HHS Public Access

Author manuscript

Medpress Nutr Food Sci. Author manuscript; available in PMC 2022 June 24.

Published in final edited form as:

Medpress Nutr Food Sci. 2022 ; 1(1): .

Therapeutic Potential of Flavonoids and Zinc in COVID-19

Harold E. Landis, DDS[1],

Bruk Getachew, Ph.D.[2],

Yousef Tizabi, Ph.D.[2,*]

[1]Integrative Medicine Fellow, University of Arizona, Tucson, AZ

[2]Department of Pharmacology, Howard University College of Medicine, Washington, DC

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 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. 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, following a brief review of 2 select flavonoids; quercetin as a potent antioxidant, and dihydromyricetin (DHM) as an effective antiviral agent together with Zn, essential for immune function, we suggest potential use of a combination of these compounds as an added prevention and/or treatment modality in COVID-19.

Keywords

Flavonoids; Quercetin; Dihydromyricetin; Zinc; Covid-19

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

[*]Correspondence: Yousef Tizabi, Ph.D., Department of Pharmacology, Howard University College of Medicine, 520 W Street NW, Washington, DC 20059, Tel: 202-806-7919, Fax: 202-806-4453, ytizabi@howard.edu.

Authorship Statement

H.E. Landis and Y. Tizabi equally contributed to the conception of the research. B. Getachew contributed to the design of the research. B. Getachew and Y. Tizabi drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Conflicts of Interest: None declared.

Declaration of 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.

provides viral entry into human cells [1]. 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 vasal endothelium, the kidneys and nervous system where it can cause severe illness and death [2]. The clinical symptoms are mainly fever, dry cough, and fatigue. Some cases are accompanied by nasal congestion, runny nose, sore throat, muscle pain, and diarrhea. Severe patients have high levels of cytokines and chemokines in plasma which can easily lead to cytokine storm. Although cytokine storm is considered a hallmark of COVID-19, its full role is yet to be elucidated [3]. Acute respiratory distress syndrome (ARDS), shock, multiple organ dysfunction syndrome (MODS), and sudden myocarditis appear in severe and terminal patients afflicted with COVID-19 [4]. As the number of cases and deaths are continuously and rapidly rising, introduction of novel nutritional or other pharmacotherapies in strengthening the immune system are critical in slowing down this devastating pandemic. In this brief review we concentrate on potential use of select flavonoids together with zinc as beneficial supplements.

Methods

To prepare this review article, PubMed, ClinicalTrials.gov, and Biomed Central databases were searched under the terms such as: “Covid-19”, “coronavirus,” “quercetin,” “dihydromyricetin” “polyphenol,” “zinc,” and “flavonoid” through November 2020. A total of 126 paperw were reviewed. We focused on the antiviral as well as any other benefits associated with the compounds of interest.

Flavonoids

Bioactive phytoconstituents, available as natural components in foods and medicinal plants, can provide preventive and other health benefits in COVID-19. Thus, components like alkaloids, flavonoids, flavanols, anthocyanins, phenolic acids, polyphenols, tannins, resveratrol, polysaccharides, and sterols, identified as “green” ACE inhibitors, may interfere with SARS-CoV-2 entry.

Flavonoid monomers mainly include quercetin, kaempferol, and myricetin, while flavanonols include dihydromyricetin (DHM). Although only recently flavonoids have caught the attention of researchers for their potential implications, flavonoid research spans several decades. In fact, protective role of falvonoids in the diet was recognized in the 1990s, when flavonoid contents of 28 vegetables and 9 fruits and teas, wines, and fruit juices were quantified [5]. 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. Various other beneficial effect such as antihypertensive, antihistamine, antidiabetic, antimicrobial, memory enhancing, and mood-boosting properties were also ascribed to these flavonoids [6,7]. 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, have resulted in their utilization as basic natural ingredient in more than hundred herbal medicines. 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 in prevention and treatment of COVID-19.

Quercetin

The natural flavonoid quercetin is frequently found in low amounts as a secondary plant metabolite 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. Quercetin itself enters the circulatory system in trace amounts only and appears predominantly as glucuronide, sulfate, and methyl metabolites. It can cross the blood–brain barrier, and has various biological effects including potent anti-oxidant and anticancer properties [6–8]. Importantly, in relevance to COVID-19, quercetin's action as zinc ionophore, meaning its ability to bind Zn and increase its transport across the cell membrane, has led to the suggestion of an antiviral activity against many RNA viruses including SARS-CoV-2 [9]. Furthermore, antithrombotic action of quercetin may be an additional desirable effect against COVID-19, as thrombotic incidences are common manifestation with this disease. In this regard, it has been demonstrated that quercetin and quercetin-3-*O*-rutinoside prevent platelet aggregation and inhibit lipoxygenase (LOX) activity in various cell culture models as well as *in vivo* [10].

