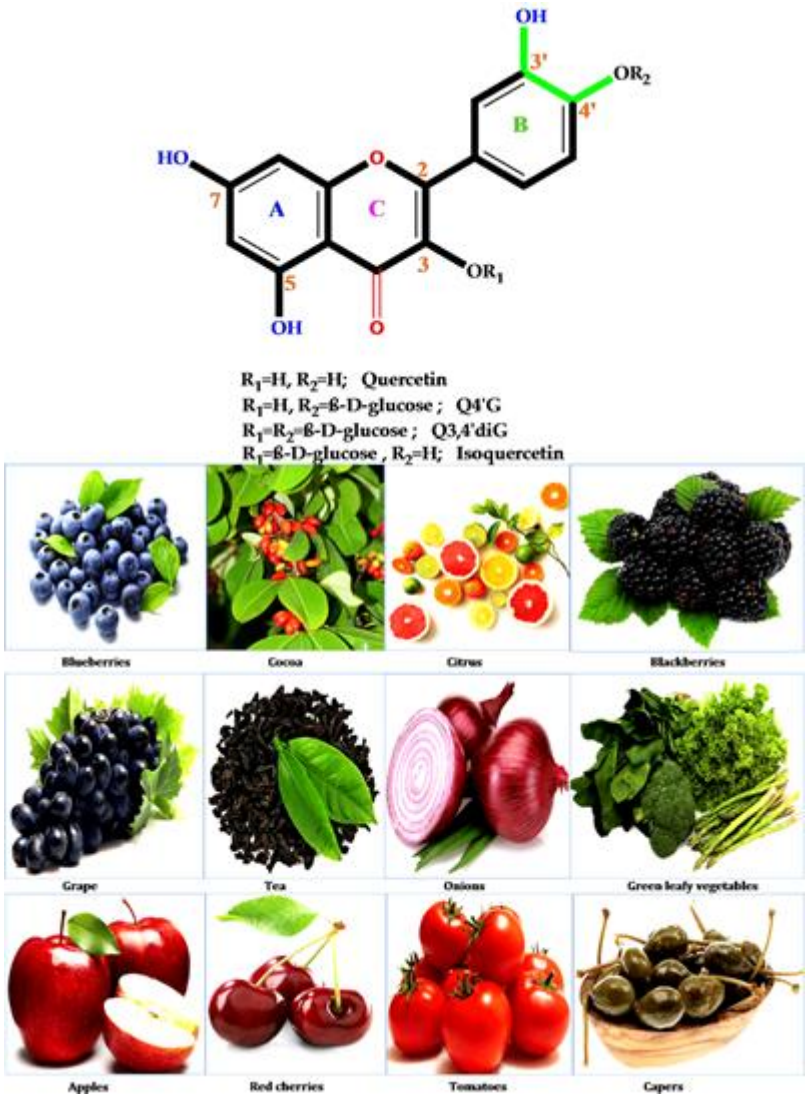
Natural products derived from plants, honey, and marine sponges that have anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) properties. https://discovermednews.com/natural-products-have-anti-sars-cov-2-properties/ Flavonoids are an important polyphenol group, found in fruits, vegetables, grains, bark, roots, stems, tea, and wine. Flavonoids contain several subgroups, including chalcones, flavones, isoflavones, and flavonols. The most studied flavonols are kaempferol, quercetin, myricetin and fisetin. The Nobel Prize winner Szent-Gyorgyi discovered ascorbic acid (vitamin C) and the flavonoid quercetin (at that time labeled as vitamin P). Quercetin is one of the most important plant molecules, with antioxidant, antiatopic, pro-metabolic, anti-inflammatory, antiviral, anticoagulant, immunoprotective, and neuroprotective activities. Numerous studies demonstrated the positive effects of quercetin in COVID-19 or post-COVID-19 syndrome, including direct inhibition of viral entry into the host cells, inhibition of viral replication, anti-inflammatory, antioxidant, immunomodulatory, and neuroprotective effects.

The chemical name of quercetin is 3,3′,4′,5,7 pentahydroxyflavone, and it is not synthesized within the human body. The word “quercetin” comes from the Latin word “quercetum”, which means “oak forest”. Quercetin has been found in various vegetables and fruits, such as berries, lovage, capers, cilantro, dill, apples, and onions, where it is conjugated with residual sugars to form quercetin glycosides. It is worth noting that quercetin is insoluble in cold water and sparingly soluble in hot water, but it is completely soluble in lipids (olive pomace oil enhances oral absorption) and alcohol. The oral bioavailability of quercetin is low, with estimates that only 20% of the administered dose reaches the blood. Upon oral administration at a dose of 200 mg, the maximum plasma concentration is 2.3 ± 1.5 μg/ml. In human subjects, pharmacokinetic studies have shown no adverse effects following up to 1,000 mg of quercetin per day. In some instances, taking more than 1,000 mg of quercetin per day may cause mild symptoms, such as headaches and stomach aches. https://doi.org/10.22038/ajp.2023.22920



Structures and most abundant sources of quercetin and its derivatives. The illustration from the article of Rasouli H et al. *International Journal of Food Properties*, 2017; *20*(sup2), 1700–1741.

Positive effects of quercetin in COVID-19 or post-COVID-19 syndrome

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, positive-sense, single-stranded RNA virus. Its genome encodes four structural proteins, namely the spike (S), envelope (E), nucleocapsid (N), and membrane (M) protein. The S protein is a glycosylated homotrimer with each monomer composed of subunits S1 and S2, separated by host cell proteases. The S1 domain comprises the N-terminal domain (NTD), the receptor binding domain (RBD) with a receptor binding motif (RBM), and two C-terminal domains. The RBD of the S1 subunit recognizes the human angiotensin-converting enzyme 2 receptor (ACE2), which is responsible for attachment to host cells.

