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Do nutrients and other bioactive molecules from foods have anything to say in the treatment against COVID-19?

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ABSTRACT

The repositioning of therapeutic agents already approved by the regulatory agencies for the use of drugs is very interesting due to the immediacy of their use; similarly, the possibility of using molecules derived from foods, whether nutrients or not, is of great importance, also because of their immediate therapeutic applicability. Candidates for these natural therapies against COVID-19 should show certain effects, such as restoring mitochondrial function and cellular redox balance. This would allow reducing the susceptibility of risk groups and the cascade of events after SARS-CoV-2 infection, responsible for the clinical picture, triggered by the imbalance towards oxidation, inflammation, and cytokine storm. Possible strategies to follow through the use of substances of food origin would include: a) the promotion of mitophagy to remove dysfunctional mitochondria originating from free radicals, proton imbalance and virus evasion of the immune system; b) the administration of transition metals whose redox activity would lead to their own oxidation and the consequent generation of a reduced environment, which would normalize the oxidative state and the intracellular pH; c) the administration of molecules with demonstrated antioxidant capacity; d) the administration of compounds with anti-inflammatory and vasodilatory activity; e) the administration of immunomodulatory compounds.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was described late in 2019 after a multiple number of pneumonia cases in Wuhan, China (Zhu et al., 2020). The disease caused by SARS-CoV-2 is named COVID-19 (coronavirus disease 2019) (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, 2020). The most common clinical features of the disease are fever, dry cough, anorexia, myalgia, dyspnea, anosmia, dysgeusia and dermal alterations (Zabetakis et al., 2020). On July 7th, 2020, over thirteen million confirmed cases of COVID-19 and more than 500,000 deaths were found globally ("COVID-19 Map," n. d.), and the number of cases is rapidly increasing. The SARS-CoV-2 pandemic leads to an extreme emergency situation that makes it essential to find new therapies and actions aimed at reducing the spread of the virus and finding new therapeutic applications for existing and approved drugs that allow its rapid application for treatment of this new disease. In the same way, based on the increasingly better knowledge of the mechanisms of action of the virus in human cells, it is essential to search for new molecules and combined therapies that may be useful in the treatment of COVID-19.

Food could be a good source of these molecules, some of them are nutrients, such as zinc or vitamins C and D, whereas others are biologically active non-nutrient molecules, such as certain compounds of polyphenolic nature. One of the great advantages of using food-derived molecules is the fact that they are natural, usually with low or no toxicity, and their approval process would be fast in case of some usefulness is reported, for example as nutraceuticals (Santini et al., 2018). In fact, some substances of this type are already being used as therapies

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against various diseases (Newman and Cragg, 2016). Meanwhile the world is waiting for vaccines or safe and effective treatments, the use of natural therapies, alone or as a combinatory therapy should be fully considered.

2. Pathogenesis of SARS-CoV-2

COVID-19 has raised the importance of the renin-angiotensin system (RAS) (Fig. 1). RAS activation increases in patients with different conditions, such as diabetes, cardiovascular diseases and others (Ribeiro-Oliveira et al., 2008). The angiotensin converting enzyme (ACE) converts angiotensin I to angiotensin II, the latter is a vasoconstrictor able to produce oxidative stress because many signaling pathways activated in response to angiotensin II are mediated by reactive oxygen species (ROS) generated by NAD(P)H oxidase activity. In turn, oxidative stress is deeply associated with the progression of different cardiovascular disorders. When angiotensin II level is high, it causes insulin resistance, endothelial dysfunction, proteinuria, and high blood pressure. ACE2 receptors produce angiotensin 1-7 by using angiotensin II as substrate (Lelis et al., 2019; Nehme et al., 2019; Ribeiro-Oliveira et al., 2008).

ACE inhibitors (ACEI) prevent the formation of angiotensin II from angiotensin I, the latter will be converted to angiotensin 1-9 by ACE2 (Lelis et al., 2019; Nehme et al., 2019; Ribeiro-Oliveira et al., 2008). In turn, angiotensin 1-9 can also be transformed by ACE2 to angiotensin 1-7 (Nehme et al., 2019; Ribeiro-Oliveira et al., 2008). Angiotensin receptor antagonists (ARBs) prevent angiotensin II from binding to the receptor. ARBs increase ACE2 (Cure and Cumhur Cure, 2020a). Angiotensin II, which cannot bind to the receptor, is rapidly converted to angiotensin 1-7 by increasing ACE2 (Cure and Cumhur Cure, 2020b). ACE and ACE2 share homology in their catalytic domain proving different key functions in the RAS.

The SARS-CoV-2 virus enters the human body through ACE2 receptors, present in lungs but also in the kidneys, heart, gastrointestinal tract, and other sites. The process of entry of the virus into the cell need the binding of glycoprotein S to ACE2, which acts as a receptor (Tai et al., 2020). After binding and entry, the fusion of the viral membrane and the host cell membrane happens. Type II transmembrane serine protease (TMPRSS2), present on the surface of the host cell, will remove ACE2 after fusion and activate receptor-like spike S proteins (Rabi et al., 2020) (Fig. 2). Activation of S proteins induces changes allowing the virus to enter the cell (Simmons et al., 2013). TMPRSS2 and ACE2 are responsible then for the entry of this virus. At the respiratory tract, nasal epithelial cells have the highest level of ACE2 expression (Sungnak et al., 2020). Once inside the cell, SARS-CoV-2 will translate its genetic material into the nucleus after liberation into the cytoplasm (Resnick et al., 1987).

