation in asymptomatic subjects with low bone density: a preliminary 28-week supplement study." European Review for Medical and Pharmacological Sciences 2017; 21: 1088-1095.
 BERNARDINI, et al. "Effects of curcumin-based supplementation in asymptomatic subjects with low bone density: a preliminary 28-week supplement study." European Review for Medical and Pharmacological Sciences 2017; 21: 1088-1095.
 BERNARDINI, et al. "Effects of curcumin-based supplementation in asymptomatic subjects with low bone density: a preliminary 28-week supplement study." European Review for Medical and Pharmacological Sciences 2017; 21: 1088-1095.
 BERNARDINI, et al. "Effects of curcumin-based supplementation in asymptomatic subjects with low bone density: a preliminary 28-week supplement study." European Review for Medical and Pharmacological Sciences 2017; 21: 1088-1095.

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THANK YOU FOR YOUR ATTENTION



SCIENCE IS OUR NATURE. SINCE 1921



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