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Polyphenols as promising biologically active substances for preventing SARS-CoV-2: A review with research evidence and underlying mechanisms

Running title: The potential role of polyphenols against SARS-CoV-2

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Abstract

Currently, antiviral drugs and/or vaccines are not yet available to treat or prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In this review, we narrated the available data, from credible publishers, regarding the possible role of polyphenols and natural extracts-containing polyphenols in the prevention of coronavirus disease 2019 (COVID-19), and their immune-boosting properties. It was revealed that polyphenols could be considered as promising biologically active substances for the prevention of COVID-19. The underlying potential mechanism behind this action is mostly due to the antiviral activities and the immune-regulation functions of polyphenols against COVID-19-infections. Antivirus polyphenolic-based medications can mitigate SARS-CoV-2-enzymes, which are vital for virus duplication and infection. It was also found that triterpenoid, anthraquinone, flavonoids, and tannins are possible keys to scheming antiviral therapies for inhibiting SARS-CoV-2-proteases. The identified pharmacophore structures of polyphenols could be utilized in the explanation of novel anti-COVID-19 designs. The advantage of using mixtures containing polyphenols is related to the high-safety profile without having major side-effects, but further randomized controlled trials are required in the upcoming studies.

Keywords: SARS-CoV2; Polyphenols; Functional foods; Boosting immune functions.

Abbreviations: **S**evere acute respiratory syndrome coronavirus 2: SARS-CoV-2; Coronavirus disease 2019: COVID-19; Coronaviruses: CoVs; Severe observation of acute respiratory syndrome: SARS-CoV; Middle East Respiratory Syndrome: MERS-CoV.

1. Introduction

SARS-CoV-2 affects all peoples, especially those who had weak immune systems and/or week immune-based responses. Coronaviruses (CoVs) belonged to the sub-family of Ortho-coronavirinae, under the Coronaviridae family and in order of Nidovirales, and this sub-family contains alpha-, beta-, gamma-, and delta-CoVs (Banerjee *et al.,* 2019). The deadliness of CoVs has been identified by the outbreaks of severe observation of acute respiratory syndrome (SARS-CoV) in 2002/2003 and the Middle East Respiratory Syndrome (MERS-CoV) in 2012/2013. SARS-CoV and MERS-CoV are going to β-CoV (Zhang *et al.,* 2020). Freshly, a new flu-like CoV (COVID-19) associated with SARS-CoV and MERS-CoV was realized in the late of 2019 and spread worldwide with a pandemic (Cohen and Normile, 2020). The total number of cases globally was 91,322,850 and 1,952,979 confirmed deaths in WHO situation report COVID-19 in January 12, 2021 (worldmeters.info).

Hitherto, no vaccine and actual SARS-CoV-2 medications based on anti-SARS-CoV therapy by the scientific community were confirmed (Jo *et al.,* 2020), while scientists are trying to develop efficient vaccines or drugs for the SARS-CoV-2 virus. The general viral infection treatment involving dietary interferences and other immune enhancers which were utilized to promote immunity towards the viral poisons. Thus, they may also be utilized to contest SARS-CoV-2 by the nutritional status of each patient and should be assessed before applying the overall treatments (Zhang *et al.,* 2020). Recently, numerous studies have exposed that phytonutrients play a vital part in the stoppage of chronic syndromes, as most can be related to nourishments (Fraga *et al.*, 2019). Various countries have entered the notion of functional-based food not only essential for human life but also to boost the physiological functions and immunity responses (Del Bo *et al.*, 2019; Quero *et al.*, 2020). The importance of the proper functioning of the body and the well-balanced immune system for the maintenance of human life has been remarkably evident over the last decades (Lopez-Varela *et al.*, 2002; Wichers, 2009).

