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Therapeutic Potential of Flavonoids and Zinc in COVID-19

Review Article

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Abstract

The Coronavirus Disease 2019 (COVID-19) is a devastating global pandemic. Although control of inflammation and supportive care is a common practice, effective and safe disease-modifying or preventive treatments, particularly alternative therapeutics are not yet available. Recent studies demonstrate that small natural molecules belonging to polyphenol family can interfere with various stages of coronavirus entry and replication and thus prevent severe symptomatology these bioactive phytoconstituents, available as natural components in foods and medicinal plants may provide preventive and other benefits against COVID-19, particularly in older adults with micronutrient deficiencies. Another age-related nutritional deficiency may be inadequate levels of the trace metal zinc (Zn), rendering this population more susceptible to COVID-19. Here, we carried out a systematic review using Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines, consulting the PubMed, Scopus and SciELO incorporating descriptors 'COVID-19', 'Polyphenols', 'Quercetin', 'Dihydromyricetin' and Zinc up to November 2021. Thus, following a brief review of 2 select flavonoids; quercetin as a potent antioxidant, and Dihydromyricetin (DHM) as an effective antiviral agent as well as the trace mineral Zn, essential for immune function, we conclude that combination of these compounds should be considered as an added prophylactic and/or adjunct treatment modality in COVID-19.

Keywords: Polyphenols, Flavonoids, Quercetin, Dihydromyricetin, Zinc, Combination therapy, Inflammation, Oxidative stress, SARS-CoV-2.

Abbreviations:

COVID-19: Coronavirus Disease 2019
Zn: Zinc
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
DHM: Dihydromyricetin
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
ACE-2: Angiotensin-Converting Enzyme-2
ARDS: Acute Respiratory Distress Syndrome
MODS: Multiple Organ Dysfunction Syndrome
LOX: Lipoxygenases
NADPH: Nicotinamide Adenine Dinucleotide Phosphate Oxidase
FDA: Food and Drug Administration
DNA: Deoxyribonucleic acid
RNA: Ribonucleic acid; BLM bleomycin
ROS: reactive oxygen species
RNS: reactive nitrogen species
SOD: superoxide dismutase

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PI3K/Akt: phosphatidylinositol 3-kinase
Nrf2: nuclear transcription factor-erythroid 2-related factor 2
TNF-α tumor necrosis factor-alpha
NF-kB: nuclear factor-kappa B
RDI daily: recommended dietary intake
NOAEL: no-observed-adverse-effect level

Introduction

The Coronavirus Disease 2019 (COVID-19) is an acute respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). First reported in Wuhan, China at the end of 2019, COVID-19 was declared as a global pandemic in March 2020. The functional receptor of SARS-CoV-2 is angiotensin-converting enzyme-2 (ACE2), which provides viral entry into human cells [1,2,3]. Upon entry, SARS-CoV-2 can target different tissues at multiple levels, starting from the cells of nose and throat down to the lung, invading through vassal endothelium, the kidneys and nervous system where it can cause severe illness and death [4,5,6]. The clinical symptoms are initially manifested as fever, dry cough, and fatigue. Some cases are accompanied by nasal congestion, runny nose, sore throat, muscle pain, and diarrhea. Severe patients have excessively high levels of cytokines and chemokines in plasma, referred to as cytokine storm, which can lead to significant inflammation and tissue and organ damage [5]. Although cytokine storm is considered a hallmark of COVID-19, its full role in COVID-19 disease course is yet to be fully elucidated [7,8,9,10]. Acute respiratory distress syndrome (ARDS), shock, multiple organ dysfunction syndrome (MODS), and sudden myocarditis appear in severe and terminal patients afflicted with COVID-19 [5,11,12,13]. It is of importance to note that most of the afflicted individuals with COVID-19 exhibit only mild or moderate symptoms, whereas 5–10% of any population may present with severe and even life-threatening disease course. The overall mortality rate due to COVID-19 is approximately 2%. Currently, supportive care measures such as ventilation oxygenation and fluid management remain standard care. A number of clinical trials are underway to identify effective drugs and/or nutrients in prevention or intervention in COVID-19 [14,15,16,17]. In this regard, recent publications have highlighted potential use of plant derivatives particularly flavonoid compounds (e.g., quercetin) in countering various detrimental consequences of COVID-19 [18, 19,20,21,22,23,24,25,26,27,28]. However, additional flavonoid compounds such as Dihydromyricetin (DHM) and the essential heavy metal zinc (Zn) supplements together with quercetin may provide further protection against COVID-19. In this review we provide justification for such a recommendation.

