Phenolic Compounds in COVID-19

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The first cases of COVID-19, which is caused by the SARS-CoV-2, were reported in December 2019. The vertiginous worldwide expansion of SARS-CoV-2 caused the collapse of health systems in several countries due to the high severity of the COVID-19. In addition to the vaccines, the search for active compounds capable of preventing and/or fighting the infection has been the main direction of research. Since the beginning of this pandemic, some evidence has highlighted the importance of a phenolic-rich diet as a strategy to reduce the progression of this disease, including the severity of the symptoms. Some of these compounds (e.g., curcumin, gallic acid or quercetin) already showed capacity to limit the infection of viruses by inhibiting entry into the cell through its binding to protein Spike, regulating the expression of angiotensin-converting enzyme 2, disrupting the replication in cells by inhibition of viral proteases, and/or suppressing and modulating the host's immune response.

Keywords: COVID-19 ; immune response ; phenolic compounds

1. Introduction

The current pandemic coronavirus disease-2019 (COVID-19) is probably the most convulsive global event in the history of mankind and it is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Its emergency occurred at the end of the year 2019 in China, where the alarms about transmissibility and morbidity were lit, because on January 19 of 2020, of the 189 people with COVID-19, only 19 did not require hospitalization, and three were detected in other countries without any relation to the possible focus, which was reported as a local food market in China [1].

Different taxonomic studies have shown that this virus is a member of the so-called SARS-related coronaviruses (SARSr-CoV) and belongs to the Coronaviridae family and *Betacoronavirus* genus. Although this one is considered a zoonosis, the final vector has not been detected yet. However, the genomic analysis shows important similarities with other Betacoronaviruses isolated from bats, such as *Rhinolophus affinis*, or other mammals as civets and pangolins. Therefore, the most widespread hypothesis is that horizontal gene transfer and recombination events occurred involving bat RaTG13 and Guangdong pangolin coronaviruses, and bat CoV ZC45 and ZXC21 strains [2][3][4][5].

In a general way, the SARS-CoV-2 is composed of open reading frames, where Open Reading Frame 1a and 1b (ORF1a and ORF1b, respectively) are responsible to encode polyproteins of the SARS-CoV-2 genome at the 5′ end (**Figure 1**), including the non-structural 3-chymotrypsin-like protease (3CL^{pro} or M^{pro}), papain-like protease (PL^{pro}) and RNA-dependent RNA polymerase (RdRp). In the other side of the virus chain, i.e., at the terminal 3′, there are found ORFs that encode the viral surface proteins, namely the Spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins [6]. Like other SARSr-CoVs, SARS-CoV-2 also uses the highly glycosylated S protein located on its viral membrane to bind the host cell receptor, the angiotensin-converting enzyme II (ACE2), and thus, enter into the human body [7]. This enzyme is present in the membrane of many cells of different organs and plays a crucial role in the regulation of blood pressure and electrolyte balance [8]. The linkage of the S protein generates an inactivation of the ACE2 protein, causing an imbalance in the proportion of peptides generated by angiotensin-converting enzyme I (ACE1) and ACE2, and triggering a pre-inflammatory response, which causes, in most cases, symptoms similar to flu [8][9]. Additionally, transmembrane protease serine 2, which is an enzyme encoded by the TMPRSS2 gene in humans, is also involved in the cleavage of S protein and ACE2, allowing the viral endocytose [10]. The infection with this virus promotes the appearance of fever, dry cough, fatigue, dyspnea, myalgias, headache, sore throat, rhinorrhea, and gastrointestinal symptoms [6]. Sometimes, the exaggerated and uncontrolled immune system response, compromise vital functions and damage organs, leading to the development of pneumonia and eventual death, independently of age, gender, and health condition. Furthermore, a characteristic that makes this disease remarkable is the appearance of persistent symptoms. Indeed, statistical data indicates that around 50% of the infected do not return to their initial health state, presenting continuous fatigue and higher levels of C-reactive protein and lactate dehydrogenase, which can be synonyms with cell death [9].