In addition to phytonutrients mainly presented in fruit and vegetables, polyphenols have recently been targeted due to their role in the prevention of several diseases as described (Fraga *et al.*, 2019). Interestingly, polyphenols have attracted much attention in recent years since their dietary consumption has been associated with the prevention of some chronic and degenerative diseases that are significant causes of death and incapacity in developing countries (Santos-Buelga *et al.*, 2019). In addition, due to the biological activities of polyphenols, particularly antimicrobial, antioxidant, anti-inflammatory, pro-apoptotic behavior, anti-proliferative, and hormonal control ability among polyphenols, countless plants have been considered and investigated because of the classification of new substances with nutraceutical possessions (Forni *et al.*, 2019). Dietary polyphenols signify several bioactive substances broadly found in plant-based food which have the capabilities to prevent the beginning and development of several diseases, and to decrease and control their signs which become a central issue in food research (Del Bo *et al.*, 2019; Quero *et al.*, 2020).

The outbreak of the COVID-19 pandemic caused by SARS-CoV-2, along with the lack of targeted medicaments and vaccines, forced the scientific world to seek new antiviral formulations. This article reviews the feasibility of using polyphenols extracted from plants as a source of bioactive components (e.g., gallates and quercetin), effective in mitigating SARS-CoV-2 and boosting the immune system. There is potential for the utilization of plant-derived polyphenols as functional foods and pharmaceutical formulations. The method of employing such formulations is fast because the raw materials for their preparation, namely herbs and useable plants, are permitted for human consumption worldwide. Approximately 100 research papers were selected from Science Direct, Scopus, MDPI, PubMed, and Web of

Science to review the recently published papers on the related topic with the aid of relative keywords.

2. Functional foods and their efficiency in boosting the immune response

In fact, malnutrition is the most common cause of immunodeficiency concerns worldwide (Schaible and Stefan, 2007). The immune system, which is joined into all physiological arrangements, defends the human body towards microorganisms' infections and other internal and external abuses (Castelo-Branco and Soveral, 2014; Maggini *et al.,* 2018). And suitable nutrition at all phases of life is an important factor to guarantee a sufficient stock of energy, macro- and micronutrients essential for the growth, upkeep, and countenance of the immune response (Maggini *et al.,* 2007). Furthermore, undernutrition is leading to weakening immune function which can be due to consumption of fast food, insufficient intakes of energy and macronutrients, and/or shortages in the essential micronutrients (Alpert, 2017; Calder, 2013; Pereira, 2003). **Fig S1**. showed the sources of variation in the immune system and its relation with suboptimal nutrient status on an increased risk of infection, as previously described (Calder and Kew, 2007; Maggini *et al.,* 2018), showing the vital role of the functional foods.

In this context, functional foods are used to strengthen other physiological functions including the immunity responses (Roberfroid, 2000). The characteristics of functional foods were tabulated in **Table 1**. Functional food components can be useful components that originate logically in or complement food as functional elements such as vitamins, minerals, dietary fiber, fatty acids, amino acids, polyphenols, phytopigments, non-saponifiable fractions, and functional plant-based proteins (Guiné *et al.*, 2009; London, 2010). **Table 2** summarises the functional foods-based products which were quoted from the available data. These foods and/or ingredients boost the immune response by different mechanisms (Powell *et al.,* 2000). Meanwhile, the deficiencies of one or more essential fatty and amino acids, vitamins, Se, Zn, Fe, Cu, and phytonutrients will affect almost all types of immunity (London, 2010; Maggini *et al.*, 2018; Zhang *et al.*, 2020). Regarding COVID-19 pandemic, these functional ingredients may mitigate SARS-CoV-2 through their immunoenhancing and antiviral activity. For example, Zhang *et al.* (2020) had claimed that vitamin A and/or its derivatives like retinoic acid could provide a promising alternative for CoV-therapy. Vitamin D has several immune-modulatory effects and might work as additional therapeutic against COVID-19 (Moriguchi and Muraga, 2000; Zhang *et al.*, 2020). Zhang and Liu (2020) had stated that Zn may affect not only COVID-19-linked symptoms like inferior respiratory tract infection and diarrhea but also SARS-CoV-2 replication. Dosing the patients with Se could be an active choice for the cure of COVID-19 as previously stated by Zhang *et al.* (2020), for instance. These functional compounds are essential substances at the molecular and cellular levels that play critical functions.

