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Role of Dietary Flavonoids in Preventing COVID-19 Infection and Other Infectious Diseases: A Mini Review

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Abstract

Flavonoids are a large group of naturally occurring polyphenolic compounds that are almost universally present in various plant parts such as fruits, berries, leaves, and tubers. These compounds are synthesized in plants in reaction to environmental stressors such as microbial infections. The antioxidant properties in these flavonoids provide us with numerous health benefits. They can be extracted from said natural sources via methods such as maceration and boiling all the way to advanced methods such as microwaves and ultrasounds.

Numerous studies have been conducted to research the protective role that flavonoids can play in preventing infectious diseases in humans. The present modalities of treating such infectious diseases rely solely on chemotherapeutic agents and adjunctive therapies such as palliative and supportive care. These chemotherapeutic agents, primarily antibiotics, cause a degeneration of our immunity and an increased susceptibly to several other diseases. Thus, it is crucial that our methods in dealing with infections focus on prevention. This can be achieved by strengthening our immune system, which is the primary line of defense against such diseases. Flavonoids can help boost our immunity, fight infections, and decrease the incidence of antibiotic resistance.

Hence, these natural compounds are being largely studied and used as nutraceuticals to supplement our daily diet and successfully reduce the occurrence of major infectious diseases in our body.

Keywords
- flavonoids
- nutraceuticals
- antibacterial
- antiviral
- antifungal

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Introduction

Flavonoids are a category of naturally and extensively occurring polyphenolic organic compounds that consist of a benzo-gamma-pyrone structure that are almost universally present in plants.[1] Polyphenols are secondary metabolites that are biosynthesized by phenylpropanoid pathway through shikimic acid.[2] They are synthesized in plants in reaction to stressful environmental changes such as microbial infections. Their biological properties and their chemical nature are dependent on their molecular structure and chemical factors, e.g., their structural class, degree of hydroxylation, polymerization, etc. Flavonoids have numerous potential health benefits in humans because of their antioxidant properties. These antioxidant properties are mediated by the functional hydroxyl groups, which scavenge free radicals and chelate metal ions. This chelation of metal ions plays a role in preventing radical generation, which, in turn, prevents damage to target biomolecules.[1] They are present in stems, roots, bark, flowers, fruits, vegetables, cereals, legumes, wine, and tea.[3] Flavonoids are extracted through plant products through many methods. Conventional methods include maceration, boiling, percolation, soaking, and hydro-distillation. The advanced techniques utilize microwaves, ultrasound, pressurized liquids, and supercritical fluids to extract flavonoids.[4]

There have been numerous studies that describe the protective role of flavonoids against a wide spectrum of human disorders and diseases including infectious diseases, degenerative conditions, and malignancies.[1] Infections are the most common type of disease processes in humans and are caused by pathogenic microorganisms that include bacteria, viruses, fungi, and parasites. An infection occurs when microbes enter the body and begin multiplying, whereas the actual disease usually occurs in a small fraction of infected people whose bodies exhibit cellular destruction and disrupt normal functions. COVID-19 is one such viral infection caused by SARS-CoV-2. It was first reported as pneumonia of unknown cause, in a hospital in Wuhan, China, in December 2019. Human saliva and throat swab have been used extensively for diagnostic tests of SARS-CoV-2.[5]

The oral cavity is a known portal of entry of the virus due to the presence of ACE2-expressing cells.[6] It primarily affects the upper respiratory tract and causes a multitude of debilitating symptoms. Because there is no definitive treatment for this viral infection, we must rely on our immune system instead. Hence, immunity plays a crucial role in the current pandemic situation. The body's immunity helps fight and overcome the disease in its incubation period. The risk of developing COVID-19 and its complications is greater in people with a compromised immune system or increased inflammatory response. The disease severity depends not only on the viral load but the host response as well. In severe infections, an acute immune reaction ensues by the release of multiple cytokines concurrently, which results in multiorgan failure or death. This is known as a cytokine storm. Flavonoids can act as strong immunity boosters that can help prevent and cure such severe diseases. In the longer run, mucormycosis in patients with a history of COVID-19 have proven to be a burden on healthcare system. Prolonged ventilation, inadequate glycemic control, and excessive use of corticosteroids along with depressed immunity have been shown to be the possible reasons for the mucormycosis outbreak.[7]

