Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Short communication

Fighting coronaviruses with natural polyphenols

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ABSTRACT

Few licensed drugs and vaccines are available concerning COVID-19, a disease caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2). Furthermore, numerous recent SARS-COV-2 variants of have arisen globally, demonstrating the need to develop broadly protective interventions for different coronavirus strains. Polyphenols are the largest class of natural bioactive compounds, categorized as flavonoids (catechins, quercetin and kaempferol) and non-flavonoids (gallic acid and resveratrol), and these compounds have been described as effective antiviral agents. This is because they can inhibit coronavirus enzymes, blocking replication and infection. The present short manuscript aimed to summarize and report the current evidence from well-known powerful flavonoid (catechin, quercetin, and kaempferol) and non-flavonoid (gallic acid and resveratrol) polyphenols obtained from plant extracts that inhibit coronavirus strains in *in vitro* models or by computer modeling. The knowledge of strategies beyond conventional treatments may be helpful in the development of new coronavirus drugs, treatments/medicines, or formulations.

1. Introduction

The year 2020 began with unknown pneumonia first been identified in December 2019 in Wuhan, China. In March 2020, the WHO announced the official name for the disease as coronavirus disease 2019 (COVID-19) (SARS-CoV-2) (Gasmi et al., 2020). SARS-CoV-2 contaminates both humans and other species. The disease causes immune system damage, resulting in respiratory mechanism complications, and has spread quickly, as it is highly contagious. SARS-CoV-2 is the third identified wave of coronavirus strains, the first two comprising Severe Acute Respiratory Syndrome (SARS), first detected in the Guangdong province, in China (2002/2003), and Middle East Respiratory Syndrome (MERS) in Saudi Arabia (2012) (de Wit et al., 2016; Rothan and Byrareddy, 2020).

The SARS-CoV-2 pandemic disease can be categorized into three phases, as follows: (I) asymptomatic properties or no detectable virus, (II) virus detection, but with a mild symptomatic period, and (III) severe respiratory symptoms and an elevated viral load. During the first and second phases, a specific adaptive immune response is required to remove the virus and prevent disease progression to the third stage (Shi et al., 2020). Alarmingly, some patients return to the hospital after being discharged, still testing positive for viral load. This suggests that it may be challenging to manage a virus-eliminating immune system in some COVID-19 patients, and vaccines may not work or work partially on these subjects (Shi et al., 2020; Garcia-Beltran et al., 2021). Acquired resistance against drugs and increasing mutations (as has occurred in Brazil) (Resende et al., 2021), remain the major challenge unmet by medical needs in the treatment of this disease. According to Garcia-Beltran et al. (2021), a relatively small number of mutations can mediate potent escape from vaccine responses. While the clinical impact of neutralization resistance remains uncertain, we highlight and emphasize the need to develop broadly protective interventions against the evolving pandemic. Therefore, the identification of novel antiviral agents is paramount (Wu et al., 2017).

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Immune system competence is affected by dietary habits, which determine the risk and severity of infections (Gasmi et al., 2020). Dietary polyphenols are powerful immune system health drivers. These consist of a complex group from secondary plant metabolites comprising over 8000 compounds, categorized as flavonoids, and non-flavonoids (Nile and Park, 2014; Bora et al., 2018; Singla et al., 2019).

Polyphenols display immunomodulatory capabilities, one of the major mechanisms involved in inflammation control and immune responses (Somerville et al., 2016). Compounds such as catechin, quercetin, kaempferol, gallic acid, and resveratrol (Fig. 1) exhibit immune, anti-inflammatory, and antioxidant activity. They have also been reported as presenting suitable structural leads with the potential to inhibit the key expression of SARS-CoV proteins (3-chymotrypsin-like protease ($3CL^{pro}$), papain-like protease (PL^{pro}), RNA-dependent RNA polymerase, and spike (S)), which play a crucial role in the binding of the viral genome to host cells, aiding in the replication and transcription of the severe acute respiratory syndrome-coronaviruses and the SARS-CoV genome (Ngwa et al., 2020; Poochi et al., 2020; Chojnacka et al., 2020; Dabeek and Marra, 2019; Park et al., 2017). The main general phenolic mechanisms comprise i) reducing virus titers and ii) decreased expression of SARS-CoV proteases PL^{pro} and $3CL^{pro}$ by interaction-blocking (Annunziata et al., 2020). Overall, the main mechanisms of action of these natural inhibitors against coronaviruses comprise binding and inhibition. Thus, the active compounds present in these natural compounds, such as phenolic compounds, are able to block viral proteins, displaying potent antiviral activity. Therefore, they are regarded as crucial in developing novel clinical study approaches (Annunziata et al., 2020; Chojnacka et al., 2020; Zhang et al., 2020).