However, for the pathogenesis of SARS-CoV-2, ACE2 has been shown not only to be the input receptor for the virus, but also to protect against lung injury. Therefore, in contrast to most other coronaviruses, SARS-CoV-2 has a higher lethality because the virus deregulates a lung protection pathway (Kuba et al., 2005; Yang et al., 2007).

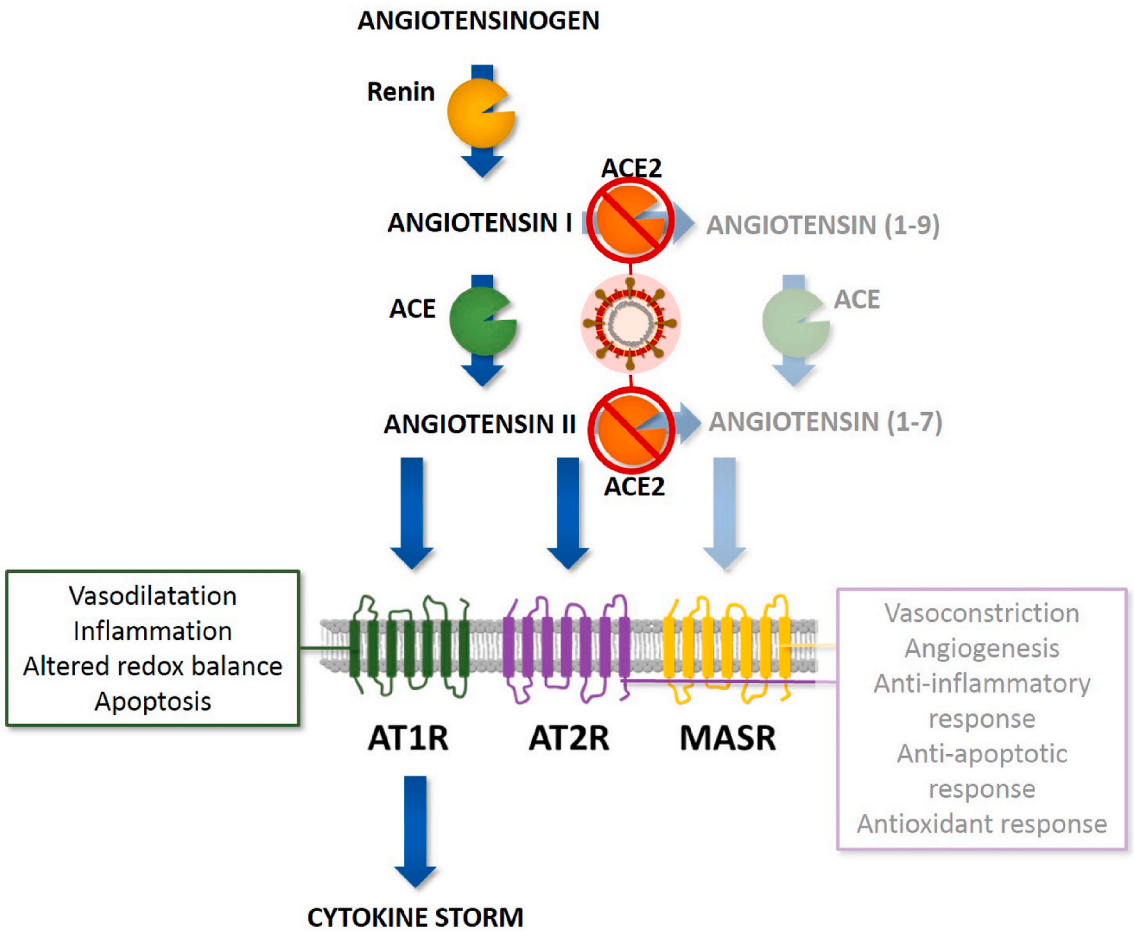

Fig. 1. SARS-CoV-2 and its interaction with the Renin Angiotensin Aldosterone System (RAS). ACE2 degrades angiotensin I to angiotensin (1–9), which is a ligand for angiotensin II receptor type 2 (AT2R). ACE2 also converts angiotensin II to angiotensin (1–7) that binds to the Mas receptor (MASR). Angiotensin (1–9) has regenerative and anti-inflammatory effects, angiotensin (1–7) mediates anti-inflammatory and vasodilatory effects and reduces reactive oxygen species (ROS) through its binding to AT2R. Thus, angiotensin (1–7) and angiotensin (1–9) counteract the vasoconstriction and pro-inflammatory effects of angiotensin II preventing tissue injuries. SARS-CoV-2 infection would reduce ACE2 expression dysregulating RAS protective pathways.