Our immune system swings into action in response to an infection. The various components of the immune system such as leukocytes, antibodies, complement system, and cytokines work toward fighting the pathogens.[8] Thus, the competency and functioning of the immune system is the major deciding factor in the occurrence, duration, and severity of an infection. The treatment of infectious diseases is solely based on chemotherapeutic agents, primarily antibiotics. Adjunctive therapy includes palliative and supportive care such as rest, diet, and increased fluid intake. Antibiotics cause several adverse effects, the worst being a degradation of our immunity and consequential increased susceptibility to various diseases. Antiviral agents have been tested and used in various viral infections but none of them have been successful in curing the patient before the incubation period. It is therefore prudent that our approach in dealing with infectious diseases shifts toward prevention. Improving our immunity can shorten the recovery period and reduce the intensity and effect of the microbes on various organs of our body. The ever-evolving nature of the coronavirus has only intensified our need to strengthen our immune system. Flavonoids not only help fend off infections and reinforce our immune system; however, their use significantly decreases the incidence of antibiotic resistance.[9] As a result, these compounds are now being largely being researched and successfully used as nutraceuticals. Previous researches have depicted that biocompatibility and biosafety is also an important requirement of the materials used for medical and dental applications whether in case of the treatment of disease or any other invasive procedure.[10–12]

Classification of Flavonoids

Flavonoids are secondary plant metabolites, which exhibit a wide range of chemical forms and ecological significance.[1,2] Flavonoids are found mainly in spermatophytes, gymnosperms, and angiosperms, along with some bryophytes, pteridophytes, and algae. They are the third largest cluster of naturally occurring products with 10,000 flavonoids recorded so far that are classified based on their biosynthetic origin.[1–3] Chemically, flavonoids can be defined as an aromatic nucleus-containing compounds. This nucleus contains three rings, namely, A, B, and a C ring (heterocyclic). They are considered one of the most extensive group of phytochemicals because of their structural diversity. Flavonoids are usually classified according to the position of attachment of ring B to ring C. Mostly, the B ring is attached to position 2 of the C ring, but it can also bind to position 3 or 4. The pattern of glycosylation and structural characteristics are deciding factors of their biological properties. A detailed classification of flavonoids is described in ►**Fig. 1**.[13]

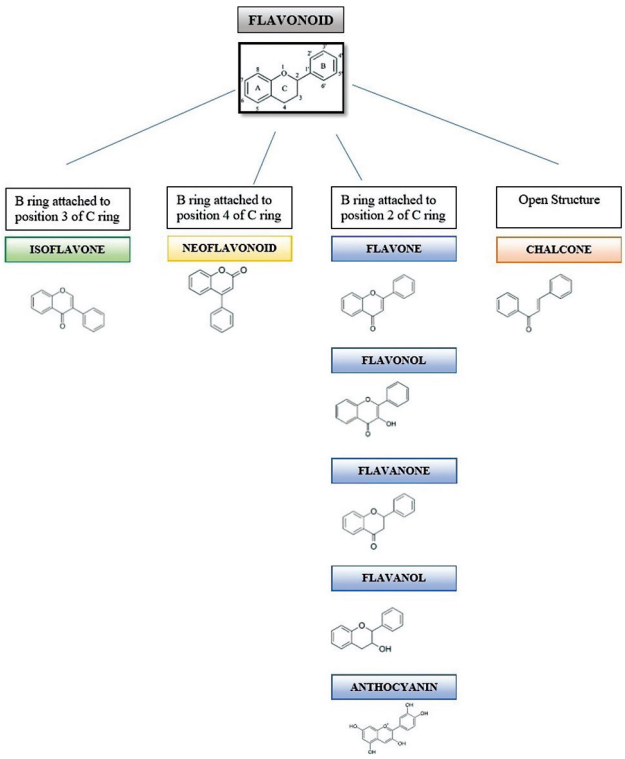

Fig. 1 Schematic representation of flavonoids classification.

Mechanism of Action

Flavonoids are chemotaxonomic compounds with numerous biological activities. Since ancient times, flavonoids have been used in various concoctions as the primary active ingredient to treat human diseases.

