Immune Polyphenols: Quercetin, Naringin, and Berry Polyphenols Provide Powerful Immune Protection

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Abstract

More than 8000 polyphenols are found in the plants we consume as food or use medicinally. In a whole foods diet that is rich in fruits and vegetables, total polyphenol intake far exceeds the consumption of traditionally recognized nutritional antioxidants like vitamin C. Yet, we oft neglect their consideration when we give dietary recommendations and design supplement protocols for immune support. Herein, we take a look at the preclinical and clinical data for the specific polyphenols, quercetin and naringin, as well as grape seed extract. The impact of dietary supplementation with commonly available berry products (including elderberry) on immune function, vaccination response, gastrointestinal health, and cold and flu symptoms is also discussed.

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In the past year, as a healthcare practitioner, you probably feel as if you have listened to or read research on just about every imaginable topic about the immune system, especially as it pertains to viruses, respiratory health, and the inflammatory response. You are not alone! In 2020, more than ever before, we see the population worldwide seeking out information about essential vitamins and minerals, botanicals, probiotics, and even melatonin as natural agents for immune resistance and infection prevention.

However, there may be one topic which you have not yet explored, as it hasn't made frontline news: the family of polyphenols, found in abundance in the fruits and vegetables we take in as part of a whole foods diet. Given that we consume between 200 to 300 mg of polyphenols per 100 g of many commonly consumed fresh fruits,[1] dietary intake of polyphenols can be substantial in a diet with a high level of fruit and vegetable intake. Herein, we look at the data backing the use of nature's protective phytonutrients, specifically quercetin, naringin, and berry polyphenols, for infection prevention and treatment.

Quercetin

One member of the polyphenol family that many are very familiar with is quercetin. Quercetin is a flavonoid found in many fruits and vegetables, including apples, cherries, berries, onions, broccoli, and tomatoes. We look to quercetin most often as a seasonal remedy for those with allergic afflictions.[2] Quercetin counteracts the allergic response by suppressing antigen-specific immunoglobulin (Ig)E antibody formation, thereby acting at a very early stage in the allergic response.[3,4] Additionally, quercetin inhibits the release of histamine and pro-inflammatory substances implicated in allergic reactions.[5] By these and other mechanisms, quercetin may improve contact dermatitis and photosensitivity,[6] allergic rhinitis,[7] and asthma.[8,9]

Along with this, quercetin has an effect of balancing the Th1:Th2 immune response, acting to downregulate Th2 allergic response–related cytokines, such as interleukin (IL)-4, and increase interferon (IFN)-γ,[10] a key cytokine in the response against viral invaders and the development of immunity.[11-14] Quercetin also happens to be found at fairly high levels in St. John's wort (*Hypericum perforatum*),[15] and may be one of the constituents that contributes to its mood-stabilizing and antiviral effects.[16-20] Studies have shown numerous mechanisms by which quercetin and other flavonoids can reduce infectivity of a wide variety of respiratory and other viruses,[21] including influenza, adenovirus, rhinovirus, and coronaviruses.[22-25] Quercetin further shows respiratory tract affinity in the protection it offers against oxidative damage and inflammation associated with particulate matter exposure.[26]

Quercetin helps protect the body against reactive oxygen species, although studies show it also has pro-oxidant effects.[27-29] In animals, quercetin

supplementation has been observed to increase levels of α-tocopherol while decreasing malondialdehyde levels, a marker of lipid peroxidation; however, variable effects on glutathione levels have also been shown.[28,29] Providing additional antioxidants along with quercetin, such as vitamin C and glutathione, may help to negate the pro-oxidant effects and enhance quercetin recycling.[30,31] Indeed, vitamin C appears to enhance the activity of quercetin, in part by stabilizing the quercetin molecule itself.[32]

In humans, evidence from clinical studies has shown quercetin has anti-inflammatory and antioxidant effects,[33] which may be even greater in disease states such as sarcoidosis where there is higher levels of oxidative stress and inflammation at baseline.[34] Quercetin has also been shown to reduce pro-inflammatory cytokine production triggered by lipopolysaccharide (LPS) stimulation of ex vivo blood samples from patients with idiopathic pulmonary fibrosis, suggesting it may be of benefit in this population as well.[35]

In humans, quercetin has been demonstrated to be safe with doses up to 5 g/day and to have antiviral potential in individuals with chronic hepatitis C.[36] In healthy individuals, quercetin supplementation has been shown to significantly reduce the incidence of upper respiratory tract infection (URTI) in trained male cyclists[37] and the number of URTI sick days and symptom severity in physically fit subjects over the age of 40.[38] An extensive recent review looks at numerous mechanisms by which the combination of quercetin with vitamin C may be effective as a prophylactic for prevention of highly prevalent respiratory infections.[21] Supplementation of quercetin also has been shown in humans to have a positive impact on blood pressure,[39] cholesterol profiles,[40] and other markers of cardiovascular disease risk.[41,42]

Naringin

Flavonoids are also found at a high level in citrus fruits, particularly in their seeds and skin.[43] Grapefruit contains over 25 different flavonoids,[44] with the predominant one being naringin,[45] a glycoside that gives grapefruit its bitter taste and many of its health benefits.[46,47] When naringin is ingested, it is converted by the intestinal microflora to the active metabolite naringenin, which is readily absorbed and exerts biological effects throughout the body.[48,49] Many look to grapefruit seed extract (GFSE) for its effects on gastrointestinal (GI) health, which naringin and other citrus flavonoids like hesperidin mediate, in part via their interactions with the gut microbiota.[50] However, this is not their only GI effect; they can also positively impact gut permeability and intestinal inflammation.[51,52]