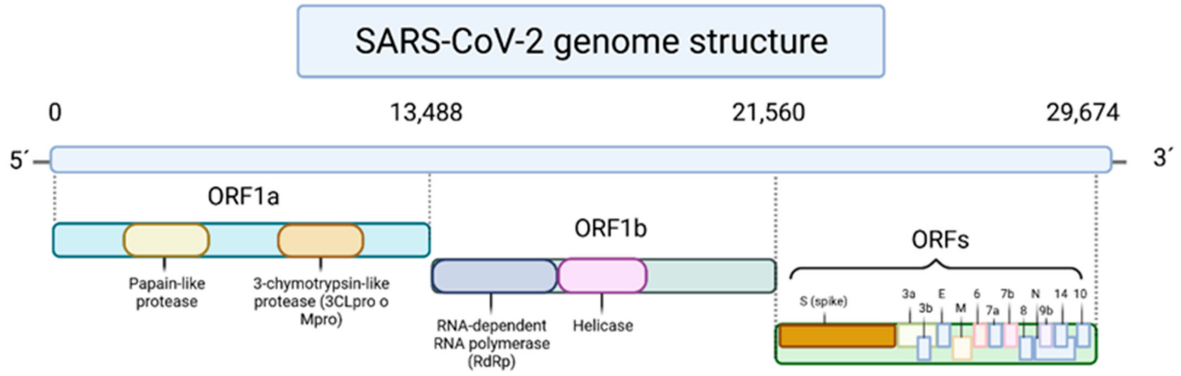

Figure 1. Genomic scheme of SARS-CoV-2 genome.

2. Phenolic Compounds in Human Health

Phenolic compounds are a heterogeneous group of molecules whose central structure can be only a hydroxybenzene or phenol ring (monophenols, e.g., gallic acid, p-coumaric), or composed of two (e.g., stilbenes, dimeric acids), three (e.g., quercetin, genistein), or more joined rings (e.g., proanthocyanins, tannins), the so-called polyphenols. Up to date, more than 50,000 different phenolic compounds are known, and they are classified according to their central structure and radical substituents, being differentiated between two main groups, which are, non-flavonoids and flavonoids [11]. Non-flavonoids compounds are composed of phenolic acids such as hydroxybenzoic and hydroxycinnamic acids, lignans, coumarins and stilbenes, highlighting among them gallic acid, caffeic acid, p-coumaric acid and resveratrol. On the other hand, flavonoids are the most abundant phenolic compounds in plants and, contrary to the previous ones, they are characterized by being a broader set of molecules, being subdivided into flavonols, flavan-3-ols, flavones, flavanones, isoflavones, flavonols and anthocyanins. Among them, kaempferol, catechin, epicatechin, apigenin, hesperetin, naringenin, genistein, cyanidin and delphinidin are the predominant ones [12][13][14]. All of them have in common the characteristic of being synthesized as plant secondary metabolites where they fulfill a wide range of biological functions. Phenolics can confer protection against ionizing radiation, respond to biological aggressions by secreting phytoalexins, act as antibacterial and antifungal agents, as well as attractants for pollinators, in addition to having capacity to accumulate certain molecules capable to modify the coloration of different organs [15].

Like humans and other animals (Metazoa) are not able to synthetize phenolics, their obtainment comes from the uptake of fruits, vegetables, medicinal plants, food supplements, among others. Their consumption is extremely important and beneficial given their notable antioxidant and anti-inflammatory properties [16]. However, their acquisition is limited owing to their bioavailability, which depends on multiple factors, such as the molecule itself, the intestinal microbiota, pH values and the consumption with other compounds. Furthermore, it is also important to take into account the inter-variability between individuals. All of these factors contribute to the different kinetic characteristics shown by each compound [17]. Currently, the polyphenols with the highest bioavailability are phenolic acids, followed by isoflavones, flavonols, catechins, flavanones, proanthocyanidins and lastly anthocyanins. However, recent studies revealed that, probably, flavanones and anthocyanins can be more bioavailable than previously reported once they suffer an extensive metabolization in intestinal microbiota [18][19]. Particularly, and focusing on anthocyanins, Ludwig et al. [20] and Mueller et al. [21] reported that cyanidin glycosides, after metabolization, can originate around 35 different metabolites, where the main ones are 2,4,6-trihydroxybenzaldehyde, p-coumaric, protocatechuic and vanillic acids, and phenolic conjugates (e.g., hippuric, phenylacetic, and phenylpropenoic acids).