They have antioxidant and anti-inflammatory properties and exhibit effective action against microbial infection. Hence, flavonoids display antibacterial, antiviral, antifungal, and chemopreventive actions. Furthermore, studies have exhibited synergy between certain flavonoids and existing pharmaceutical products. Flavonoids deactivate or interfere with the microbial adhesions by forming hydrophobic, covalent or hydrogen bonding with protein complexes (►**Table 1**).[14–33] A few lipophilic flavonoids act by causing the disruption of microbial membranes. A detailed description of the antibacterial mechanism of flavonoids is depicted in ►**Fig. 2**. Many studies have shown flavonoids to cause the inhibition of many enzymes linked to virus growth.[1] They display inhibitory action against HIV, Dengue, Polio Virus, Herpes Simplex Virus, and Sindbis virus. Flavonoids also prevent viral polymerase binding of viral capsid proteins. These properties were suggested as antiviral modes of action[34–36] (►**Fig. 3**). The antifungal action of flavonoids have been described in ►**Fig. 4**.

Antibacterial Action

The antibacterial action of flavonoids has been well researched and documented. Plants extracts used since centuries have been studied and screened for antibacterial properties. Certain preparations containing a high concentration of flavonoids have shown antibacterial activity. Among these, specific structures or classes of flavonoids have been isolated such as apigenin, epigallocatechin gallate, galangin, luteolin, quercetin glycosides, kaempferol derivatives. These phytochemical compounds have a wide range of inhibitory actions against bacterial cells. They are of three broad types: (i) inhibition of nucleic acid synthesis: Flavonoids that displayed this activity were robinetin, myricetin, and epigallocatechin. The B ring on the flavonoids has been suggested to play a role in the hydrogen bonding of the nucleic acid bases that explains the inhibitory effect on DNA and RNA synthesis. The antibacterial action of quercetin has been attributed to the inhibition of DNA gyrase. (ii) Inhibition of cytoplasmic membrane function: sophoraflavanone G has shown an antibacterial activity by reducing the fluidity of the membrane of the bacterial cells. Epigallocatechin gallate, a flavonoid found commonly in green tea has exhibited strong antibacterial activity. It may disrupt the lipid bilayer by disrupting them or causing fusion of the cell membrane layers. Galangin has also shown to cause cell membrane damage while quercetin caused an alteration of membrane potential and increased permeability of the inner cell membrane. (iii) Inhibition of energy metabolism: Flavonoids hamper the energy metabolism in bacterial cells by interrupting their oxygen consumption and by inhibiting NADH-cytochrome c reductase.[34]

Anti-Viral Action

The importance of antiviral activity of flavonoids has risen in the past few years, particularly due to the increased frequency of viral infections. Numerous *in vitro* studies have shown significant antiviral properties of flavonoids such as viral enzyme inhibition, cytopathic effect, and virion number reduction. Flavonoids have also shown potential inhibitory activity against coronaviruses, including the current pandemic outbreak (COVID-19), Herpes Simplex Virus-1, Hepatitis A, B, and C viruses, and influenza virus. The underlying molecular mechanisms of flavonoids involve the inhibition of viral replication, increased interferon-γ levels, inhibition of virion production, and virion assembly.[35] Flavonoids exhibit an inhibitory activity against SARS-CoV-2 by preventing the entry of the virus into cells and their replication by targeting and binding to essential proteins involved in the viral life cycle. These phytocompounds also showed remarkable immunomodulatory activity including the inhibition of several inflammatory cytokines, thus curbing the possibility of a cytokine storm.[36]

There are several studies showing the antiviral effects of flavonoids. Apigenin, luteolin, quercetin, and quercetagetin have been found to exhibit an antiviral activity against HCV. Flavonoids such as epigallocatechin gallate and chamaejasmin have the potential to affect the Dengue virus replication, and even pinocembrin targets the molecular machinery used by the Zika virus to replicate its own genome.[35]

Anti-Fungal Action

Fungal infections affect millions of people worldwide every year and can even be fatal. These diseases are more prevalent