GFSE has strong antimicrobial activity that has been demonstrated against numerous food-borne and opportunistic pathogens including *Pseudomonas*, *Salmonella, Escherichia coli*, *Enterococcus*, *Staphylococcus*, and *Candida* species, as well as pathogens known to cause periodontal disease.[53-57] Laboratory studies and simulations further suggest that naringin may have activity against influenza virus,[58] hepatitis C virus,[59] and rotavirus,[60] as well as multiple viruses that are transmitted by mosquitos: Zika virus,[61] dengue virus,[62] and chikungunya virus.[63]

Naringin also has protective anti-inflammatory and antioxidant properties that help protect numerous organs of the body, including the kidneys,[64,65] eyes,[66] brain,[67] and, in particular, the lungs.[68] Various types of animal models have shown naringin to be protective against pulmonary inflammation and its sequelae. Naringin reduces the neutrophil infiltration, airway inflammation, airway hyperresponsivity, and symptoms of cough associated with cigarette smoke exposure.[68,69] It reduces inflammation, airway hyperresponsivity, and symptoms of cough in allergen-induced models of asthma,[70] inhibiting Th2 cells and enhancing the Th1 response.[71] Naringin not only decreases LPS-induced inflammation and lung injury but also reduces lung edema, goblet cell hyperplasia, and mucus hypersecretion, and promotes sputum excretion.[72,73] In toxin-induced lung injury, naringin had protective effects similar to *N*-acetylcysteine, and substantially reduced pulmonary inflammation and fibrosis.[74]

Berry and Grape Polyphenols

Berries and grapes (which are also technically berries) are an excellent source of polyphenols. The most noteworthy polyphenol—and the grape's greatest claim to fame—is resveratrol, which is found primarily in the skins of grapes.[75] The grape seeds and skin, including the products remaining after the processing associated with wine or juice, have a very high antioxidant capacity, making this a valuable by-product for potential use in animal feed or the supplement industry.[76,77] The seeds and skins of grapes and berries are rich in the also-important procyanidins and proanthocyanidin members of the polyphenol family, including gallic acid, catechin, and epicatechin, as well as quercetin.[78,79]

Both animal and human studies have shown enhanced antioxidant status and reduced levels of inflammation with grape seed extract supplementation.[80-84] In animals, grape seed extract products have been shown to benefit the central nervous system, reducing inflammation, amyloid-β accumulation, and the impact of age on various markers of antioxidant status.[85,86] In humans, we see their benefits to metabolic health elucidated in a 2020 systemic review and meta-analysis of randomized controlled trials, finding they positively impact fasting glucose, cholesterol balance, and inflammation.[87]

These are not the only benefits of berry polyphenols—we also find that these potent antioxidants with prebiotic potential have a positive impact on immune function and gastrointestinal health.[88] The addition of berry extract products to the diet of animals has been shown to enhance immunoglobulin levels and the vaccination response,[84,89-91]

increase levels of healthy gastrointestinal flora (including lactobacilli and bifidobacteria), and reduce intestinal inflammation and levels of potentially pathogenic bacteria.[88]

In a randomized, double-blind, placebo-controlled trial (RDBPCT) of subjects ranging in age from 55 to 72, intake of a boxthorn berry product was shown to significantly increase levels of lymphocytes (within normal ranges) and IgG levels.[92] Significant improvements were seen in overall feelings of well-being, which included sub-parameters of dizziness, fatigue, and sleep, while a trend of improvement was also seen in short-term memory and focus. In another RDBPCT of individuals ages 65 to 70, supplementation with a wolfberry-enhanced milk product significantly increased influenza-specific IgG levels and seroconversion rate after influenza vaccination.[93]

In human subjects, regular intake of 100% grape juice has been shown to increase levels of γδ (gamma delta)-T cells (which function as a bridge between the innate and adaptive immune response[94]) as well as vitamin C levels.[95] Human consumption of a cranberry polyphenol blend was also shown to significantly increase proliferation of γδ-T cells (in culture) compared to placebo, which was accompanied by a significant reduction in cold and flu symptoms.[96] Intake of berry-derived preparations has also been shown to increase levels of lactobacilli and bifidobacteria in the human gut.[88]

Black elderberry (*Sambucus nigra*), is one berry that is particularly well known for its immune-stimulating and antiviral effects. Bioactive compounds found at high levels in elderberry include quercetin and its derivatives, rutin, and cyanidin-based anthocyanins.[97,98] In addition to inhibiting both influenza A and B, elderberry extract also has been shown in cell studies to inhibit *Streptococcus pyogenes*, group C and G *Streptococci*, and *Branhamella catarrhalis*, common bacterial causes of upper respiratory infections.[99]

In a RDBPCT of adults and children clinically diagnosed with influenza, more than 90% of those who were given black elderberry extract had a significant improvement in symptoms within two days, while the same level of improvement was not seen until day six in the placebo group.[100] Two other RDBPCTs in adults diagnosed with influenza had similar outcomes: those given elderberry products had an improvement of symptoms earlier and symptoms were less severe or there was a reduced need for medications to manage symptoms.[101,102]

With more than 8000 known polyphenols found in the plant species we consume either medicinally or as food,[1] the aforementioned health benefits represent only a small fraction of the potential advantages of consuming a whole foods diet that is rich in fruits and vegetables. Although supplementation is always an option, the studies discussed above pointedly remind us: don't forget to eat your fruits and vegetables!

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