Over the last few decades, the vision about phenolic compounds has changed drastically. If before they were considered xenobiotics with the ability to reduce the absorption of proteins and other bioactive compounds, today, their presence in food is increasingly important, as many depth studies have shown their ability to counteract oxidative stress, and therefore, preventing, or attenuating the symptoms of many chronic diseases, such as diabetes and cardiovascular pathologies, and also to control weight [22][23]. These compounds already showed ability to regulate the appetite and lipid metabolism, inhibit the differentiation of adipocytes and serve as beneficial gut microbiota prebiotics [24]. Furthermore, they are able to reduce the activity of disaccharidases (i.e., *α*-glucosidase and *α*-amylase) and the absorption of sugars, and improve the use of monosaccharides by muscle cells [25]. These capacities are essentially due to their chemical, standing out the presence of multiple hydroxyl groups, which can easily interact with gastrointestinal enzymes involved in carbohydrate metabolism, and hence, interfering with their functions [26]. In the same way, other enzymatic activities have been described regarding phenolics, such as the ability to inhibit the DNA polymerases α and δ (which are involved in cells proliferation), as well as to interact with zinc metalloproteinases, including those involved in ACE system [27]. Lastly,

their consumption also shows to have a positive effect on the incidence of cardiovascular diseases, observing a direct relationship between the consumption of these compounds and the reduction of the risk of hypertension, dyslipidemia, coronary and arterial diseases events [28][29]. In this way, phenolic compound consumption has been related to a vasodilator effect at the peripheral level, such as in the endothelium, relating this effect to the management of oxidative stress and the blocking of reactive oxygen species [17][30][31]. Specifically, quercetin and resveratrol, have been shown to be efficient inhibitors of the signaling pathway of the protein Mammalian Target of Rapamycin, which is related to problems of arteriosclerosis, cardiac muscle degeneration and vascular integrity [32]. Besides, both compounds can also regulate the concentration of low-density lipoprotein cholesterol in the blood, improve the oxidative balance due to their high antioxidant capacities and reduce the degenerative effects associated with this metabolic state [29]. In addition, resveratrol, cherries' cinnamic acids and anthocyanins have been shown capacity to regulate the basal levels of the control systems of circadian rhythms, through the modulation of the expression of CLOCK-BMAL1 genes. Since these genes are involved in the determination of liver sensitivity to insulin and are affected by dark cycles, the action of anthocyanins will allow restoring the correct metabolization of fatty acids [33].

Besides, phenolics also possess antimicrobial activities. They already showed capacity to interfere with the growth of *Escherichia coli* H157: H7, *Salmonella* sp., *Listeria monocytogenes* and *Citrobacter*, with the benefit that the appearance of resistance is a less common event than in the use of conventional antibiotics [14][34].

Furthermore, they also play a relevant feature in the control of viral infections of Dengue virus [35], human immunodeficiency virus [36], severe fever with thrombocytopenia syndrome virus [37], hepatitis B virus and influenza virus [38][39][40], through inhibitory mechanisms of interaction, binding and replication of the virus in the host cells.

Therefore, several works already indicated that the consumption of phenolic compounds through the daily diet offers a wide range of benefits. Even so, it is believed that some of them are still to be discovered, and in this aspect, bioinformatics tools, as the use of molecular docking that allows extensive potentials studies using the information indexed in databases, such as Phenol-Explorer (http://www.phenol-explorer.eu, accessed on 10 June 2021) or the USDA Nutrient Data Laboratory Flavonoid Database (https://www.ars.usda.gov/northeast-area/beltsville-md-bhnrc/beltsville-human-nutrition-research-center/methods-and-application-of-food-composition-laboratory/mafcl-site-pages/database-resources/, accessed on 10 June 2021), play an important role. In fact, these tools are considered effective for the search for new treatments against various diseases, once they permit modulating the molecular dynamics of these compounds with different target proteins [10][11][41][42][43][44][45].