Table 1 Target organism of flavonoids

Source	Category	Target microorganism	Reference
Pelargonium sidoides extract	polymeric proanthocyanidins	Anti-adhesive property	14
Cranberry	A-Type proanthocyanidins	UTI–*E. coli*	15
Cranberry	Type A oligomers	UTI–*Streptococcus mutans*	16
Cranberry	Proanthocyanidins	Decrease inflammatory mediators	17
Tea	Epigallocatechin Gallate	*Helicobacter pylori* inhibition	18
Tea	Epigallocatechin Gallate	*E. coli*inhibition of virulence factors such as formation of biofilm and Bacterial motility of the swarm	19
Tea	Epigallocatechin Gallate	Flu virus-prevents binding of viral virulent particles to the target receptor cells by binding to the viral haemagglutinin	20
Tea		Adenovirus and Enterovirus-inhibition	21,22
Tea		Candida albicans–inhibition in superinfection of oral cavity, intestine, vagina	23
	Rhamnetin, Myricetin, Morin, Quercetin	*Chlamydia pneumoniae* inhibition (decreases infectivity by 50%) in acute respiratory tract infections	24
Propolis	Galangin, izalpinin, and rhamoncitrin	*M. gypseum*, *T. mentagrophytes*, *T. rubrum* (bacterial and fungal dermatitis–external topical use)	25
Cranberry	Proanthocyanidin	*E. coli*, *S. mutans*, *S. aureus*-inhibition	26
		Influenza A virus and type 1 HSV	27
Raspberry, Cloudberry, Strawberry	Ellagitannins	Certain strains of *Salmonella*, *Helicobacter*, *Staphylococcus*, *E. coli*, *Clostridium*, *Campylobacter* and *Bacillus* (gram-negative intestinal bacteria)	28
Mango Kernel	Gallotannins	*Bacillus subtilis, Clostridium botulinum B. cereus*, *C. jejuni*, L. monocytogenes, *S. aureus*, *E. coli*, and *Salmonella enterica* (food borne bacteria)	29
Ocotea odorifera	Ellagitannin	*Candida parapsilos*	30
	Ellagitannins	HIV infection	31,32
		HSV-1, HSV-2, and EBV	33

in people with impaired immune systems such as patients of AIDS, cancer, diabetes, and organ transplantation. COVID-19 patients have also reported to develop fungal illnesses such as mucormycosis. There exist very few therapeutic agents for fungal infections compared to bacterial infections. Additionally, drug resistance in microbes is growing every day due to the elevated use of such antifungal agents. Medicinal plants

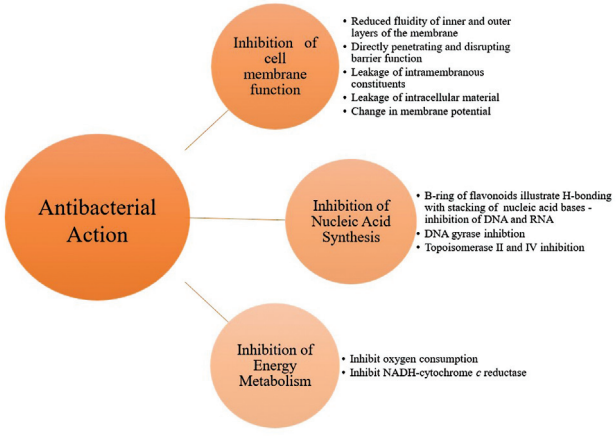

Fig. 2 Antibacterial action of flavonoids.

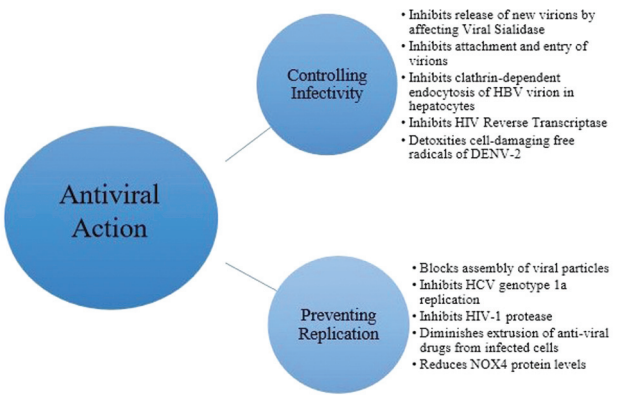

Fig. 3 Antiviral action of flavonoids.

