Review Article

SARS-CoV-2 and bioactive compounds: a Literature Review

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ABSTRACT

Aims: This literature review seeks to summarize the role of some bioactive compounds during COVID-19.
Methodology: A PubMed literature review was conducted using combinations of the key words “natural products,” “nutrients,” and “COVID-19.” All study types were considered and relevant articles were utilized for this review.
Results: COVID-19 is an infectious disease caused by the SARS-CoV-2 coronavirus, and dietary factors can influence the transmission and/or progression of the disease. Vitamin C, vitamin D, zinc, turmeric, ginger and propolis have antiviral, anti-inflammatory and immunomodulatory activity and can be a great ally in the fight against the new coronavirus.
Conclusion: Despite the diverse scientific evidence that points to the benefits of bioactive compounds in the treatment of COVID-19, more randomized and controlled studies are needed to determine the ideal doses of consumption or supplementation and the times when this administration is safe.

Keywords: COVID-19, health, natural products, nutrients.

1. INTRODUCTION

With the arrival of COVID-19, many existing global health problems became more evident. In addition to energy shortages, climate change and environmental degradation, food insecurity is increasingly visible. Although all people have the right to access food in adequate quantity and quality, the pandemic had a significant impact on this process. According to the Eat Report (2020), 820 million people still do not have access to food in adequate quantities and qualities. It is also known that both malnutrition and obesity can worsen the clinical outcome of patients with COVID-19. Regarding food quality, individuals decreased their consumption of healthy foods and increased their consumption of ultra-processed foods. Such changes in food consumption negatively impact the health of individuals [1].

The consumption of healthy foods, rich in vitamins, minerals and bioactive compounds that can help in the functioning of the immune system [2]. In general, viral infection increases oxidative stress and inflammatory cytokines which can cause cell malfunction [3]. On the other hand, the consumption of foods rich in bioactive compounds can strengthen physiological functions, thus allowing a better response of the immune system to the disease, that is, can play a role in preventing and/or treating COVID-19 [4].

This review focuses on the mechanisms of action of bioactive compounds can affect the proliferation and spread of the COVID-19 virus. To this, a literature search was performed using PubMed from database inception to May 2023. Articles written in english, spanish portuguese are included. The search terms included “natural products and COVID-19”; “nutrients and COVID-19”.

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2. LITERATURE REVIEW

2.1 Vitamin C

In general, viral infection increases oxidative stress and inflammatory cytokines which can cause cell malfunction [3]. In order to mitigate the infection scenario, there is a greater metabolic demand for vitamin C [5]. Thus, the ingestion of substances such as ascorbic acid, if used regularly and in adequate doses, can help the immune system efficiently [6, 7]. Supplementation has the potential to treat respiratory and systemic infections, and may relieve chest pain, fever and chills, in addition to decreasing the average recovery time from flu syndrome [8, 9].

Hypotheses about the use of vitamin C and its potential in mitigating the symptoms of patients with COVID-19 are being investigated, not only for mild conditions, but also in patients with critical conditions [10]. In consideration of the development of possible lung lesions in viral infections such as SARS-CoV-2, antioxidants play a role in managing these conditions by protecting important structural components of cells [7]. Thus, the adequacy of the consumption of foods that are sources of Vitamin C and, in some cases, supplementation with this micronutrient can assist in maintaining health, in addition to participating as adjuvant therapy in infections by viral diseases [11, 12].

In severe cases, intravenous administration of vitamin C has also been studied and indicated [13]. A recent study proposed a protocol for the administration of vitamin C to patients with COVID-19. This protocol includes administration in a single or divided dose in 2 to 4 times a day from 0.2 to 0.5 g/kg of body weight per day of vitamin C, and in more severe patients the amount can be increased to 0.4 to 1 g/kg of body weight per day of vitamin C. When the dose administered is greater than 50 g per day, it is recommended that vitamin C be offered through the central venous access. The recommended infusion rate is 0.25 to 0.5 g/min, between 1 to 4 hours depending on the dose. In addition, calcium and/or magnesium supplementation is recommended, as vitamin C can interfere with the levels of these minerals. Through the enteral route, it is suggested to administer 220 mg zinc sulfate (50 mg elemental zinc) daily, 400 mg thiamine daily, 6 mg melatonin daily and 1600 IU vitamin E every other day. In addition, it should be offered from 5,000 to 10,000 IU of vitamin D a day, with the objective of reaching serum 25-OH levels between 80 to 90 nmol/L. The same authors report that up to 100 g daily vitamin C is safe, as long as the patient's evolution is accompanied by laboratory tests, such as blood count, kidney function, iron, ferritin, electrolytes [14].