A significant number of studies have shown polyphenol efficacy against several pathogens, including the herpes simplex virus (HSV) (Musarra-Pizzo et al., 2020; El-Toumy et al., 2018), Epstein-Barr virus (Kapadia et al., 2002), enterovirus 71 (Chung et al., 2015), influenza virus (Sundararajan et al., 2010; Wu et al., 2017), and other viruses that cause respiratory tract-related infections (Xu et al., 2010; Zhang et al., 2014).

In this scenario, strategies beyond conventional treatments continue to encourage scientists to find new options strongly. Therefore, this short communication aims to summarize and report supporting evidence regarding the potential *anti*-coronavirus activity of flavonoids (catechin, quercetin and kaempferol) and non-flavonoids (gallic acid and resveratrol), promoting further research towards enhancing novel strategies to reduce coronavirus effects and improve population's immune system.

2. The potential use of polyphenols to prevent coronaviruses

A limitation of conventional medicine (vaccines and antibiotics) in treating COVID-19 is noted, and with the clinical neutralization impact, resistance remains uncertain (Garcia-Beltran et al., 2021). Therefore, therapies applying bioactive compounds have been reported as a rich source of mechanisms able to reduce the risk for COVID-19 disease. As described above, polyphenols consist of a large class of compounds comprising plant secondary metabolites that can be categorized simply as flavonoids (catechin, quercetin, and kaempferol compounds) and non-flavonoids (gallic acid and resveratrol), and can be subdivided into subclasses (Fig. 1) (Nile and Park, 2014; Bora et al., 2018; Singla et al., 2019).

Flavonoids comprise the most vast and important class of natural products. Notably, they belong to a class of plant secondary metabolites displaying a polyphenolic structure and can be subdivided into different subclasses, depending on the C ring carbon to which the B ring is attached and the degree of C ring unsaturation and oxidation (Fig. 1) (Panche et al., 2016). Catechins is a remarkably class of flavonoids (subclass flavonol). These are include (−)-epigallocatechin gallate (EGCG), (−)-epigallocatechin (EGC), and (−)-epicatechin gallate (ECG), that are commonly found in green tea leaves (Song et al., 2005; Bernatoniene and Kopustinskiene, 2018; Bora et al., 2018). Ghosh et al. (2021) selected eight polyphenols from green tea that exhibited antiviral activity against several

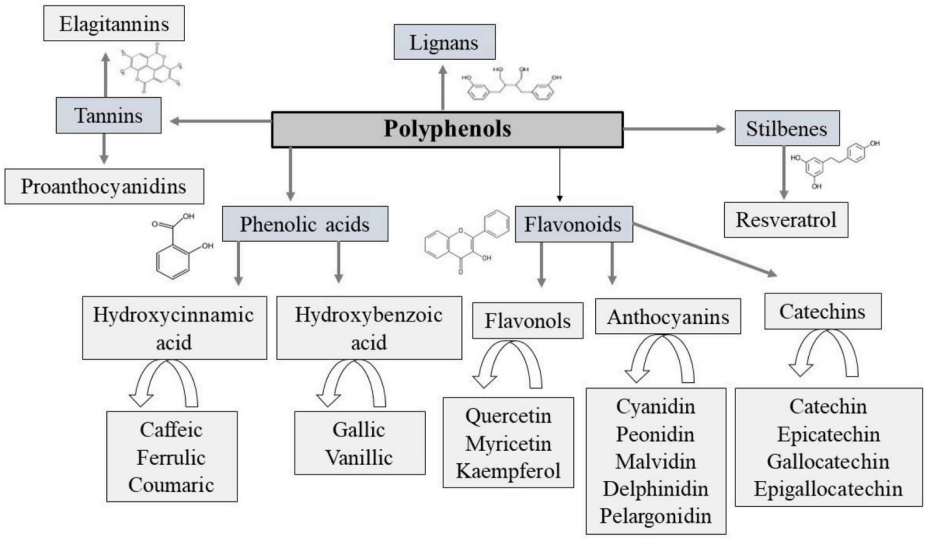

Fig. 1. Polyphenol classes and subclasses of compounds. Figure adapted from: Nile and Park (2014).