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 5 most potent compounds for binding to the interface site and potentially disrupting the initiating infection process. 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 against COVID-19. Moreover, earlier studies showed that quercetin has the capacity to block the entry of SARS-CoV into host cells. Recently, it was speculated that quercetin could be involved in immune regulation and that it could be of potential therapy in lung injury associated with COVID-19 due to its anti-inflammatory, antiviral, and immunomodulatory effects. Based on these findings, it has been suggested that quercetin be incorporated into trials against COVID-19 [11,12].

The United States Food and Drug Administration has already approved oral doses of quercetin as safe for human consumption. Quercetin given nasally was effective in a rat model of allergic rhinitis [49], and the safety of quercetin has been favorably assessed. Previously found beneficial effects on cardiovascular health biomarkers after regular consumption of quercetin, could deliver an additional positive outcome as patients with pre-existing cardiometabolic syndromes such as hypertension are at increased risk during Covid-19 infection. A phase one clinical trial of quercetin carried out in 1990's showed it to be safe and provided evidence of antitumor activity. 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 sex may affect quercetin levels [13]. 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. In addition, quercetin has a better bioavailability when consumed as a cereal bar ingredient instead of capsule. This is because quercetin's homogenous solid dispersion with other cereal ingredients results in a larger surface area and hence a better absorption [14]. 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. Finally, as mentioned above, vitamin C as an antioxidant can protect against oxidative degradation of quercetin and hence improve its absorption and bioavailability [13].

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). These plants have been used for a long time in Asian traditional medicine to treat different health problems. 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 [15].

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. DHM is also poorly absorbed into the bloodstream and has a low bioavailability. Since low bioavailability limits the pharmacologic efficacy, several preparations with better solubility or permeability have been identified *in vitro* studies. These include microemulsion, nanoparticles, soluble cocrystals, nanoencapsulation, and solid dispersions and inclusion complex. In this regard, a nanoscale DHM-phospholipid complex significantly increased oral bioavailability in rats. Since this flavonoid has been studied against a wide range of DNA and RNA viruses, it is anticipated that compounds with sufficient bioavailability will find therapeutic use in COVID-19. Indeed, use of herbal medicine against COVID-19 has been amply touted in recent months [16].

Several *in vitro* studies have shown that DHM inhibits lipid-peroxidation, 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). 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, tumor necrosis factor-alpha (TNF-α) and increases in the production of anti-inflammatory cytokines such as IL-10, as

well as reduction of nitric oxide [17]. Thus, it may be suggested that the antioxidant and antiinflmmatory activities of DHM render it a sutiable dietary supplement aginst 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. This is because zinc has an essential role in immune and airways function, wound healing and tissue repair [18,19]. 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 for insulin and blood pressure regulation as well as regulation of gene expression has been ascribed to zinc. 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 as alluded to earlier act as zinc ionophores [9]. Indeed, a combination of quercetin and zinc has been advocated in treatment of bladder cancer [20].

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. Tolerable upper limits for zinc are estimated to be 7 mg for children aged 1–3 years, 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. However, over 17 % of the global population is estimated to be zinc deficient and 20 % of national diets contain insufficient zinc to meet minimum health requirements [21]. 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. Other consequences of zinc deficiency include an increased risk of vitamin A deficiency that is also critical for immune function.

Zinc's ability to reduce the risk of viral respiratory tract infections, including SARS-CoV-2, together with its inflammatory activity can result in improved mucocillary clearance and prevention of the ventilator-induced lung injury [22]. Indeed, potential utility of zinc as an adjuvant therapy for SARS-CoV-2 may be broader than just antiviral and/or immunological support. This is because Zinc also plays an important role in hemostatic modulation by acting as an effector of coagulation/anticoagulation and fibrinolysis [23]. The latter is of considerable significance as coagulation consequences of COVID-19, leading to stroke has been amply documented [24]. Thus, it may be concluded that addition of zinc as a nutritional supplement in combatting COVID-19 is highly recommended.

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 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

Acknowledgement:

Supported by NIH/NIGMS 2 SO6 GM08016 and Howard University College of Medicine Bridge Funds and Pilot Study Awards Program (BFPSAP) 2020-2021

Biographies

Yousef Tizabi, Ph.D is Professor of Pharmacology at Howard University College of Medicine. His expertise are in Neuropharmacology, Neurodegenerative and Neuropsychiatric disorders. He is focused on development of novel pharmacotherapies including use of herbal medicine such as curcumin, resveratrol, etc. for prevention and/or treatment of such disorders.

Harold E. Landis, DDS is a practicing dentist as well as a Fellow of Integrative Medicine at University of Arizona, Tucson, AZ

Bruk Getachew, Ph.D. is a Research Associate in the Department of Pharmacology at Howard University College of Medicine. He has extensive collaboration with Dr. Tizabi.