2.2 Vitamin D

Vitamin D can act by preventing an uncontrolled immune system function in the face of the pathology triggered by SARS-CoV-2, which is associated with the release of pro-inflammatory cytokines within the cells of the host [11, 15]. In addition, calcitriol (1,25-dihydroxyvitamin D3) plays a modulating role in the expression Angiotensin-Converting Enzymes 1 (ACE1) and 2 (ACE2), thus increasing protection against lung injury [16, 17].

Therefore, the decrease in ACE2 activity in the lungs improves the health outcomes of patients with the new coronavirus [18]. CRP, an inflammatory marker in response to cytokines, was found reduced in patients with high levels from vitamin D, according to the University of Cinccinati [19]. Another factor of great relevance was the appearance of clots in patients who presented with severe COVID-19, where high serum concentrations of D-dimer would be associated with a high prothrombotic prevalence in patients in ICU [20].

2.3 Zinc

Regarding minerals, zinc is being much discussed in the current literature, which directly affects the immune system. It is known that the elderly is more likely to have zinc deficiency, being a trigger for the development of pneumonia, since the risk of the organism is increased when contracting entero-viral pathogens and bacteria that can cause intestinal dysfunction and decrease the absorption of nutrients, further leading to the compromise of the mineral in the body [21].

The implications for the use of zinc in patients with COVID-19 are diverse. First, zinc positively affects innate and acquired immunity [22]. Second, it is known that zinc has a potent antiviral action against several types of viruses, such as single strand positive sense RNA virus (+) ssRNA, being extremely important in the treatment of viral infections [4]. In the current scenario of COVID-19, zinc plays an important role in inhibiting the RNA-dependent RNA Polymerase (RdRp), present in the virus, and its ionophores act by blocking the replication of SARS-CoV-2 within the cell [23]. Third, according to Mayor-Ibarguren et al. (2020) [24], low levels of zinc have been observed in the most severe cases of COVID-19. IL-6 has also been linked to severe lung injury. IL-6 (-174G/C) polymorphism carriers have higher IL-6 values in addition to changes in zinc homeostasis [25]. Finally, some authors point out that zinc may inhibit ACE2 activity [21], in addition to potentiating the action of antiviral drugs [22].

2.4 Curcumin

More than 300 clinical trials have shown benefits of curcumin against inflammatory diseases, metabolic diseases, liver disease and cancers. In addition, studies show the effectiveness of this bioactive compound against different viruses, such as the human immunodeficiency virus (HIV) [26], Chikungunya and Zika virus [27], which can be an alternative in the treatment of COVID-19 [28].

The effects of curcumin in combating viral infections occur due to its ability to prevent the virus from entering the cell [29] in addition to inhibiting the oxidative stress caused by inflammation [30]. Specifically, in COVID-19, curcumin can bind to the receptor-binding domain of the viral spike protein, thereby preventing the binding of that protein to the ACE2 receptor and, consequently, preventing replication of the virus [31]. Furthermore, in pulmonary inflammation, there is evidence that turmeric decreased the expression of pro-inflammatory cytokines [28] and acts as an antithrombotic [29, 32].

2.5 Ginger

Studies validate that the compounds found in ginger are satisfactory for the relief of symptoms of inflammatory diseases, positively interfering in the immune response, in addition to having antipyretic, analgesic, antidiabetic, anticancer, antioxidant and anti-inflammatory effects [33]. Although it does not directly affect leukocyte activities, its action contributes to the strengthening of immunity. It is a source of the phytochemical gingerol, which acts to reduce the secretion of IL-1, IL-12 and TNF-α. Shogaol, another potent phytochemical, is able to inhibit the production of prostaglandin E2 and pro-inflammatory cytokines such as IL-1β and TNF-α [34, 35].

In the composition of ginger essential oil, its constituents are used pharmacologically in the treatment of chronic inflammation, pulmonary obstruction, asthma and rheumatoid arthritis. In addition, it has the ability to inhibit the synthesis of prostaglandins and platelet

aggregation, which, as previously stated, is a clinical condition frequently seen in patients with COVID-19 [36, 37].

A study of mice treated with ginger extract, the results suggest that the volatile oil of ginger influences the cell-mediated immune response and the nonspecific proliferation of T lymphocytes, and may have beneficial effects in various clinical conditions, such as inflammation [38]. In addition, ginger influences the expression of antioxidant enzymes [39, 40]. Furthermore, ginger also has anti fibrotic properties – in studies with animal models, pulmonary fibrosis was reduced as well as oxidative stress and inflammatory status [41].