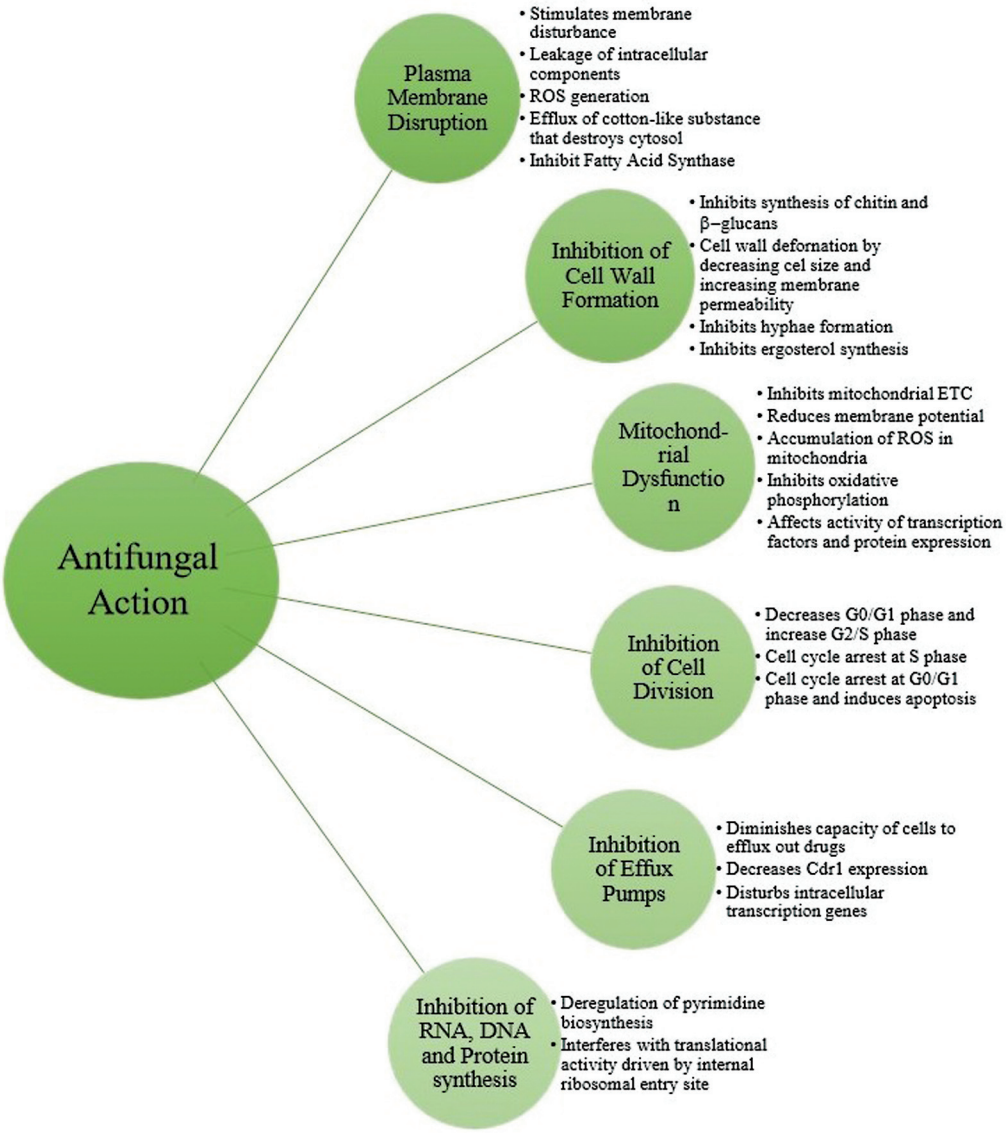

Fig. 4 Antifungal action of flavonoids.

with bioactive compounds are thus being applied comprehensively as an alternative and safer treatment modality. Flavonoids with antifungal activity have been screened from plants by employing spore germination, broth dilution and disk diffusion. They have shown to be effective against various species of pathogenic fungi such as *C. albicans, C. krusei, C. glabrata, T. deformans,* and *A. flavus*. Several modes of action have been exhibited by flavonoids in inhibiting their growth. These include plasma membrane disruption that causes reduction in fungal cell size, leakage of intracellular components, and cell death. Flavonoids can also cause cell wall deformations and mitochondrial dysfunction through various pathways. Furthermore, fungal cell division, nucleic acid and protein synthesis, and efflux pumps are inhibited by certain flavonoids as well. These flavonoids are effective even in synergetic combinations with existing antifungal drugs.[37]

Flavonoid Sources

Understanding various sources of flavonoids is very essential for their health-promoting effects. Flavonoids are available richly in plant and human diet products. Black rice being the rich source of it, flavonoids are also seen in blackberries, blueberries, propolis, honey, red beans, nuts, tea, and wine. Natural sources of flavonoids and their classes and subclasses is essential in understanding and implementing these products in daily dietary supplements (►**Table 2**).