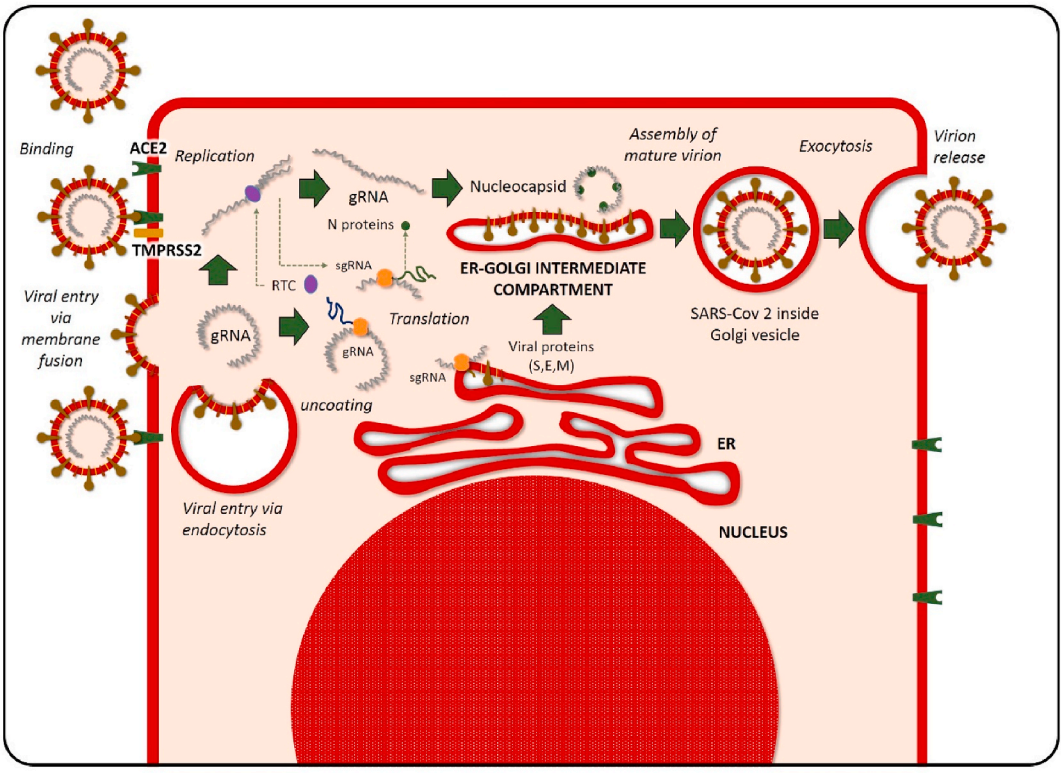

Fig. 2. Internalization and viral replication. The process of entry of SARS-CoV-2 into the cell needs the binding of glycoprotein S to angiotensin-converting enzyme 2 (ACE2) (present in lungs but also in the kidneys, heart, gastrointestinal tract, and other sites), which act as a receptor. Type II transmembrane serine protease (TMPRSS2) present on the surface of the host cell would remove ACE2-activated receptor-like spike S proteins inducing changes that allows the virus to enter the cell. Once inside the cell, SARS-CoV-2 will translate its genetic material into the nucleus after liberation into the cytoplasm.

As previously described, ACE2 is expressed in the intestinal tract. According to that, it has been proposed that intestine could also be an important entry site for the SARS-CoV-2. This is also important when considering the chance of a fecal-oral transmission. The distribution of ACE2 receptors in different tissues and organs might be in the basis for the described multiorgan failure found in some patients (Hashimoto et al., 2012). However, the advice from the Center for Disease Control and Prevention that states that no evidence has been found about the chance of getting COVID-19 by touching contaminated surfaces or objects and then touching mucous membranes should also be considered. (Zhang et al., 2020).

The binding of SARS-CoV-2 to ACE2 is produced under conditions of low cytosolic pH (Cure and Cumhur Cure, 2020b). Some conditions, such as hypertension or diabetes, and also aging, are associated with low cytosolic pH, which increases the opportunity for the virus to enter cells (Resnick et al., 1987). Angiotensin II increases pH, this alkalinizing effect is maintained even after a heavy acid load (Costa-Pessoa et al., 2013). ACEI and ARBs reduce angiotensin II, then acidize cytosolic pH. Angiotensin 1-7 causes no changes in the pH and changes in its concentration have no effect on the viral load. ARS activity and angiotensin II levels decrease with aging, particularly in hypertense or diabetic patients; therefore, COVID-19 may be more severe because of a lower cytosolic pH. It has been proposed that angiotensin 1–7 may protect against acute respiratory distress syndrome in COVID-19 because its vasodilatory effect (Cure and Cumhur Cure, 2020c). Although there are doubts about if an increase in angiotensin 1-7 would has a preventive effect, and it has been seen useful only in an experimental model (Komukai et al., 2010).

2.1. Role of mitochondria, redox imbalance, and mitophagy in SARS-CoV-2 infection

Certain risk groups, such as the elderly, diabetics, and cancer patients share a condition: the deterioration of mitochondrial function, which leads to pro-oxidant redox imbalance at cellular level. This is associated with a cellular pH imbalance favorable to the presence of protons that would facilitate the interaction between the virus and the ACE2 receptor and, thus, its route of entry into the cell (Haas, 2019). Additionally, aging and age-related diseases are worsened by the subsequent blockade of these ACE2 receptors and their corresponding activation pathway, canceling its physiological function and its vasodilatory, antioxidant, alkalizing and anti-inflammatory effects, amplifying the cycle of oxidation, inflammation, and vasoconstriction (Gheblawi et al., 2020). Mitochondria are essential organelles responsible for energy production, but also involved in the biosynthesis of metabolites, apoptosis, several aspects of the immune response, etc. Energy metabolism plays a key role in cells involved in the innate immunity (Rambold and Pearce, 2018). For this reason, maintaining integrity and activity of the mitochondrial network is a key aspect for the immune system function. Selective mitochondrial autophagy (mitophagy) is involved in the control of mitochondrial number in the cell by removing damaged organelles, which helps the cell to survive and to respond to aggressions, including infections (Giampieri et al., 2019). A deficient function of autophagy machinery will lead to an exacerbated inflammatory response (Michaličková et al., 2020). A reduction in the expression of genes associated with mitochondria has recently been shown in ACE2-positive Leydig and Sertoli cells, a finding indicative of increased impairment of mitochondrial function in these patients (Wang and Xu, 2020). Furthermore, it has been proposed that the mechanism by which SARS-CoV-2 escape from the innate immune surveillance is based on mitochondrial alterations, placing senescent