Both *in vitro* and *in vivo* studies have demonstrated that quercetin has antioxidant, anti-

inflammatory, antiviral, immunoprotective, antiatopic, and pro-metabolic effects. Quercetin and its derivatives have shown inhibitory activity against many viruses including human respiratory syncytial virus (HRSV), herpes simplex virus (type 1 and 2), hepatitis B and C virus, parainfluenza virus (type 3), SARS-CoV-1, and SARS-CoV-2. The incubation with quercetin pentaacetate inhibited HRSV adhesion on the surface of human epithelial cells and down-regulated viral replication. https://doi.org/10.22038/ajp.2023.22920

Positive effects of quercetin in SARS-CoV-2 infection include:

1. A direct inhibition of viral entry into the host cells

A recent computational docking model study, which investigated small molecules capable of binding to either SARS-CoV-2 S protein or the S protein/human ACE2 interface, has identified quercetin as one of the highest-scoring ligands at the S protein/ACE2 interface. Moreover, the combination of quercetin and the structurally related flavone luteolin, thought to be powerful blockers of the RBD on the SARS-CoV-2 S1 subunit, may provide additional benefits. Also, quercetin inhibits the acid sphingomyelinase ceramide system, which is remarkably involved in SARS-Cov-2 internalization into the host epithelial cells. https://doi.org/10.1016/j.ejphar.2021.174615

2. Inhibition of viral replication

The nuclear factor erythroid 2-related factor 2 (NRF2), also known as nuclear factor erythroid-derived 2-like 2, transcriptionally upregulates a network of cytoprotective genes, including antioxidant genes, such as genes encoding for glutathione biosynthesis, heme oxygenase-1, and several other antioxidant proteins. A study conducted on lung biopsy samples from individuals diagnosed with COVID-19 found that the NRF2 signaling pathway was suppressed, suggesting that activation of NRF2 triggers responses against SARS-CoV-2. Several studies have reported that quercetin is a potent NRF2 agonist. In a mouse model, feeding with quercetin activated the NRF2 pathway in the lungs, as evidenced by the expression of NRF2-regulated genes.

The main protease of SARS-CoV-2, or 3-chymotrypsin–like protease (3C-like protease), is activated after coronavirus infections. Due to its proteolytic activity, 3C-like protease plays a key role in the replication of coronaviruses. Previous studies have demonstrated that quercetin and its derivatives can inhibit 3C-like protease by destabilizing its structure. https://doi.org/10.1016/j.jpha.2021.09.009

3. Anti-inflammatory and antioxidant activities

Quercetin can suppress inflammatory responses by scavenging free radicals and significantly reducing tumor necrosis factor-alpha (TNF-α) generation. Also, quercetin inhibits pro-inflammatory pathways activated by the nuclear factor kappa B (NF-κB) pathway, which triggers the expression of interleukin (IL)-6, c–reactive protein, and cyclooxygenase-2. Quercetin also reduces inflammatory mediators including prostaglandins and leukotrienes by inhibiting inflammatory enzymes such as COX and lipooxygenase. The co-administration of vitamin C and quercetin exhibits a synergistic effect due to their

overlapping antiviral and immunomodulatory properties. https://doi.org/10.1016/j.jpha.2021.09.009

4. Immunomodulatory activities

Quercetin may modulate immune system responses, affecting the Th1/Th2 balance. Incubation of cultured blood peripheral mononuclear cells with quercetin resulted in stimulation of T-helper cells to release Th-1-derived interferon-γ and downregulation of Th2-derived IL-4. *In vivo,* quercetin administration improved natural killer cell lytic activity, neutrophil chemotaxis, and lymphocyte proliferation.

5. Neuroprotective effects of quercetin

Quercetin has neuroprotective effects, which include the downregulation of proinflammatory signaling pathways mediated by NF-kB and iNOS, promotion of neuroregeneration, protection of neurons from oxidative stress, and inhibition of amyloid-β peptide aggregation and tau phosphorylation. It has been demonstrated that the combination of quercetin and epicatechin, flavonol which crosses the blood-brain barrier, synergistically reduces ischemic neuronal cell death, preserves mitochondrial respiratory capacity, and provides protection against hypoxic-ischemic brain damage. Biomolecules 2023 Nov; 13(11): 1585. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10669388/

Quercetin may have beneficial effects in transmissible spongiform encephalopathies. A recent study has shown that quercetin binding alters the morphology of mouse prion protein fibrils, leads to large aggregate formation, and suppresses cytotoxicity in neuroblastoma cells. Protein misfolding and aggregation have also been reported in COVID-19. According to the authors, this effect of quercetin is distinct from the typical action of anti-amyloidogenic drugs that inhibit the formation of amyloid fibrils. https://doi.org/10.3390/pharmaceutics12111081

6. Anticoagulant activities of quercetin

Quercetin is a potent inhibitor of protein disulfide isomerase (PDI), an enzyme implicated in platelet-mediated thrombin formation at the site of vascular injury. A multicenter Phase II study in cancer patients showed that administration of isoquercetin at a dose of 1 g/day over 56 days resulted in a significant decrease in D-dimer, P-selectin, and platelet-dependent fibrin formation compared to placebo. This suggests that isoquercetin supplementation may contribute to the prevention of hypercoagulability in cancer patients. https://doi.org/10.1016/j.jpha.2021.09.009

Conclusion

Previous studies have reported antioxidant, antiatopic, pro-metabolic, anti-inflammatory, antiviral, anticoagulant, immunoprotective, and neuroprotective effects of quercetin. According to recent findings, quercetin supplementation could play a therapeutic role in

SARS-CoV-2-infected patients.