Although immunological mechanisms driving COVID-19 pathogenesis are still largely unknown, new understanding has emerged about the innate and adaptive immune responses elicited in SARS-CoV-2 infection, which are mainly focused on the dysregulated inflammatory response in severe COVID-19. Polyphenols are naturally occurring products with immunomodulatory activity, playing a relevant role in reducing inflammation and preventing the onset of serious chronic diseases. Mainly based on data collected before the appearance of SARS-CoV-2, polyphenols have been recently suggested as promising agents to fight COVID-19, and some clinical trials have already been approved with polyphenols to treat COVID-19. The aim of this review is to analyze and discuss the in vitro and in vivo research on the immunomodulatory activity of quercetin as a research model of polyphenols, focusing on research that addresses issues related to the dysregulated immune response in severe COVID-19. From this analysis, it emerges that although encouraging data are present, they are still insufficient to recommend polyphenols as potential immunomodulatory agents against COVID-19

Methods

Using PRISMA guidelines and consulting PubMed, Scopus and SciELO with key words such as ‘COVID-19’, ‘Polyphenols’, ‘Quercetin’, ‘Dihydromyricetin’ and ‘Zinc’, more than 200 relevant articles were reviewed to provide the summary and recommendations detailed in this presentation. No specific clinical trials were evaluated, rather the search was concentrated on essential information relevant to the topic..

Flavonoids

Bioactive phytoconstituents, available as natural components in foods and medicinal plants, provide preventive and curative health benefits in COVID-19. Bioactive food components like alkaloids, peptides, flavonoids, flavones, anthocyanins, phenolic acids, polyphenols, tannins, resveratrol, polysaccharides, and sterol have been identified as “green” ACE inhibitors [20, 21,22,23,24,25,26,27,28,29,42]. It is of relevance to note that flavones are the 3-hydroxy derivatives of flavanones, also a type of flavonoid that is colorless and occurs in plants as a glycoside.

Flavonoid monomers mainly include quercetin, kaempferol, and myricetin, while flavanones include Dihydromyricetin (DHM). They are considered the largest group of phenolic phytochemicals in higher plants belonging to secondary plant metabolites found in fruits, vegetables, seeds, roots, propolis, and other plant products such as tea and wine [23]. There are more than 9000 structurally identified flavonoids. Although only recently flavonoids have caught the attention of researchers for their potential implication, flavonoid research spans several decades. Multiple health-promoting effects, ranging from nutraceutical, pharmaceutical, medicinal, and cosmetic applications to anti-carcinogenic properties have been ascribed to these compounds [23]. In fact, protective role of flavonoids in the diet was recognized in the 1990s [43], when flavonoid contents of 28 vegetables and 9 fruits and teas, wines, and fruit juices were quantified [44,45]. Shortly thereafter, an assessment based on dietary history of quercetin, kaempferol, myricetin, luteolin, and apigenin concluded that flavonol and flavone intake reduced mortality from coronary heart disease [45]. Various other beneficial effect such as antihypertensive, antihistamine, antimicrobial, memory enhancing, and mood-boosting properties were also ascribed to these flavonoids [46,47,48,49,50,51]. Indeed, flavonoids are now considered as chief antioxidants, free radical scavengers and chelators of divalent cations. This, together with their lack of systemic toxicity and their ability to synergize with conventional drugs, as well as their “pleiotropic” effects, meaning that they

can influence different cellular targets and affect multiple pathways [52,53], have resulted in their utilization as basic natural ingredient in more than hundred herbal medicines [5,50]. Recent reports on antimicrobial and anti-inflammatory effects of flavonoids and their possible protective role against COVID-19 led us to examine in more detail potential utilization of quercetin and DHM alone or in combination with the trace element zinc (discussed below) as nutritional supplements to aid in prevention and/or treatment of COVID-19.