RNA viruses to determine potential M^{pro} inhibitors. The authors found a suitable binding affinity to M^{pro} (−7.1 to −9.0 kcal/mol). Besides that, they described that three flavonoids (gallocatechin-3-gallate, epigallocatechin gallate, and epicatechin gallate) interact powerfully with one or both catalytic residues (Cys145 and His41) of the SARS CoV-2 main protease (M^{pro}). Supporting this concept, among twenty-three phenolic compounds, (−)-, catechin gallate and (−)-gallocatechin gallate displayed high inhibitory activity in a dose-dependent manner against SARS-CoV nucleocapsid (N) protein activity at 0.005 μg mL^{-1}, by quantum dots conjugated with the RNA oligonucleotide system. At 0.05 μg mL^{-1}, (−)-catechin gallate and (−)-gallocatechin gallate resulted in over 40% of inhibition (Roh, 2012) (Table 1).

As catechins, other flavonoids have been studied and that support the idea that flavonoids can be used to prevent the spread of coronaviruses. Theaflavin, an antioxidant compound found in black tea as catechin, after a screened using computer modelling, was identified as a potential inhibitor amongst the eighty-three compounds used in Chinese conventional medicine of an enzyme that catalyzes RNA replication SARS-CoV-2 (Lung et al., 2020) (Table 1). Yu et al. (2012) screened sixty-four bioactive compounds regarding potential inhibitory effects on SARS-CoV helicase nsP13 *in vitro*. Myricetin and Scultellarein, powerful flavonoids belonging to the flavanol and flavones suclasses, respectively, display the ability to inhibit the SARS-CoV helicase protein *in vitro* by affecting ATPase activity. Furthermore, these compounds did not exhibit cytotoxicity activity in normal breast epithelial MCF10A cells, demonstrating their potential and possible use as novel inhibitory chemicals against SARS-CoV. In this sense, Lin et al. (2005) screened *Isatis indigotica* roots and phenolic Chinese herbs for *anti*-SARS-CoV $3CL^{pro}$ effects and reported that the plant-derived compounds aloe emodin and hesperetin (flavanone subclass) displayed dose-responsive attributes. Moreover, among five compounds from *Isatis indigotica* and seven phenolic compounds identified as Chinese herbs, Hesperetin (8.3 μM) displayed high potential in inhibiting $3CL^{pro}$ cleavage activity in a cell-based assay (Table 1).

Zhuang et al. (2009) screened seven medicinal herb extracts inhibitory effects on the wild-type of SARS-CoV and HIV/SARS-CoV S pseudovirus infections. Only the Cinnamomi Cortex Extract (CCE) and Caryophylli Flos Extract (CFE) showed moderate IC_{50} inhibitory effects (<100 μg mL^{-1}) at 30.3 ± 2.6 μg mL^{-1} and 58.8 ± 5.6 μg mL^{-1}, respectively. These extracts were divided into four fractions: 1) ethanol; 2) ethylacetate; 3) *n*-butanol and 4) mixed methods; and a dose-dependent effect against HIV/SARS-CoV

Table 1
Effect of bioactive compounds obtained from polyphenols and their antiviral activities.