References

1. Devaux CA, Rolain JM, Raoult D. ACE2 receptor polymorphism: Susceptibility to SARS-CoV-2, hypertension, multi-organ failure, and COVID-19 disease outcome J Microbiol Immunol Infect 2020;53(3):425–435. [PubMed: 32414646]
2. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395(10234):1417–1418. [PubMed: 32325026]
3. Hojyo S, Uchida M, Tanaka K, Hasebe R, Tanaka Y, Murakami M, et al. How COVID-19 induces cytokine storm with high mortality. Inflamm Regen 2020;40:37. [PubMed: 33014208]
4. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020; 46(5):846–848. [PubMed: 32125452]
5. Williamson G, Kay CD, Crozier A. The Bioavailability, Transport, and Bioactivity of Dietary Flavonoids: A Review from a Historical Perspective. Comp Rev Food Sci Food Saf 2018; 17:1054–1112.
6. Ademiluyi AO, Oboh G. In vitro anti-diabetes and antihypertension potential of phenolic extracts of selected underutilized tropical legumes. J Basic Clinical Physiol Pharmacol 2012;23(1):17–25. [PubMed: 22865445]
7. Spagnuolo C, Moccia S, Russo GL. Anti-inflammatory effects of flavonoids in neurodegenerative disorders. Eur J Med Chem 2018;153:105–115. [PubMed: 28923363]
8. Dobrydnev AV, Tkachuk TM, Atamaniuk VP, Popova MV. Quercetin-amino acid conjugates are promising anti-cancer agents in drug discovery projects. Mini rev. Med Chem 2020;20(2):107–122. [PubMed: 31595850]
9. Derosa G, Maffioli P, D'Angelo A, Di Pierro F. A role for quercetin in coronavirus disease 2019 (COVID-19). Phytother Res 2020 9:10.1002/ptr.6887. Epub ahead of print.

10. Gryglewski RJ, Korbut R, Robak J, Swies J. On the mechanism of antithrombotic action of flavonoids. Biochem Pharmacol 1987;36(3):317–22. [PubMed: 3101704]
11. Haslberger AG,Jacob U, Hippe B, Karlic H. Mechanisms of selected functional foods against viral infections with a view on COVID-19: Mini review. Funct Food Health Dis 2020;5:195–209.
12. Sargiacomo C, Sotgia F, Lisanti MP. COVID-19 and chronological aging: senolytics and other anti-aging drugs for the treatment or prevention of corona virus infection? Aging 2020; 12(8):6511–6517. [PubMed: 32229706]
13. Guo Y, Mah E, Bruno RS. Quercetin bioavailability is associated with inadequate. plasma vitamin C status and greater plasma endotoxin in healthy adults. Nutrition 2014;30:1279–1286. [PubMed: 25280405]
14. Dabeek WM, Marra MV. Dietary Quercetin and Kaempferol: Bioavailability and Potential Cardiovascular-Related Bioactivity in Humans. Nutrients. 2019;11(10):2288.
15. Zhang J, Chen Y, Luo H, Sun L, Xu M, Yu J, et al. Recent update on the pharmacological effects and mechanisms of dihydromyricetin. Front Pharmacol. 2018;9:1204. [PubMed: 30410442]
16. Dzobo K, Chiririwa H, Dandara C, Dzobo W. Coronavirus disease-2019 treatment strategies targeting interleukin-6 signaling and herbal medicine. OMICS;2020. Epub ahead of print..
17. Tang N, Ma J, Wang KS, Mi C, Lv Y, Piao LX, et al. Dihydromyricetin suppresses TNF-α-induced NF-κB activation and target gene expression Mol Cell Biochem 2016;422:11–20. [PubMed: 27686451]
18. Prasad AS, Beck FW, Bao B, Fitzgerald JT, Snell DC, Steinberg JD, Cardozo LJ. Zinc supplementation decreases incidence of infections in the elderly: effect of zinc on generation of cytokines and oxidative stress. Am J Clin Nutr 2007;85(3):837–44. [PubMed: 17344507]
19. Chasapis CT, Ntoupa PA, Spiliopoulou CA, Stefanidou ME. Recent aspects of the effects of zinc on human health. Arch Toxicol 2020;94(5):1443–1460. [PubMed: 32394086]
20. Lee YH, Tuyet PT. Synthesis and biological evaluation of quercetin-zinc (II) complex for anti-cancer and anti-metastasis of human bladder cancer cells. In Vitro Cell Dev Biol Anim 2019;55(6):395–404. [PubMed: 31089950]
21. Hess SY. National risk of zinc deficiency as estimated by national surveys. Food Nutr Bull 2017;38(1):3–17. [PubMed: 28118744]
22. Skalny AV, L. Rink L, Ajsuvakova OP, Aschner M, Gritsenko VA, Alekseenko SI, et al. Zinc and respiratory tract infections: Perspectives for COVID-19 (Review). Int J Mol Med 2020;46(1):17–26. [PubMed: 32319538]
23. Mammadova-Bach E, Braun A. Zinc homeostasis in platelet-related diseases. Int J Mol Sci 2019;20(21):5258.
24. Gąsecka A, Borovac JA, Guerreiro RA, Giustozzi M, Parker W, Caldeira D, Chiva-Blanch G. Thrombotic complications in patients with COVID-19: pathophysiological mechanisms, diagnosis, and treatment. Cardiovasc Drugs Ther 2020;19:1–15.