Quercetin

The natural flavonoid quercetin is frequently found in low amounts as a secondary plant metabolite such as in fruits, nuts and vegetables. It is arguably the most investigated flavonoid to date, and onions and apples are the most commonly consumed dietary sources, though most studies use pure quercetin [54]. Quercetin itself enters the circulatory system in trace amounts and appears predominantly as glucuronide, sulfate, and methyl metabolites [55]. It can cross the blood–brain barrier [56], and has various biological effects including potent anti-oxidant properties as it inhibits oxidative species generating enzymes such as xanthine oxidase, lipoxygenases (LOX), and nicotinamide adenine dinucleotide phosphate oxidase (NADPH)[29,30,31,57,58,59,60]. It may also act as an antidiabetic agent [30,61,62,63]. Because quercetin has senolytic activity it can affect cell cycle, interact with type II estrogen binding sites, and inhibit tyrosine kinases [64], hence the suggestion of its potential utility as an anticancer drug [30,65-66]. Importantly in relevance to COVID-19, quercetin's action as zinc ionophore has led to the suggestion of an antiviral activity against many RNA viruses including SARS-CoV-2 [31,32,67,68,69]. Furthermore, antithrombotic action of quercetin may be an additional desirable effect against COVID-19, as thrombotic incidences are common manifestation with this disease [20,33,70]. In this regard, it has been demonstrated that quercetin and quercetin-3-O-rutinoside prevent platelet aggregation and inhibit LOX activity in various cell culture models as well as in vivo [60,71].

Isolated quercetin is marketed as a dietary supplement, mostly as the free quercetin aglycone, and frequently in daily doses of up to 1000 mg/day exceeding usual dietary intake levels. In silico modelling of the interaction between the SARS-CoV-2 viral spike protein and ACE2, quercetin was identified as one of the top five most potent compounds for binding to the interface site and potentially disrupting the initiating infection process [72]. Considering that this was detected in a database consisting of 8,000 small molecule candidates of known drugs, metabolites, and natural products, it gives credence to potential antiviral use of quercetin. This contention is further supported by finding that quercetin was active against infection in a model of virus cell entry as it inhibited the 3C-like protease of SARS-CoV in vitro [73,74]. Moreover, earlier studies showed that quercetin has the capacity to block the entry of SARS-CoV into host cells [73]. Recently, it was speculated that quercetin could be involved in immune regulation [12,75], and that it could be of potential therapy for lung injury associated with COVID-19 due to its anti-inflammatory, antiviral, and immunomodulatory effects [19,20,21,27,76,77,78,79]. Based on these findings, it has been suggested that quercetin be incorporated into trials against COVID-19 [34,80].

The United States Food and Drug Administration (FDA) has already approved oral doses of quercetin as safe for human consumption. Quercetin given nasally was effective in a rat model of allergic rhinitis [80], and the safety of quercetin has been favorably assessed [81]. Quercetin at high doses, like any other bioactive compound, could have potentially off-target effects. Following local application by a nasal spray the possibility exists that quercetin could diffuse or be transported to other tissues such as the lungs. Quercetin is widely used as a nutritional supplement and may be beneficial against a variety of diseases. Previously found beneficial effects on cardiovascular health biomarkers after regular consumption of quercetin [82], could deliver an additional positive outcome as patients with pre-existing cardiometabolic syndromes such as hypertension are at increased risk during Covid-19 infection [11,12,83]. Additionally, due to its neuroprotective properties, its application in various neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, Huntington's disease, multiple sclerosis and amyotrophic lateral sclerosis as well as epilepsy has been suggested [36,41]. Although many of the effects of quercetin have proven beneficial the potential of its reprogramming of the cellular energy metabolism should be taken into account [84,85]. A phase one clinical trial of quercetin carried out in 1990's showed it to be safe and provided evidence of antitumor activity [86]. Further anticancer potentials of quercetin have been recently reviewed [30,35]. To date, one study of quercetin in Covid-19 has been entered into a clinical trial www.clinicaltrials.gov.