2.6 Propolis

Propolis has been used by medicine for many years for the treatment of various diseases due to its wide therapeutic properties as antimicrobial, antioxidant and antiviral activity in the human body [42]. Its composition is defined by several factors such as region, climate, seasons and environmental conditions. However, most of the bioactive compounds present in propolis are from the class of polyphenols, including flavonoids, tannins, stilbenes and phenolic acids [43].

In clinical studies, propolis has demonstrated antiviral activity in different types of viruses such as HSV-1, HSV-2, influenza virus types A and B, parainfluenza virus, adenovirus, HIV, among others [44]. In addition, the flavonoids present in several types of propolis (quercetin, luteolin and kaempferol) can develop an anti-inflammatory and antiviral action, whereas those found in red propolis can act as an anti-inflammatory and hyperthermia reducing agent, being able to exert a beneficial action in treatment by COVID-19 [39]. In addition, propolis strengthens the immune system by increasing the activity of NK cells that fight tumor cells and develops antimicrobial action against Gram-positive bacteria [45]. The effects on the immune system are also associated with a reduction in prostaglandins, leukotrienes and pro-cytokines, inflammatory with increased IL-10 [42].

Studies with propolis and coronavirus are scarce. One of the main mechanisms by which propolis acts as an antiviral involves its potential effect of inhibiting the entry of the virus into cells, thus decreasing its replication [44]. The caffeic and p-coumaric acids found in the propolis extract can bind to HSPA5 present on the cell surface, preventing the viral protein from binding to that location. This effect can also be developed by Caffeic Acid Phenethyl Ester (CAPE), which in addition to suppressing lipoxygenases, inhibits the production of leukotrienes by macrophages [46]. In addition, CAPE is considered a RAC/CDC42-activated kinase 1 (PAK1) blocker, capable of decreasing the expression of the PAK1 pathway, thus decreasing pulmonary fibrosis caused by COVID-19 [47].

Thirty years ago, Debiaggi et al. (1990) [48] conducted a study with human coronavirus OC43 and demonstrated that chrysine and kaempferol inhibited viral replication. Another flavonoid found in propolis that has an important effect is quercetin. In an in vitro study, Nguyen et al. (2012) [49], showed that epigallocatechin gallate and quercetin inhibit the SARS-CoV main protease 3CLpro, the main protease responsible for virus replication. Another in vitro study also showed that quercetin inhibits both of the SARS-CoV proteases, 3CLpro and PLpro, in addition to inhibiting 3CLpro protease in cases of Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV) [50]. According to Nabirotchkin et al. (2020) [51], a quercetin modulates the cellular Unfolded Protein Response (UPR), a pathway that, when activated, increases the expression of chaperones located in the endoplasmic reticulum and is used at different times in the replication of the virus during infection.

The viral spike connects with the receptor protein so that the virus's genetic material is then deposited in the cell. The preferential receptor by SARS-CoV-2 is called ACE-II. SARS-CoV-2 spike protein is estimated to have a strong binding affinity to human ACE-II. So, one of the therapeutic targets is to block the ACE-II receptor so that the virus stops infecting new cells. A study looking for flavonoids in propolis extract with the ability to bind these receptors was done and showed that rutin, myricetin, quercetin, CAPE and hesperetin have a better affinity against ACE-II enzyme than natural inhibitor MLN-4760 among the evaluated compounds. It's important to notice that the smaller binding energy and Ki value, the more tightly bound the ligand is [52]. The administration of antivirals such as IFN-α, ribavirin, chloroquine phosphate and arbidol together with propolis, can develop a positive recovery effect for patients infected with SARS-CoV-2 [42]. However, some people have an aversion to propolis and may develop allergies and contact dermatitis, requiring an evaluation and monitoring of patients who will receive this substance [46].

In summary, Table 1 shows the articles that were carried out using some of the bioactive compounds in COVID-19, followed by the dose or therapeutic plan, main results and mechanisms of action.