mitochondria as a factor in increasing susceptibility to the virus and as a key agent in immune evasion of the virus simultaneously (Malavolta et al., 2020). In this way, therapy with drugs contributing to adequate mitochondrial function will exert a protective effect reducing the susceptibility to the virus and therapeutic, reducing the effects derived from the infection associated with the production of free radicals and the activation of the inflammatory response and cytokine storm. In this sense, we point to the compounds inducing mitochondrial autophagy as candidates for the treatment of COVID-19 disease (Michaličková et al., 2020; Yan and Li, 2018).

3. Substances from foods potentially useful in treating COVID-19

There are different nutrients and other molecules from food sources that could be useful in the treatment and/or prevention of COVID-19. In this section we will review these substances. Table 1 shows the foods that are the richest in these molecules.

3.1. Zinc

Zinc is a mineral nutrient that acts as a cofactor for many key cell reactions, playing an important role in the growth of cells. Zinc also plays a role in the development and it has functions associated with metabolism and the immune system (Hoang et al., 2020). It has been described *in vitro* that increased intracellular Zn^{2+} levels are able to disturb the replication of several RNA viruses, including influenza virus, polio virus, and SARS-CoV (te Velthuis et al., 2010). These authors suggested that intracellular Zn^{2+} levels affect a common step in cell replication cycles. Enzymatic studies using recombinant RNA-dependent RNA polymerases (RdRPs) (SARS-CoV nsp 12) purified from *Escherichia coli* revealed that Zn^{2+} directly inhibited SARS-CoV RdRp elongation and reduced template binding (te Velthuis et al., 2010).

According to estimations, approximately 20% of the population in the world has low levels of zinc in the blood, and the numbers become more relevant in older adults. The deficiency of zinc leads to a diminished production of antibodies. This situation also alters the innate immune system, for example by reducing the activity of natural killer cells. In the same way, zinc deficiency is responsible for a lower production of cytokines by mononuclear cells. Finally, zinc deficiency also reduces chemotaxis response and the respiratory burst of neutrophils (Ibs and Rink, 2003). The difficulty of inorganic Zn salts to access cells can be solved with the administration of organozinc compounds. Currently, in this sense, chloroquine plays a major role, acting as an ionophore, allowing zinc to enter the infected cell (Xue et al., 2014). Furthermore, zinc has beneficial immunomodulatory effects against respiratory infections, which improve the immune response, including the response against SARS-CoV (Jayawardena et al., 2020; Shankar and Prasad, 1998), and it is a transition metal whose intracellular redox activity (Quiles et al., 2020) contributes to the antioxidant defense during the powerful oxidative response inherent in COVID-19 (Cure and Cumhur Cure, 2020a). Zinc acetate, a compound approved by the FDA (Galzin NDA: 020,458), is a zinc-based drug already in use, this drug meets the described characteristics to which we attribute the indicated effects against COVID-19.

Table 1
Main sources of food-derived compounds potentially useful in treating COVID-19.

Compound	Main sources
Zinc	Whole grains and whole grain products
	Dairy products
	Oysters
	Red meat
	Poultry
Resveratrol	Grapes
	Red wine
	Nuts
	Berries
	Chocolate
Hydroxytyrosol	Virgin olive oil
	Leaves of the olive tree (*Olea europaea*)
Curcumin	Rhizome of turmeric (*Curcuma longa*)
Quercetin	Apples
	Berries
	Cilantro (coriander)
	Onions
	Capers
	Lovage
	Dill
Vitamin C	Green and red peppers
	Tomatoes
	Broccoli, Brussels sprouts, and cauliflower
	Leafy greens (Spinach, cabbage, turnip greens)
	Sweet and white potatoes
	Winter squash
Vitamin D	Dairy products
	Eggs
	Fish

3.2. Resveratrol

Resveratrol belongs to the family of polyphenols present in plant foods, such as grape, nuts, red wine, berries, chocolate, and others. Resveratrol belongs to the stilbene family, which is classified as phytoalexins because stilbenes are synthesized by plants in response to ultraviolet rays, bacterial and fungal lesions or toxins (Wahedi et al., 2020). It is well known that resveratrol protects from a series of diseases including malignancies, cardiovascular and respiratory diseases, and others (Horne and Vohl, 2020). At the cellular level, resveratrol acts as an antioxidant, cytostatic, antiviral, anti-inflammatory and it extends the life span of the cells (Wahedi et al., 2020). Resveratrol is also an agonist for sirtuin deacetylase SIRT1. Sirtuins are master regulators of metabolism with multiple objectives. SIRT1 deacetylates Trp 53, destabilizing it and leading the cell to activate the cell cycle and inhibit apoptosis (Navarro et al., 2017).