It is of importance to note that quercetin bioavailability is generally poor and because of its lipophilicity has low water solubility. Moreover, several factors such as glucose moieties, dietary fat, vitamin C as well as age and gender may affect quercetin levels in positive or negative ways [64,87,88,89,90,91]. In this regard it is noteworthy that food intake is a major source of quercetin and unlike majority of supplements, most of the quercetin in food is attached to sugar moieties such as glucose or rutinose. Thus, onion-derived quercetin, which is mainly quercetin glucoside, has a better bioavailability than apple-derived quercetin, which contains quercetin rhamnoside and quercetin galactoside [92,93]. In addition, quercetin has a better bioavailability when consumed as a cereal bar ingredient instead of capsule [94]. This is because quercetin's homogenous solid dispersion with other cereal ingredients results in a larger surface area and hence a better absorption [64,94,95]. Also, ingestion of quercetin with short chain fructooligosaccharide improves its bioavailability as this saccharide suppresses the bacterial degradation of quercetin aglycone in the large intestine and allows for more quercetin absorption [96]. Vitamin C as an antioxidant can protect against oxidative degradation of quercetin and hence improve its absorption and bioavailability [64,97,98]. It would be of significant interest to determine whether combination of quercetin with zinc and DHM (discussed below) would also enhance its bioavailability. Nonetheless, search for other methods of improving bioavailability of flavonoids in general and quercetin in particular using nano-capsulation or a phospholipid delivery system are under way [24,28].

Dihydromyricetin (DHM)

Dihydromyricetin (DHM) is a unique flavanonol, a subgroup of flavonoids isolated from Japanese raisin trees (Hovenia dulcis Thum) and Chinese Rattan tea (Ampelopsis grossedentata)

[99,100]. This subgroup is a class of secondary plant metabolites that perform many physiological functions in plants and have been shown to have antioxidant, anti-inflammatory and neuroprotective properties, and their use has been associated with motor and memory improvements [100]. DHM specifically has been recommended for diverse conditions such as metabolic diseases, including diabetes [101], liver disease [102], septic acute kidney injury [103], inflammatory bowel disease [104], atherosclerosis [105], cancer [106], neurodegenerative diseases including Alzheimer's disease [107,108].

After ingestion by animals, some DHM is metabolized in the gastrointestinal tract and liver, and the rest is absorbed into the bloodstream and is widely distributed throughout the body, including the heart, lungs, kidney and the brain tissue [109]. DHM is poorly absorbed into the bloodstream, with a bioavailability of only 4.02%. Furthermore, the time required for it to reach peak plasma concentration is 2.67 h after oral administration at a dose of 20 mg/kg [110]. The uptake and transport of DHM occurs mainly through a passive diffusion mechanism, which can partially explain the low bioavailability of DHM after oral administration [111]. DHM is completely excreted in urine and feces after 12 h. Seven to eight DHM metabolites have been identified in urine, feces, and blood [109], all of them produced by common metabolic routes such as dihydroxylation, methylation, glucuronidation, reduction, and isomerization [85,88]. Whether these metabolites have any pharmacologic effect is still unknown.

Although there have been few DHM toxicity studies, some important information has already been obtained. For example, the lethal dose 50% for oral administration in mice is >5 g/kg [113]. At concentrations ranging from 150 mg/kg (500 mmol/L) to 1.5 g/kg (5,000 mmol/L), DHM did not cause any acute toxicity or had significant side effects in mice [114]. However, nephrotoxic components of some herbal medicine including flavonoid glycosides was recently reviewed [115,116]. Since low bioavailability limits the pharmacologic efficacy [117], several preparations with better solubility or permeability have been identifies in vitro studies. These include microemulsion [118], nanoparticles [119], soluble cocrystals [120], nanoencapsulation [121], and solid dispersions and inclusion complex [13]. In this regard, a nanoscale DHM-phospholipid complex significantly increased oral bioavailability in rats [122].