Table 1. Potential of bioactive compounds in COVID-19

Bioactive Compounds	References	Dose/Therapeutic plan	Conclusions	Mechanism of action
Vitamin C	[14]	30 – 60 g/day (with calcium and/or magnesium supplementation)	Improves in the oxygenation index.	Neutralizes free radicals preventing them from causing tissue damage and also activating the factor nuclear kappa B (NF-kB) pathway; reduction of oxidative stress and inflammatory state.
	[53]	1,5 g/6h/day	Improvement in chest radiologic findings and lower mortality.	
	[54]	50 mg/kg/day	Did not significantly improve organ dysfunction scores, c-reactive protein levels or vascular injury. The study itself reports that possible limitations may have interfered with the results found. One of these limitations is that the dosage of vitamin C administered, that is, 50 mg/kg every 6 hours for 96 hours, may be insufficient for the control of the sepsis associated ARDS.	
	[55]	6 g intravenous infusion per 12 hr on the first day and 6 g once for 4 days	Patients with > 60 years and severe or critical disease, the risk of mortality was significantly reduced – about 20%, with higher dose vitamin C than standard therapy. For moderate cases, oxygen support status was improved for 28 patients, and 17 of them were in the high-dose vitamin C group and 11 in the standard therapy group, which represents a 28% advantage for those who received ascorbic acid.	
	[56]	24 g/day	The test group showed lower mortality (6 deaths) compared to the	

			control group (11 deaths), but showed a slight increase in total days of hospitalization (2.2 days) and no significant improvement needing invasive and non-invasive mechanical ventilation.	
Vitamin D	[57]	-	The hospitalized compared to non - hospitalized individuals had a significantly lower mean plasma 25 (OH) D level (18.38 ng/mL vs. 20.45 ng/mL).	Modulates the release of inflammatory chemokines and cytokines by macrophages; modulates the role in the expression Angiotensin-Converting Enzymes 1 (ACE1) and 2 (ACE2); acts controlling pathways of cell proliferation and differentiation, apoptosis and angiogenesis.
	[19]	-	24% of critically ill patients were deficient in vitamin D while only 7,3% of non-critical patients were deficient, which shows a correlation between the severity of the disease and the levels of the vitamin.	
	[58]	Patients with levels below 50 nmol/L, supplementation of 50,000 IU twice a week until adequate levels of 25 (OH) D are reached (100-150 nmol/L)	The achievement of plasma vitamin D values is associated with a reduction in the risk of worsening and a decrease in the mortality rate.	
Zinc	[59]	< 50 µg/dL or > 50 µg/dL about to 8 days	Critically ill patients showed low zinc concentrations (< 50 µg/dL) compared to patients with mild to moderate symptoms (63.1 µg/dl). Patients who received doses less than 50 µg/dL needed more recovery time (25 days) compared to those who received doses greater than 50 µg/dL (8 days). Lower concentrations of IL-6 and CRP were also identified in these	Development of innate immunity defense cells natural killer cells (NK) and neutrophils; involved in the metabolic processes of carbohydrates and lipids, reproductive function, cardiovascular and nervous system; intrinsic role in all stages of lymphocyte and leukocyte functioning, from proliferation to maturation.

			subjects (>50 µg/dl). Increasing serum zinc levels, mortality rates fell by 7%.	
	[60]	15 or 23 mg of elemental zinc every 2-4 hours	A high dose of oral zinc salt resulted in clinical recovery, improved oxygenation, and less shortness of breath among those patients.	
Curcumin	[61]	160 mg of nano-curcumin capsules and placebo capsules to the control group	Expression level of IL-1β and IL-6 decreased after treatment with nano-curcumin compared with the pre-treatment state and the placebo group. 62% of patients had improvements in fever (from > 37.3 ºC to < 37.3 ºC) compared to the control placebo group, which did not obtain significant improvement.	Prevent the virus from entering the cell and also its potent action in inhibiting viral replication; inhibits oxidative stress caused by inflammation; acts under the NF-kB and mitogen activated protein kinase (MAPK) pathways, thus blocking the expression of pro-inflammatory cytokines produced in these pathways; play an anticoagulant function by inhibiting the cyclooxygenase pathway, platelet aggregation and calcium signaling pathway.

3. CONCLUSIONS

The present study reviewed some nutritional factors that may facilitate or hinder the multiplication of the COVID-19 virus. Some compounds, due to their antioxidant and anti-inflammatory action, contribute to the neutralization of ROS and inflammatory cytokines. Vitamin C, zinc and propolis act as antioxidants, anti-inflammatory, antiviral and are very important for the regulation of immune function. Vitamin D, curcumin and ginger, in addition to these functions, have been shown to have an antithrombotic effect. However, despite the benefits presented here, some points must be taken into account. First, the clinical studies presented here did not report which viral types were studied and the action of these bioactive compounds may be different for the different variants of COVID-19. Second, it is important that new studies and randomized controlled studies are carried out to determine safe and effective doses for the ingestion of these compounds, in addition to determining in which situations the use of these nutrients may or may not be indicated, according to the variants of the virus. Finally, it is very important to remember that a healthy diet is essential for the immune system to have a variety of these nutrients, bioactive compounds, calories, proteins and microelements, which is more interesting than the ingestion of a single compound or nutrient.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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