In neuronal cultures, resveratrol treatment (40 μM, after excitotoxicity) decreases the production of superoxide anion, prevents the overload of intracellular Ca^{2+} associated with mitochondrial failure, decreases the release of the lactate dehydrogenase enzyme, and decreases death. It also promotes mitophagy (increasing Beclin 1 level, favoring the recruitment of LC3-II, reducing LAMP1, and decreasing the levels of the mitochondrial matrix protein HSP60). Resveratrol (1.8 mg/kg; i. v.; administered at the beginning of reperfusion) increased the levels of phosphorylated AMPK in the cerebral cortex of rats subjected to middle cerebral artery occlusion. A similar effect was found in primary cultured neurons exposed to glutamate-induced excitotoxicity. Therefore, resveratrol acted as an autophagy-inducing agent, and it has shown an important role in mitochondrial function in the mentioned neuronal models (Pineda-Ramírez et al., 2020). In both models, inhibition of AMPK activation with Compound C obstructed the effect of resveratrol, showing that its protective effect depends, partially, on the activation of the AMPK/autophagy pathway. An increase in the autophagic process might increase intracellular pH and thus it might be a way to reduce SARS-CoV-2 infection.

We have found three studies analyzing the role of resveratrol in relation to ACE2 receptors. A study performed in rats fed with 50 mg kg^{-1} · day of resveratrol showed an increase in the level ofACE2 protein (Tiao et al., 2018). Another study performed in mice fed a high-fat diet compared to mice fed a high-fat diet supplemented with resveratrol showed a significant increase in ACE2 gene expression in mice supplemented with resveratrol. Therefore, resveratrol added to the diet can help reduce the deleterious consequences of diets rich in fat on the ACE2 gene expression (Oliveira Andrade et al., 2014). Lastly, an *in vitro* study performed in smooth muscle cells from human aorta showed that the expression of the ACE2 gene and protein were significantly enhanced in

the cells after 24 h incubation with resveratrol (Moran et al., 2017).

Navarro et al. analyzed if the application of inhaled resveratrol can protect mice with a lung condition from accelerated aging (Navarro et al., 2017). These researchers found that resveratrol treatment delayed loss of lung function, maintained lung structure, and blocked DNA damage in parenchymal cells. As above-mentioned, resveratrol is a known SIRT1 deacetylase agonist and the authors suggested that it acts at pulmonary level promoting the destabilization of p53 and decreasing the expression of Bax (proapoptototic proteins) and, consequently, decreasing apoptosis and increasing survival of alveolar epithelial type 2 cells. Furthermore, it maintains the levels of PGC1α, a stimulator of mitochondrial biogenesis. All these effects led the study authors to suggest that inhalation resveratrol prophylaxis is a potential approach to curb the deterioration of lung function and structure associated with aging while maintaining the integrity of ACE2.

3.3. Hydroxytyrosol

Hydroxytyrosol, or 3,4-dihydroxhyphenyl ethanol, is a polyphenolic compound with amphipathic properties that has a molecular weight of 154.16 g/mol. One of the most important characteristics is its phenylethyl alcohol structure, which is thought to be the basis of its biological functionality. Hydroxytyrosol can be found as a member of the minor components of extra virgin olive oil. Olive tree (*Olea europaea*) leaves are one of the main sources of hydroxytyrosol. This molecule has an extensive range of well-documented biological activities (Robles-Almazan et al., 2018). It has great antioxidant, anti-inflammatory and antiatherogenic capacities (Granados-Principal et al., 2010). Additionally, its powerful antimicrobial activity has also been documented (Zoric et al., 2013).

Removability of reactive species is among the most important properties of hydroxytyrosol. These ROS scavenger properties have been demonstrated at the extracellular level, where hydroxytyrosol eliminates reactive species generated by UV rays (Zwane et al., 2012). In addition, it has a scavenger capacity at the intracellular level, particularly against superoxide anion, hydrogen peroxide and hypochlorous acid. Moreover, it can act as a metal chelator (Granados-Principal et al., 2010). Several studies (Killeen et al., 2014) showed that hydroxytyrosol is able to modulate the proinflammatory transcription factor NF-κB. As it is well known, NF-κB controls the expression of approximately 150 genes, many of them involved in inflammatory responses, such as cell adhesion molecules, chemokines, but also cytokines, such as interleukins 1, 6, 17 and the tumor necrosis factor alpha. Regarding respiratory diseases, Visioli et al. have reported that hydroxytyrosol reduces oxidative stress related to the respiratory burst of neutrophils (Visioli et al., 1998). It has also been reported that hydroxytyrosol has the ability to reduce the production of superoxide anion, both in *vivo* and *in vitro* experimental models (Braga et al., 1997). In the same way, it has been observed that this polyphenol eliminates hydrogen peroxide after respiratory burst in stimulated human neutrophils. This effect has been shown to be dose dependent (O'Dowd et al., 2004). Furthermore, concerning the antibacterial activity of hydroxytyrosol, it has been reported that the growth of different Gram-positive and Gram-negative bacteria typical from respiratory tract infections is inhibited (Bisignano et al., 1999). The above-mentioned suggests that hydroxytyrosol may be used in the treatment of infections produced by several bacterial sources in the context of respiratory tract infections. Hydroxytyrosol has also been found to be effective in the treatment of some viral diseases, such as influenza virus (Yamada et al., 2009) and HIV (Bedoya et al., 2016). Finally, Liu et al. have shown that hydroxytyrosol is effective against pulmonary fibrosis in rats (Liu et al., 2015). All the results described above suggest that hydroxytyrosol is a natural molecule of potential interest in treating COVID-19, reducing the oxidative and inflammatory response, and it may be a good adjuvant therapy in combination with other treatments, such as antivirals.