Viral strain	Assay method	Plant species	Key compounds present	Biological action	Reference
MERS-CoV	Vero E6 cells	–	Resveratrol	Reduced cell death induced by a MERS-CoV infection from 250 to 125 μM; Nucleocapsid protein translation is dose-dependent according to resveratrol doses	Lin et al. (2017)
MERS-CoV	Proteases 3-chymotrypsin-like, papain-like coronavirus cysteine, and glucosidase protein	*Broussonetia papyrifera*	Polyphenols	3CL and PL CoV protease were inhibited in a dose-dependent manner	Park et al. (2017)
SARS-CoV	Quantum dots-conjugated oligonucleotide system	–	(−)-catechin gallate and (−)-gallocatechin gallate	Accentuated *anti*-SARS-CoV nucleocapsid binding protein activity; Over 40% inhibition at 0.05 μg mL^{-1}	Roh (2012)
SARS-CoV	Plaque reduction assay	*Cinnamomi* sp.	Procyanidin	Procyanidins showed moderate *anti*-wt SARS-CoV activity; Inhibition of initial viral access through the clathrin-dependent endocytosis pathway	(Zhuang et al., 2009)
SARS-CoV	$3CL^{pro}$ cleavage assay	*Isatis indigotica*	Aloe emodin Hesperetin	Dose-dependent ability to inhibit $3CL^{pro}$	Lin et al. (2005)
IBV	Vero cells	*Sambucus nigra*	Polyphenols	Reduction of virus titers in a dose-dependent manner; viral replication and infection process inhibitions, altered virus structures and membrane vesicles	Chen et al. (2014)
IBV	CEK cells	*Forsythia suspensa* Vahl.	Forsythoside A	Dose-dependent reductions of viral load, nucleocapsid protein and IBV infection	Li et al. (2011)
FIPV1146 (FCoV)	$3CL^{pro}$ inhibition assay	Lichen and other species	Quercetin 7-rhamnoside 7-benzyl luteolin Steviol	$3CL^{pro}$ inhibition	Theerawatanasirikul et al. (2020)
SARS-CoV-2	Computer modelling	*Ipomoea obscura* (L.)	Polyphenols	ACE2 and M^{Pro} effectively attaches	(Poochi et al., 2020)
SARS-CoV-2	Computer modelling	*Camellia sinensis*	Theaflavin	RNA-dependent RNA Polymerase attachment	(Lung et al., 2020)
SARS-CoV-2	Computer modelling	Range of Chinese traditional medicines	Kaempferol Quercetin	Replication and entry in spike CL^{pro} proteins	(Zhang et al., 2020)

Abbreviations: IBV, infectious bronchitis virus; SARS-CoV-2, SARS-related coronavirus 2019, SARS-CoV, SARS-related coronavirus; MERS-CoV, Middle East Respiratory Syndrome coronavirus; MOI, Multiplicity of infection; ACE2, angiotensin converting enzyme 2; $3CL^{pro}$; 3-chymotrypsin-like protease; M^{Pro}, papain like protease; FCoV, Feline coronavirus. Table adapted from Mani et al. (2020).

S and HIV/VSVG pseudovirus infections was observed. In addition, CCE and CFE extracts were tested for inhibitory effects concerning clathrin-dependent endocytosis in using a plaque reduction assay, and exhibited contrary responses; where CCE inhibited the SARS-CoV infection (viruses were mixed with the herbs), thereby inhibiting viral entry into the host cells, and CFE displayed a fragile inhibitory activity (Table 1).

Also, polyphenols isolated from *Broussonetia papyrifera* present inhibitory effects against SARS-CoV proteases 3-chymotrypsin-like and papain-like coronavirus cysteine (SARS-3CL^{pro}, SARS-PL^{pro}, MERS-3CL^{pro}, and MERS-PL^{pro}). Glucosidase inhibitory capacity tests indicate that both cysteine proteases and α-glucosidase are dose-dependent. The highest inhibitory effect on SARS-CoV PL^{pro} ($IC_5 = 3.7$ μM) was observed in prenylated flavone derivatives, with commercial polyphenols such as quercetin ($IC_{50} = 8.6$ μM) and kaempferol ($IC_{50} = 16.3$ μM) displayed similar behavior. In this sense, Poochi et al. (2020) using an *in silico* technique, demonstrated that five bioactive compounds from *Ipomoea obscura* (L) leaf extracts are able to inhibit the ACE2 protein and M^{pro}, main proteins in virus replication of coronavirus by blocking viral receptivity (Table 1).