Taking into account the described above and knowing that, generally, obese and/or diabetic individuals and people who suffer some morbidities are more susceptible to develop the most serious symptoms of COVID-19, it is not surprising that phenolics have really some anti-SARS-CoV-2 actions, as already documented by these modern tools.

3. Phenolic Compounds in COVID-19

In accordance with the mentioned above, namely in the ability of phenolics to interact in viruses, multiple studies revealed phenolics can also inhibit infection by previous coronaviruses, which are, the SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). Both viruses present an identic mechanism of infection when compared to that of SARS-CoV-2 [46][47][48].

Focusing on the SARS-CoV-2, its infection and continuous replication into cells can cause an excessive and non-specific immune response in some patients, originating an exacerbated production of pro-inflammatory markers (e.g., interleukins (IL), namely the IL-6, tumor necrosis factor α, macrophage inflammatory protein 1a, monocyte chemoattractant protein 1, and interferon-gamma inducible protein-10) [49][50]. Consequently, severe attacks can occur in many organs, including lungs and kidneys, leading to eventual cell death, sepsis, organs failure, and sometimes, patient death [50]. In this context, some phenolic compounds have been shown to have a determining effect on the modulation of interleukin synthesis induction routes, allowing them to be promising tools in the management of this response [51]. These can act at different levels, modulating gene expression and inhibiting the activity of certain receptors related to the initiation of chronic inflammatory response cascades, such as nuclear factor kappa-B, or mitogen-activated protein kinase and cyclooxygenase-2 [52].

In addition to their anti-inflammatory properties, phenolics already proved to be able to prevent the entry or fusion of this virus in cells by binding to the S protein, modifying its binding site, and thus, avoiding the recognition process with the host, as described in **Figure 2** [42][53][54]. Additionally, phenolics can also interact with membrane-binding receptors, mainly ACE2 proteins, which are the main point of recognition and entry into the host cell by the SARS-CoV-2 virus and block

them [8]. Among phenolics, hesperetin shows a notable ability to binds with ACE2 protein, preventing the ligation of the virus S protein [42].

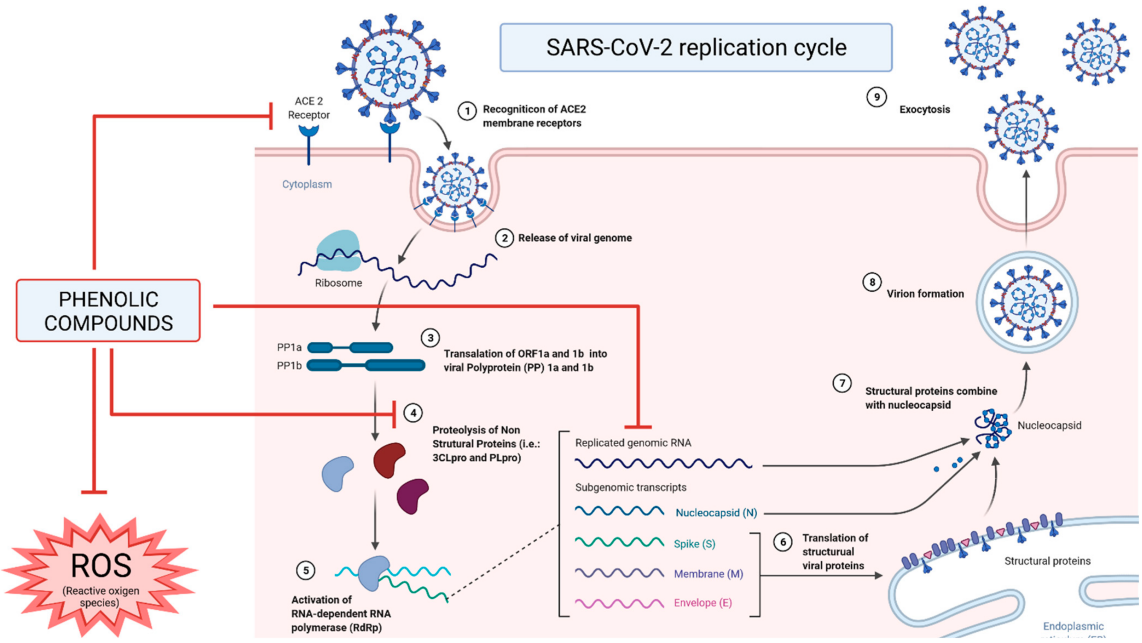

Figure 2. Mechanisms of action and inhibition of phenolic compounds against severe acute respiratory syndrome of coronavirus 2 (SARS-CoV-2) on its replication cycle and in the host's immune response.