In regard to COVID-19, DHM effects against a wide range of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) viruses has been studies and it is anticipated that compounds with sufficient bioavailability will find therapeutic use in COVID-19. Specifically, it was shown that DHM is an effective inhibitor for SARS-CoV-2 Mpro, (coronavirus main protease), which is essential for SARS-CoV-2 replication. Moreover, DHM prevented bleomycin (BLM)-induced pulmonary inflammation and fibrosis in mice, suggesting that DHM could be a potential medicine for the treatment of COVID-19 and its sequelae [123]. DHM also has antithrombotic effects via inhibition of platelet activation and reduction of fibrin generation as a result of endothelial protection [124]. This action, similar to that of quercetin (discussed above) would be an additional desirable effect against COVID-19.

Several in vitro studies have shown that DHM inhibits lipid-peroxidation [125,126,127,128], which suggest that DHM can protect cell membrane lipids against the damage induced by an excess of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Indeed, DHM may reduce oxidative damage via several mechanisms including: a direct radical-scavenging and iron (Fe+2)-chelation [129]; increasing the enzymatic activity of superoxide dismutase (SOD), which catalyzes the dismutation of superoxide anion to molecular oxygen [130,131]; modulation of CAMP-activated protein kinase to cause inhibition of the oxidative stress response [132]; as well as activating phosphatidylinositol 3-kinase (PI3K/Akt) and modulating the nuclear transcription factor-erythroid 2-related factor 2 (Nrf2), which participates in the induction of enzymes involved in detoxifying and antioxidant properties [133,134,135].

The anti-inflammatory effect of DHM, on the other hand, have been attributed to decreases in the production of pro-inflammatory cytokines such as interleukin IL-1β and IL-6, and increases in the production of anti-inflammatory cytokines such as IL-10, as well as reduction of nitric oxide [135,136]. In addition, DHM has been shown to reduce tumor necrosis factor-alpha (TNF-α) levels through inhibition of nuclear factor-kappa B (NF-kB), a protein complex that controls cytokine production and regulates apoptosis [137].

It is therefore evident that both quercetin and DHM share a number of positive effects such as anti-inflammatory, anti-oxidant and immune modulatory characteristics that can be of significant counter-balance to the detrimental effects of SARS-CoV-2 virus. Although the bioavailability of both these compounds is of a relative concern, it appears that their combination would nonetheless be of benefit in prevention and/or as adjunct treatment in COVID-19 as their mechanisms of action might provide an additive or synergistic effect. This potential outcome, together with the following discussion on zinc provides a strong justification for the combined use of these 3 substances as an adjunct strategy in prevention and/or treatment of COVID-19.

Zinc

Zinc is one of the most commonly over-the-counter naturopathic medicine used for a variety of clinical indications including prevention and treatment of viral respiratory infections, tissue repair and a healthy immune system [114]. This is because zinc has an essential role in immune system, as well as in airways function, wound healing and tissue repair [139,140,141]. It may also modify the host's response to an infection as it is an essential co-factor element with a broad range of functions in the body. In addition, a role in regulation of gene expression as well as in insulin and blood pressure modulation has been ascribed to zinc [142]. The fact that Zn can be formulated as a stand-alone nutraceutical or as a combination product containing other minerals, vitamins and herbs makes it ideal for a combination therapy, particularly with flavonoids, which are known to act as zinc ionophores [143]. Indeed, a combination of quercetin and zinc has been advocated in treatment of bladder cancer [144]. The daily recommended dietary intake (RDI) of elemental zinc is around 2 mg for infants (up to 6 months of age), and gradually increases to 11 mg for males, and 8 mg per day for females older than 13 years [145]. Tolerable upper limits for zinc are estimated to be 7 mg for children aged 1–3 years and increasing up to 25 mg for adults and females of any age who are pregnant or lactating. The no-observed-adverse-effect level (NOAEL) for adults is around 50 mg/day [146].