Quercetin and kaempferol (flavonol subclass) compounds are widely found in fruit and vegetables such as berries, spinach and kale (Dabeek and Marra, 2019). They display anti-inflammatory, anti-cancer, anti-allergic, and antiviral activities, among others (Ulusoy and Sanlier, 2020). Choi et al. (2009) reported that quercetin 7-rhamnoside (Q7R), a disaccharide glucoside, displays antiviral activities against porcine endemic diarrhoea virus (PEDV). This compound inhibited PEDV replication at 0.014 μg mL^{-1} and at 50% of the inhibitory concentration (IC_{50}). The 50% cytotoxicity concentration (CC_{50}) of Q7R was more significant at 100 μg mL^{-1}. Structural analogs were also analyzed, and quercetin, apigenin, luteolin and catechin also demonstrated moderate *anti*-PEDV activity. Ribavirin, interferon-α, coumarin and tannic acid display relatively lower efficacy levels compared to Q7R. This polyphenol and its analogs could be considered lead compounds in the development of *anti*-PEDV drugs along with other related antiviral agents (Choi et al., 2009).

Moreover, Song et al. (2011) demonstrated the effect of Q7R (Fig. 1) on PEDV replication, reporting antiviral activity through the CPE reduction test. DNA fragmentation and flow cytometry were used to verify DNA fragmentation rates and reactive oxygen species (ROS) levels induced by infection. The inhibitory effect was not directly associated due to Q7R's antioxidant properties. Therefore, it did not directly interact with the PEDV fragments, but it did affect the early stage of PEDV infection by obstructing its viral mRNA production.

Infectious bronchitis virus (IBV), a γ-coronavirus, is the causative agent in infectious bronchitis (IB) (Li et al., 2011). Chen et al. (2014) analyzed crude ethanol extracts of *Rhodiola rosea* roots, *Nigella sativa* seeds, and *Sambucus nigra* fruit against this virus. The infected Vero cells were pretreated with the extracts and quantified by plaque assays. The extracts showed a different behavior. *Rhodiola rosea* and *Nigella sativa extracts* did not present inhibitory properties against IBV infection *in vitro* when compared to the control samples. Nevertheless, *Sambucus nigra* extracts are well-known for containing high quercetin levels, leading to a significant virus titer reduction by dose-dependent, inhibition, viral replication and infection mechanisms. In addition, this treatment led to the development of envelopes and the presence of modified membrane vesicles as observed by electron microscopy. This demonstrates that *Sambucus nigra* extracts can compromise the IBV virion structures, likely causing non-infectious behavior. Thus, the results can be shown that *Sambucus nigra* extract can be used as a potential *anti*-IBV agent (Table 1).

The COVID-19 outbreak has encouraged scientists to apply different and new techniques, such as computational modelling. This is a cheap, quick and high sensitivity method that allows for comparison between molecule affinity and a specific receptor (Mani et al., 2020; Theerawatanasirikul et al., 2020). In this regard, Theerawatanasirikul et al. (2020) applied a computer-aided technique in a study concerning feline infectious peritonitis virus (FIPV). Initially, a virtual screening technique was used to identify the active site on the 3CL^{pro} protease for the binding process through a protease inhibitor assay to check for available natural compounds. Then, fifteen of the most likely compounds were identified and assessed by *in vitro*. 7-methylluteolin (28.5 ± 4.2 μM) and stictic acid (29.4 ± 4.6 μM) exhibited the lowest IC50 values. Q7R (Fig. 1) also demonstrated modest inhibition of IC50 (77.2 ± 13.8 μM), while steviol and 7-benzyl luteolin (flavone subclass) showed no inhibition of IC50 (> 500 μM).

Chinese scientists have been virtually analyzing the potential of Chinese traditional medicine to inhibit SARS-CoV-2 (Chojnacka et al., 2020). Zhang et al. (2020) using an *in silico* technique effectively identified one hundred and fifteen compounds and highlighted thirteen as promising and requiring further research, emphasized for quercetin and kaempferol (Fig. 1) (Table 1), which have been previously investigated and present significant potential in treating several diseases (Ezzati et al., 2020; Imran et al., 2019). Several of these compounds, such as catechin, quercetin, kaempferol and other plant-derived flavonoids have been reported as powerful candidates for the development of *anti*-coronaviral drugs and support the idea that flavonoids are an important source of bioactive compounds against coronaviruses (Park et al., 2017).