Phenolics can also interact with the amino acids present in the active sites of M^{pro}, $3CL^{pro}$ and PL^{pro} proteases, interfering with their activity and blocking the synthesis of several proteins necessary for the correct replication of the virus [47][55]. Similarly, it has been observed that phenolics can also stop the activity of RdRp in an analogous way exerted by the antiviral remdesivir, and hence, prevent the replication of the virus [56][57][58].

Table 1 summarizes the main anti-SARS-CoV-2 effects attributed to phenolic compounds.

Another aspect by which phenolic compounds can act against SARS-CoV-2 infection is due to their ability to control and manage the oxidative stress state once patients with COVID-19 presented higher total oxidative and reduced glutathione levels [59]. For this reason, it is not surprising that the daily intake of phenolics can, through a multifactorial approach at several metabolic and regulatory levels, mitigate this situation of oxidative stress and attenuate the severity of the symptoms [60][61].

Table 1. Anti-SARS-CoV-2 effects attributed to phenolic compounds.

Phenolic Compounds	Main Outcome	Reference
Cyanidin	M^{pro} inhibitor	[62][63][64][65]
Daidzein		
Dieckol		
Genistein		
Mearnsitrin		
Myricitrin		
Psoralidin		
Quercetin 3-*O*-β-D-glucoside		
Rutin		
Xanthoangelol E		
Benzoic acid	RdRp inhibitor	[66][67]
Cyanidin		
Daidzein		
Ellagic acid		
Gallic acid		
Genistein		
Kaempferol 3-*O*-rutinoside		
Naringenin		
Oleuropein		
Quercetin		
Quercetin 3-*O*-rutinoside		
Resveratrol		

Phenolic Compounds	Main Outcome	Reference
Myrcetin	Non-structural SARS-CoV-2 helicases inhibitor	[68]
Scutellarein		
Cyanidin 3-*O*-glucoside	PL^{pro} inhibitor	[55][69][70]
Epigallocatechin		
Epigallocatechin gallate		
Hypericin		
Kaempferol		
Quercetin		
Cryptotanshinone	TMPRSS2 inhibitor	[10][68][71]
Ellagic acid		
Gallic acid		
Kaempferol		
Luteolin		
Quercetin		

Phenolic Compounds	Main Outcome	Reference
Afzelin	ACE2 inhibitor	[42][68][71][72][73]
Apigenin		
Baicalin		
Biorobin		
Caffeic acid		
Catechin		
Chlorogenic acid		
Chrysin		
Ellagic acid		
Curcumin		
Cyanidin		
Delphinidin		
Epigallocatechin		
Epigallocatechin gallate		
Ferulic acid		
Galangin		
Gallic acid		
Hesperetin		
Isoferulic acid		
Kaempferol		
Luteolin		
Myricitrin		
Naringenin		

Phenolic Compounds	Main Outcome	Reference
Nobiletin		
Nympholide A		
Pinocembrin		
Quercetin		
Rhoifolin		
Rutin		
Scutellarein		
Taiwanhomoflavone A		
Tangeretin		
ε-Viniferin		
Chrysin		
Ellagic acid		
Gallic acid	Interact with Spike protein	[42][68][71][72][73]
Hesperetin		
Pinocembrin		
Artepillin C	Inhibit p21-activated kinase 1	[74]
Ellagic acid		
	Inhibit furin	[75]
Gallic acid		

Abbreviations: Mpro, Main Protease; PL^{pro}, papain-like protease; RdRp, RNA-dependent RNA polymerase; TMPRSS2, transmembrane protease serine 2; ACE2, Angiotensin-Converting Enzyme II.

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