Nutraceuticals - Commercially Available in The Market

Natural sources of therapeutic agents have a higher preference over synthetic agents. There is an ongoing search for natural agents, which can protect body from various

Table 2 Natural sources of flavonoids

Natural source	Plant product	Flavonoid class	Flavonoid subclass
Fruits	Apples	Flavonols	Quercetin, rutin, fisetin, kaempferol
	Grape seeds/grapes	Flavonol	Quercetin, rutin, kaempferol
		Flavonone	Narigenin
		Anthocyanin	Anthocyanin
	Citrus fruits	Flavonol	Quercetin, rutin
		Flavonone	Eriodictyol, hesperidin
		Flavononol	Taxifolin
		Flavone	Luteolin
Berries	Strawberries	Flavonol	Fisetin
	Cranberries, blueberries	Anthocyanidin	Peonidin
	Raspberries, blackberries	Flavonol	Kaempferol
Vegetables	Red pepper	Flavonols	Quercetin, myrecetin, Rutin
	Cucumber	Flavonols	Fisetin, kaempferol
	Broccoli	Flavonol	Kaempferol
		Flavone	Luteolin
	Lettuce, brussel sprouts, green beans, squash, spinach	Flavonol	Kaempferol
	Carrots, Celery, green pepper	Flavone	Luteolin
Cereal	Rice bran	Flavone	Tricin
Legumes	Soyabean, fava beans	Isoflavone	Genistein
	Chickpea	Isoflavone	Biochanin
	Red clover	Isoflavone	Biochanin, genistein
	French bean seeds	Flavonone	Abyssinones
	Vetch	Flavone	Diosmetin
Nuts		Flavonol	Myricetin
Tubers	Onion	Flavononol	Fisetin
	Sweet potato	Anthocyanidin	Peonidin
Miscellaneous	Milk, chocolate	Flavone	Apigenin
	Tea/coffee	Flavonol	Rutin, myricetin,
		Flavone	Luteolin
		Catechin	Theaflavin
	Red wine	Flavonol	Myricetin
	Olive oil	Flavone	Luteolin

infections and diseases. This has given rise to various supplements rich in flavonoids available for use. Details of flavonoid supplements available for use is enlisted in ►**Table 3**.[38–45]

Conclusion

Flavonoids are potential agents in the prevention of ailments and diseases. In the present scenario with ongoing COVID-19 pandemic, the emphasis has been on the prevention of disease and reducing the risk of transmission.[46] While various agents, such as melatonin derivatives with antioxidant and immunomodulatory properties have been assessed for their therapeutic potential against SARS-CoV-2, the arrival of newer virulent strains has driven the attention of the researchers towards the use of natural agents in building immunity.[6] Flavonoids with their nutraceutical and therapeutic action and minimal or no adverse effects, have gained significant role in the field of health and pharmacy. This review paper highlights the modes of action of flavonoids against infectious agents with their natural sources.[47]

Table 3 List of nutraceuticals-flavonoids available for use

Flavponoid type	Dosage	Use	Reference
Rutin	750 mg/day	Anticarcinogenic, neuroprotective, antioxidant, cardioprotective	38
Diosmin + hesperidin	1000 mg/day (3 months)	Chronic venous diseases, hemorrhoids	39
Hidrosmin	600 mg/day	Chronic venous diseases	40
Flavoxate	100-200 mg 3-4/day	Muscle spasms of the urinary tract	41
Genistein	30-60 mg/day	Anticancer, antimicrobial, anti-inflammatory, reduce symptoms of menopause	42
Silibinin	200-400 mg/day	Hepatoprotective	43
Galangin		Antibacterial, antiviral, antitumor, antidiabetic	44
Quercetin	500-1000 mg/day	Immunity booster, anti-inflammatory, anti-allergy	45

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Conflict of Interest
None declared.

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