3.4. Curcumin

Curcumin [1,7-bis (4-hydroxy-3-methoxyphenyl) −1,6-heptadiene-3,5-dione] is a polyphenol extracted from the rhizome of turmeric (*Curcuma longa*). It is a yellow pigment of polyphenolic nature that is found in tropical and subtropical regions around the world. Curcumin is a spice widely used in gastronomy, mainly in Asian countries. In addition to its culinary use, curcumin is a traditional herbal medicine in different countries since ancient times. The main properties attributed to curcumin are based on its great antioxidant capacity, but also on its role as an anti-inflammatory agent. It has also been shown that curcumin possesses antimutagenic and antimicrobial properties. It has been also demonstrated to be useful in the fight against several types of cancer. Antiviral properties have also been attributed to curcumin. In this sense, it has been described how curcumin is able to inhibit human immunodeficiency virus (HIV) replication (Prasad and Tyagi, 2015). Antiviral activity of curcumin has also been described against Chikungunya and Zika virus (Mounce et al., 2017). However, despite the large number of studies conducted with this compound, many of the intracellular changes causing the known effects are still unknown (Bielak-Zmijewska et al., 2019; Nelson et al., 2017; Vera-Ramirez et al., 2013). Curcumin use was found to increase ACE2 receptor expression in rat tissue (Pang et al., 2015). In this study, authors reported that curcumin administration to rats to which angiotensin II was applied as an intravenous infusion partially prevented fibrosis at the myocardial muscle. This effect was related to the observed increase in the protein expression of ACE2 in this organ. In a study using molecular docking with target receptors that might be associated with the viral infection, such as SARS-CoV-2 protease, spike glycoprotein-RBD and PD-ACE2 and that were compared as references with the known ligand or drugs, it was been reported that curcumin might be useful because it has the ability to bind to the above-mentioned receptors (Utomo et al., 2020). The wide variety of beneficial health effects shown by curcumin, including its high antioxidant and anti-inflammatory capacities, as well as its antifibrotic effects on the lung (Punithavathi et al., 2000) makes curcumin a molecule with promising effects in treating COVID-19.

3.5. Quercetin

Quercetin is a flavonol, which is one of the six subfamilies of flavonoids. It represents the most abundant flavonoid molecule found in different fruits and vegetables, including apples, berries, onions, dill, lovage, cilantro (coriander) or capers (Anand David et al., 2016). It is a yellow compound soluble in lipids and alcohol. Many pharmacological activities of quercetin have been reported. Among these, the anticancer capacity and the ability to fight against viruses can be highlighted. Moreover, it is useful treating allergic diseases and, from the point of view of cardiovascular disorders, metabolic diseases and different conditions in which inflammation is a key factor (Batiha et al., 2020).

Quercetin has also been associated with autophagy induction. It seems that quercetin could activate protective autophagy in ovarian cancer cell lines and in primary ovarian cancer cells concomitantly by activating the intrinsic apoptosis p-STAT3/Bcl-2 axis in this process (Liu et al., 2017). Likewise, a quercetin (Qu) modified polysorbate 80 (P-80)-coated AuPd core-shell structure (Qu@P-80@AuPd) can activate autophagy of SH-SY5Y cells and promote the fusion of autophagosomes and lysosomes, (Liu et al., 2019).

The antiviral activity of quercetin has been described for example for the Japanese encephalitis virus (JEV), the human T-lymphotropic virus 1, the mosquito-borne disease (Johari et al., 2012), the dengue virus type-2 and hepatitis C virus (Bachmetov et al., 2012). Other quercetin derivatives, such as quercetin-3-O-D-glucuronide, quercetin-enriched lecithin formulations, and quercetin 7-rhamnoside have been found to be useful against the treatment of the porcine epidemic diarrhea virus and influenza-A virus, respectively (Fan et al., 2011; Song et al., 2011). Quercetin has been also investigated in the context of respiratory

diseases. In this sense, Henson et al. (2008) in a double-blind parallel randomized controlled trial supplemented 18 adults with quercetin for 21 days before the Western States Endurance Run; but no effect on illness rates were found after the race. However, other authors have found that quercetin reduced illness after intensive exercise (Nieman et al., 2007).

Concerning the potential usefulness of quercetin for COVID-19, a recent study identified quercetin as a molecule of interest, probably with capacity to reduce the interaction between the virus and the receptor ACE-2 using supercomputer-based *in silico* drug-docking to the COVID-19 viral spike protein (Sargiacomo et al., 2020). Although this is a *in silico* approach that needs to be tested, it suggests that quercetin may be useful from this point of view. Another issue about the putative effect of quercetin against COVID-19 comes from a quercetin derivative, quercetin-3-b-galactoside. This compound has been identified through molecular docking, SPR and FRET bioassays, and mutagenesis studies as a new class of inhibitors against SARS-CoV $3CL^{pro}$ (Chen et al., 2006). SARS-CoV $3CL^{pro}$ shares some features with SARS-CoV2; therefore, quercetin might exert some protective or curative role against COVID-19, particularly considering its antioxidant (Xu et al., 2019) and anti-inflammatory (Li et al., 2016) properties, as well as the effects of quercetin observed against other viruses described above.