Over 17 % of the global population is estimated to be zinc deficient [147], and 20 % of national diets contain insufficient zinc to meet minimum health requirements [148,149]. While zinc

insufficiency/deficiency is known to diminish antibody and cell-mediated immunity in humans, which can increase the risk of infections, this may only become apparent upon immune system provocation [150,151]. Zinc's ability to reduce the risk of viral respiratory tract infections, including SARS-CoV-2, can shorten the duration and severity of the illness. It is suggested that in addition to its direct antiviral properties, zinc has the potential to reduce inflammation, improve mucocillary clearance, prevent ventilator-induced lung injury, and modulate antiviral immunity [152].

Zinc can inhibit the enzymatic activity and replication of SARS-CoV RNA polymerase and may inhibit ACE2 activity [147,152-154]. Zinc is also thought to potentiate the therapeutic effects of chloroquine [155], as chloroquine also acts as a zinc ionophore increasing Zn2+ influx into the cell [152]. Other consequences of zinc deficiency include an increased risk of vitamin A deficiency that is also critical for immune function. Zinc's effect on carrier proteins and activation enzymes is necessary for vitamin A production [156]. The potential role of zinc as an adjuvant therapy for SARS-CoV-2 may be broader than just antiviral and/or immunological support. Zinc also plays a complex role in hemostatic modulation acting as an effector of coagulation, anticoagulation and fibrinolysis [157,158,159]. As discussed above, this is of considerable significance as coagulation consequences of COVID-19, leading to stroke has been amply documented [156-160, 160-162].

Although zinc supplementation was shown to be effective in prevention of pneumonia in children aged two to 59 months [163], the effectiveness of zinc in preventing or treating SARS-CoV-2 infections is yet to be systematically evaluated. Nonetheless, given the positive attributes discussed above, addition of zinc as a nutritional supplement in combatting COVID-19 is highly recommended [164].

Conclusion

Besides antivirals, anti-HIV protease inhibitors, and anti-inflammatory agents that are currently used against the severe cases of COVID-19, natural compounds isolated from the plant such as flavonoids represent an additional therapeutic option. Flavonoids' lack of systemic toxicity plus their ability to synergize with conventional drugs and mineral/micronutrients makes them an ideal nutritional supplement to interfere with the coronavirus life cycle. Moreover, higher level of intracellular zinc can affect RNA-dependent RNA polymerase and decrease replication mechanism of RNA viruses. It is therefore concluded that combination of the potent antioxidant quercetin and antiviral DHM with mineral zinc as supplements could offer an adjunct strategy in prevention and/or treatment of COVID-19 (Figure 1).

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Authors' Contribution:

All authors contributed to the concept and design of study as well as acquisition and interpretation of data. The first draft of manuscript was initiated by HL, which was expanded by BG and YT. The final submitted version was approved by all authors. YT is the PI on the acknowledged grants and the corresponding author for this article.

Conflicts of Interest/ Competing Interests:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

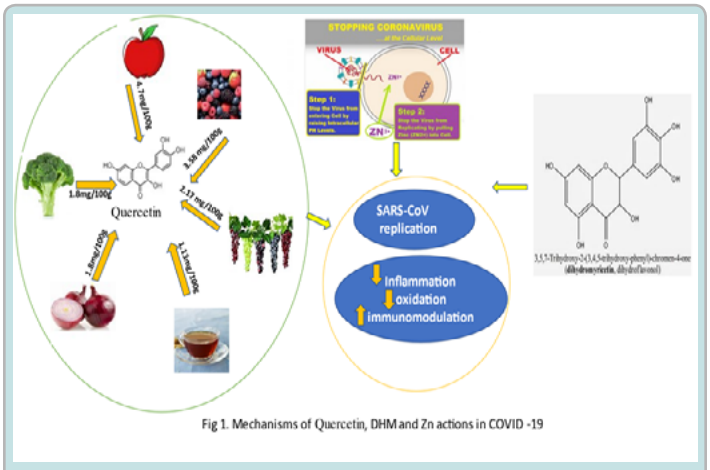

Figure 1: Mechnisms of Quercetin, DHM and Zn actions in COVID-19.

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