Phenolic acids (non-flavonoid class, Fig. 1) are considered the most important polyphenol compounds due to their performance potential, high concentration and wide availability, as they are found in whole fruits and skins, and in the seeds of fruits and vegetables. They are generally described as containing one carboxylic acid group that can be attached to molecules such as amides, esters, or glycosides, or found, rarely, in free form (Singla et al., 2019). These phenolic acids are mainly categorized into two sub-groups, hydroxybenzoic and hydroxycinnamic acid. Some phenolic acids, such as gallic acid, caffeic acid and chlorogenic acid, have been extensively reported as displaying antiviral activity against coronavirus strains, but also against hepatitis B and C viruses, influenza A virus, and herpes simplex (Weng et al., 2019), as phenolic acid displays excellent absorption ability and can improve antiviral activity (Kumar and Gael, 2019).

Weng et al. (2019) studied the human coronavirus NL63 (HCoV-NL63), a type of coronavirus belonging to the α-coronavirus genus of the Coronaviridae family. Like SARS-CoV-2, HCoV causes mild upper respiratory tract illnesses with symptoms including runny noses, cough, and sore throats in young children and young adults (Huang et al., 2017). Weng et al. (2019) examined the potent *anti*-HCoV-NL63 activity of *Sambucus FormosanaNakai* extract, a traditional medicinal herb belonging to the Adoxaceae family,

an elderberry species. Caffeic acid, chlorogenic acid, and gallic acid were reported as the phenolic acid constituents in this extract. To assess the antiviral mechanism of these compounds against HCoV-NL63, plaque formation, virucidal activity, and virus attachment assays were carried out. The detected phenolic acids exhibited antiviral capacity able to reduce the progeny production of HCoV-NL63 particles *in vitro*, mainly caffeic acid, which resulted in a noteworthy reduction of virus yield (IC50 = 3.54 μM), plaque formation (5.4 μM), and virus attachment (IC50 = 8.1 μM).

Forsythoside A (FTA), is a pharmacologically active compound comprising three chemical moieties, including aglycone (caffeic acid), phenylethanoid aglycone (hydroxytyrosol) and sugars, obtained from *Forsythia suspensa* fruits, and has been exhibited to have anti-bacterial and immunomodulatory properties (Zeng et al., 2017). Li et al. (2011) analyzed inhibiting effects of FTA on IBV using CEK cell monolayers. They reported that the concentration of 0.64 mM FTA showed a tendency towards *anti*-IBV effects. In addition, the IBV nucleocapsid gene was detected, and it was found that viral loads decreased with the increase of up to 0.64 mM concentrations of FTA, indicating that Forsythoside A displays the potential to inhibit *in vitro* IBV infection (Table 1).

Recently, Umar et al. (2021) performed a molecular docking assay analyzing sixteen gallic acid derivatives. This study described the action of gallic acid derivates against the five key proteins of SARS-CoV-2 (nsp3 (papain-like protease), nsp5 (main protease), nsp12 (RNA-Dependent RNA polymerase), nsp13 (helicase), and nsp14 (nidoviral uridylate-specific endoribonuclease). Between these sixteen compounds, three promising inhibitors of the selected SARS-CoV-2 non-structural proteins were 4-O-(6-galloylglucoside), 3-O-(6-galloylglucoside), and epicatechin gallate. This finding revealed the potential of these compounds showing a possible option treatment against coronaviruses.

One of the most well-known stilbenes is resveratrol (3,5,4′- trihydroxystilbene), which is commonly found in grapes (Singla et al., 2019). This compound has been described as a powerful polyphenolic compound with a broad spectrum of action against several diseases (Lee et al., 2016; Hoca et al., 2020). Similarly, Lin et al. (2017) reported that resveratrol (Fig. 1) prevents MERS-CoV infections in a Vero E6 cell model. Two resveratrol concentrations of 250 and 125 μM were tested and seemed to alleviate monolayer destruction, demonstrating that resveratrol can reduce the cell death induced by a MERS-CoV infection at this concentration range. In addition, MERS-CoV RNA levels in resveratrol cells treated at 250, 200, 150, 62.5, and 31.25 μM were significantly lower than in MERS-CoV-infected cells after 24 h. Resveratrol reduces the infectious titer by plaque and reduction after 48 h. Furthermore, MERS undergoes nucleocapsid protein translation in a dose-dependent manner, especially from 250 to 125 μM. Resveratrol reduced sMERS-CoV-mediated apoptosis more efficiently at 200 μM through decreased Caspase 3 cleavage levels. Finally, resveratrol is able to inhibit MERS-CoV when administered at lower dosages (62.5 μM), consecutively. In this context, polyphenols, flavonoids and non-flavonoids may display antiviral features against a broad spectrum of human respiratory coronaviruses and comprise valuable tools in developing future antiviral agents. Therefore, possible preventive treatments could be administered to improve the immune system against the current COVID-19 strain, as well as other coronavirus strains (Weng et al., 2019; Umar et al., 2021).