3.6. Vitamin C

The functions of the water-soluble vitamin C (ascorbic acid) in biological systems are associated with the capacity of this molecule to change between the two redox states. This ability leads vitamin C to act as a cofactor in several human enzymes and as a powerful antioxidant and co-antioxidant (Padayatty and Levine, 2000). Scurvy, a condition that can be mortal, is the main result of a continued lack of vitamin C intake (Granger and Eck, 2018). Concerning its role as antioxidant, ascorbate is able to scavenge several types of free radicals, although under certain circumstances vitamin C may become prooxidant (Frei et al., 1989). Ascorbic acid also participates in different biological processes being some of them related to the immune system (Carr and Maggini, 2017). Concerning the antiviral properties of vitamin C, it has been described that this molecule may be useful for patients affected by different herpes viruses or influenza virus (Colunga Biancatelli et al., 2020). These antiviral effects might be due to at least two aspects. The first is that usually low levels of vitamin C are found in the blood of patients affected by different acute infectious diseases and, secondly, because ascorbate has the capacity to increase the production of interferons and to downregulate the production of different cytokines, it has demonstrated positive effects from the point of view of immunomodulation in patients affected with different viral infections (Colunga Biancatelli et al., 2020). Concerning the participation of vitamin C in the protection against upper respiratory tract infections (URTIs), a meta-analysis of 29 controlled trials with 11,306 participants has shown no prevention of URTIs after a regular vitamin C intake of around 1 g/day. However, the same trials found that vitamin C shortened and alleviated URTIs that occurred during the period of vitamin C administration (Hemilä and Chalker, 2013). In the present COVID-19 pandemic, several attempts to use vitamin C against SARS-CoV2 have been already initiated, including a phase II clinical trial (NCT04264533) to evaluate high-dose IV vitamin C in ICU patients with severe COVID-19-associated pneumonia (Peng, 2020). Those responsible for this clinical trial are assessing the need for mechanical ventilation and the use of vasopressor drugs. The risk of failure in organs other than the lung, the total length of ICU stays as well as mortality based on periods of 28 days will also be analyzed. Another study (Cheng, 2020) has shown that a single dose of intravenously administered vitamin C is successful in treating 50 patients in China who had moderate to severe symptoms of COVID-19. Specifically, the dose used was 10 or 20 g a day administered over a period of between 8 and 10 h. It is thought that in the case of critically ill patients, a bolus dose of vitamin C might also be required. For this study, the researchers reported positive results regarding the oxygenation index in real time. In addition, it has been reported that all patients achieved cure and discharge from hospital. While waiting for the results of the clinical trial described above and others that have been initiated, one thing seems clear, the ability of vitamin C to defend the body against oxidative stress and its ability to modulate the immune system, including the inflammatory aspects, make it pertinent to consider the possibility that vitamin C could be useful in the management of COVID-19.

3.7. Vitamin D

Vitamin D belongs to the group of fat-soluble vitamins. It can be incorporated into the body through the diet by the dietary intake of dairy products, eggs, fish, etc., in the form of vitamin D2 (ergocalciferol) or transformed into the skin by the effect of the sun to vitamin D3 (cholecalciferol). The active form of vitamin D is 1,25-dihydroxicholecalciferol (calcitriol). Vitamin D is involved in the absorption of calcium, magnesium and phosphate, but it is also related to multiple actions on the body, including immune system regulation (Aranow, 2011). Furthermore, the deficiency in vitamin D has been associated with several disorders, such as diabetes, alterations in the regulation of the immune system, cancer, inflammation, hypertension, cognitive alterations, cardiovascular diseases and osteoporosis, among others (Holick, 2017).

Concerning COVID-19 and vitamin D, in a retrospective study including 780 confirmed patients, authors found that elder men with pre-existing conditions and with levels of vitamin D below normality were associated with increasing risk of suffering from COVID-19 (Raharusun et al., 2020). In a recent cross-sectional analysis performed with data from 20 European countries (Ilie et al., 2020), authors observed a negative correlation between the circulating levels of vitamin D and the number of cases of COVID-19 per million people for each country. A similar negative correlation was also found between vitamin D and deaths caused by COVID-19 per million people. Moreover, in a retrospective investigation in a cohort of 107 patients from Switzerland from which 27 were positive for SARS-CoV-2, authors found significantly lower levels of 25-hydroxyvitamin D in patients with positive PCR for SARS-CoV-2 compared with patients with negative PCR (D'Avolio et al., 2020). These studies, together with other subjective observations in addition to that older people tend to have low vitamin D levels, make that this population group becomes the most affected by COVID-19, leading to many scientists and health professionals to suggest that vitamin D supplementation could be useful in managing the disease. However, is there a logic in recommending this beyond the correlations and associations mentioned?

Vitamin D supports immune function by maintaining cell physical barrier integrity. It is also responsible for this role by increasing the capacity of the cell to produce antimicrobial proteins. Additionally, vitamin D increases the response of cells associated with innate (mainly monocytes and macrophages) and adaptive immunity (dendritic cells and T-cells) leading to a more anti-inflammatory state (Adams et al., 2020). The role that vitamin D deficiency plays in the onset and severity of respiratory infections with viral origin and severe lung damage has been revealed by epidemiological studies (Hansdottir and Monick, 2011). Furthermore, calcitriol has been shown to protect against acute lung damage. This role at the lung level seems to be exerted by calcitriol through the expression of ACE2 and other members of the renin-angiotensin system. (Xu et al., 2017), this represents a clue about the importance of vitamin D deficiency as a pathogenic conditioner for COVID-19. Therefore, based on the existing evidence, it might make sense to start studies in COVID-19 patients undergoing vitamin D supplementation to really assess the usefulness of vitamin D. Furthermore, and in any case, given the prevalence of people, especially the elders, with low levels of vitamin D, precisely the population group that is being hardest hit by COVID-19, it would be desirable to launch campaigns

aimed at correcting such deficiencies.