3. Future perspectives

This assessment offers evidence that polyphenols contain inhibitor compounds that act against the coronavirus family and may be useful in broadly protective interventions for many coronavirus strains in the evolving pandemic. Vaccines have been developed and show up to >94% efficiency in phase III clinical studies carried out in different countries (Baden et al., 2021). Nevertheless, the recent emergence of novel circulating variants has raised significant concerns about the geographic and temporal efficacy of these interventions (Garcia-Beltran et al., 2021). The examples indicated herein, which are naturally occurring in nature (fruit, flower, root, and stem), provide a valuable and powerful resource of biologically active compounds displaying antiviral properties.

The use of nutraceutical compounds like polyphenols has increased (Chojnacka et al., 2020), due to the development of new biotechnology and medical techniques, as well as the integration of research areas such as proteomics, metabolomics and genomics, among others (Kumar et al., 2018). Novel processing technologies and formulation strategies have enhanced the discovery process of new bioactive compounds (Putnik et al., 2018), and been able do decrease the instability of natural bioactives in order to improve their delivery, bioavailability, and their antiviral activity for use as antiviral functional foods (Braithwaite et al., 2014).

A good example of polyphenol-based nutraceuticals that may be efficient in treating patients infected by COVID-19 and other coronaviruses comprise grape extract (GE) and green tea extract (GTE). GE is a recognized source of bioactive compounds (anthocyanins, proanthocyanidins and resveratrol), whilst GTE is a source of catechins, tannins, and other phytochemicals, including (−)-epigallocatechin gallate (EGCG), (−)-epigallocatechin (EGC) and (−)-epicatechin gallate (ECG) (Fig. 1) (Song et al., 2005; Bora et al., 2018). Notably, antiviral GE and GTE activities against various viruses, such as hepatitis C virus (HCV) (Lin et al., 2013; Lee et al., 2016), hepatitis A virus (HVA) (Su & D'Souza, 2011; Randazzo et al., 2017), hepatitis B virus (HBV) (Huang et al., 2014; Chen et al., 2016), human enteric virus (Su & D'Souza, 2011; Randazzo et al., 2017), human immunodeficiency virus type 1 (Nair et al., 2002; Nance et al., 2009), human norovirus surrogates ((feline calicivirus (FCV) (F9)) (Oh et al., 2013; Joshi et al., 2015) and murine norovirus (MNV-19) (Su & D'Souza, 2011).

Besides these effects, polyphenols like GE and GTE have been reported as being able to effectively decrease the replication of various pro-inflammatory cytokines and chemokines, such as tumor necrosis factor (TNF-α), interleukins (IL-1b, IL-6 and IL-8), inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2), by inhibiting NF-kB-mediated COX-2 expression, which supports targeting the COX-2 signaling pathway (Chen et al., 2016; Annunziata et al., 2020). Overall, these results indicate that GE and GTE are promising for use in the food industry (in the formulation of potential nutraceutical supplements) and medical areas as an inexpensive and novel natural alternative.

4. Conclusion

Flavonoids (catechin, quercetin, and kaempferol) and non-flavonoids (gallic acid and resveratrol) display the potential to be used as a source for novel formulations and further antiviral medication against coronaviruses, such as those of the current COVID-19 pandemic. Furthermore, *In vivo* and *in vitro* studies, as well as the development of these methods, should be applied to further explore molecular mechanisms, active constituent toxicity, side effects, circulating compound levels, and pharmacokinetic properties in order to develop a potent natural drug against COVID-19 and other coronaviruses. In addition, screening other compounds and their analogs from different sources and their mixtures are required to understand their chemical interactions and synergistic and antagonistic effects and describe their health implications.

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