Table 2 shows a summary of the potential targets against which the substances analyzed in this section would exert their action.

3.8. Combined therapy

The combined use of effective therapeutic agents having different mechanisms of action could provide a synergistic response and greater therapeutic potency. In this sense, in the context of the present review, various proposals have been made. For example, based on a gene enrichment analysis, triple therapy with quercetin, vitamin D and estradiol has been suggested (Glinsky, 2020). This study investigated genes that SARS-CoV-2 need in its way to enter the cell, namely ACE2 and FURIN. The authors used these genes to build molecular maps. Once panels of repressors and activators were found, they were used to analyze pharmacological compounds, synthetic or natural, already recognized, known to exert their action on any of the genes that appeared in the genetic maps constructed so that they could serve to treat COVID-19. In addition, following a systems biology analysis approach, the combined use of vitamin C, curcumin and glycyrrhizic acid (an active compound derived from licorice root, which is considered an ingredient in traditional Chinese medicine) has been suggested. In this study (Chen et al., 2020), the authors suggested the use of this combination based on the capacity of this mixture to regulate the immune system to fight against the infections associated with COVID-19. The aim was also to reduce, at least in part, the exacerbated inflammation and consequently to prevent the onset of the cytokine storm. Roy et al. (2020) suggested the combined use of curcumin and zinc. This proposal was based on the well-known antiviral capacity of curcumin (for example, by the inhibition of the entry of the virus into the cell) and in the ability of zinc to inhibit the RNA polymerase. These authors speculate that zinc plus curcumin might lead to the formation of ionophore complexes resulting in a stronger and synchronized antiviral action. It has also been suggested a combinatory therapy of nutrients/food-derived bioactive molecules with antivirals. In this sense, the study of a synergistic use of vitamin D and remdesivir has been suggested (Arya and Dwivedi, 2020). Zinc has also been proposed to be combined with chloroquine since the latter increases zinc uptake into the lysosomes. Moreover, this is also based on the observed induction of apoptosis in malignant cells when zinc and chloroquine are administered together (Xue et al., 2014). However, as stated, except the study about chloroquine and zinc (Xue et al., 2014), the rest of all above-mentioned proposals are hypothetical suggestions based on computer studies or separate evidence, although, to our knowledge, no experimental studies have yet been conducted to test these or other combined therapy proposals. Necessarily, any of these proposals must go through the promotion of studies at the preclinical level followed by the subsequent randomized controlled clinical trials before being able to assert the actual usefulness of these therapies.

4. Conclusions

Waiting for the generation of vaccines and for proven, safe, and effective treatments, any therapy showing to be safe and capable of mitigating the effects of the disease on the body should be welcomed. Foods are the basis for the maintenance of living beings, and alterations of eating patterns can lead to the appearance of diseases. Moreover, the possibility of using nutrients or bioactive compounds from the diet for the prevention of diseases, and even at a therapeutic level, is well known. The use of the molecules analyzed in the present review, all tested for safety and non-toxicity, could be a therapeutic tool to be assayed against COVID-19, either alone or in combination with other nutritional substances, antivirals or other drugs. Science is awaiting this possibility, and although the available trials are currently very scarce, they must be performed with the hope that these molecules will serve to treat patients and to reduce the severity of COVID-19 and its high mortality.

Table 2
Potential targets for the analyzed molecules.

Compound	Potential target pathways
Zinc	Replication inhibition
	Immunomodulatory effects
	Intracellular redox activity
	Antibodies production
	NK cells activity
	Cytokines production by mononuclear cells
	Chemotaxis response reduction
	Neutrophil respiratory burst reduction
Resveratrol	Sirtuin deacetylase SIRT1 agonist
	AMPK activation
	PGC1alpha levels maintenance
	Mitochondrial biogenesis activation
	Mitophagy promotion
	ACE2 protein level increase
	DNA damage reduced
	Destabilization of p53 promoted
	Bax expression decreased
Hydroxytyrosol	Neutrophil respiratory burst effective-caused oxidative stress reduction
	Pulmonary fibrosis decrease
Curcumin	ACE2 level increase
	Antiviral activities
	SARS-CoV-2 protease, spike glycoprotein-RBD and PD-ACE2 binding
	Virus-ACE2 interaction reduction
	Antioxidant capacity
	Anti-inflammatory
Quercetin	Antiviral activity
	Autophagy promotion
	Virus-ACE2 interaction reduction
	Antioxidant capacity
	Anti-inflammatory
Vitamin C	Antioxidant capacity
	Biological processes related to the immune system
	Interferon production
	Cytokines production downregulated
Vitamin D	Cell physical barrier integrity maintenance
	Increased antimicrobial protein production
	Anti-inflammatory state
	ACE2 and other members of the RAS expression

Credit author statement

José L. Quiles: Conceptualization, Writing-original draft. Lorenzo Rivas-García: Writing -review & editing. Alfonso Varela-López: Writing -review & editing, Visualization, preparation of figures. Juan Llopis: Conceptualization, Writing -review & editing. Maurizio Battino: Conceptualization, Writing -review & editing. Cristina Sánchez-González: Conceptualization, Writing-original draft.

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Declaration of competing interest

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