3. The potential uses of plant extracts containing polyphenols against SARS-CoV-2

3.1. Overview of the health-benefits of polyphenols

Polyphenols constituents are categorized by the attendance of one or more hydroxy group on an aromatic circle. These components are categorized by their molecular mass, chemical construction, and intricacy to flavonoids (flavones, flavonols, flavanones, flavanonols, iso-flavonoids, flavanols, anthocyanidins, and chalcones) and non-flavonoid ones (phenolic acids, stilbenes, curcuminoids, lignans, and tannins) (Quero *et al.*, 2020). **Fig S2**. portrayed the plant polyphenolics classifications according to Phenol-Explorer (http://www.phenol-explorer.eu). Such polyphenols are valuable to human health and are capable to decrease the diseases perils (Rasouli *et al.*, 2017). Thus, polyphenols have recently attracted much attention to the scientific community due to their dietary intake which is related to the deterrence of some chronic and wasting diseases that establish the main reasons of death. The unique properties of their nature and position of the substituents have concerned for biological utilization, namely, antiviral, antibacterial, antioxidant, and anti-inflammatory activities. These polyphenols have been isolated from a great number of plants, such as fruits, vegetables, legumes, nuts, seeds, herbs, spices, tea, coffee, dark chocolate, and so on (Quero *et al.*, 2020; Rasouli *et al.*, 2017; Santos-Buelga *et al.*, 2019; Silva and Pogačnik, 2020). Among the sources of polyphenols, citrus is a promising source due to its content from bioflavonoids including apigenin, acacetin, luteolin, diosmetin, chrysoeriol, and glycosides which play key roles in providing an extensive range of health useful effects. However, polyphenols' super-healthy properties depend on the amount ingested and their bioavailability (Silva and Pogačnik, 2020).

3.2. Polyphenols and immune system

Many factors cause immune disorders, including environmental stress and changes in the immune regulators that can lead to many human diseases. Bioactive components can play a vital role in immunity through intrusive with immune cell regulation and pro-inflammatory cytokine synthesis. Recently, a huge number of *in vitro* and *in vivo* studies demonstrated the immunomodulatory part of polyphenols. These studies have shown that people with a specific diet, especially polyphenols-rich ones, are at reduced risk for a variety of diseases (Rasouli *et al.*, 2017; Yahfoufi *et al.*, 2018). Additionally, polyphenols are developing therapeutic tools for controlling and protecting the body from several autoimmune disorders due to their immunomodulatory effects (Khalifa *et al.*, 2020; Khan *et al.*, 2019). The immune modulation effect of polyphenols is related to the impact on immune cells, pro-inflammatory gene expression, and modulate cytokines production (Yahfoufi *et al.*, 2018). In addition to the antioxidant properties such as reactive oxygen species scavenging of polyphenols and their donations to the rule of inflammatory signing. Polyphenols also showed high-effects in increasing the natural killers in fruits (Yahfoufi *et al.*, 2018). For their effect on the balance between pro and anti-inflammatory cytokine secretion, polyphenols compounds such as catechins and quercetin have been added to various foods. Additionally, numerous flavonoids can inhibit the expression of various pro-inflammatory cytokines and chemokines (Comalada *et al.*, 2006). Furthermore, the epigallocatechin gallate and curcumin can induce epigenetic changes in cells. Thus, polyphenols compounds can be efficiently used to control the immune response.

3.3.The antiviral activities of polyphenols

The literature review demonstrated that polyphenols have been investigated for their potential antiviral efficiency against SARS-CoV-2 in molecular modeling studies, cell-free polyphenol–protein interaction studies, and in cell-based virus infection studies (Chojnacka *et al.*, 2020; Paraiso *et al.*, 2020). Convincing data shows that polyphenols such as epigallocatechin gallate, resveratrol, and curcumin are prime candidates for preclinical and clinical trials. As a cautionary note, the efficacy of tested polyphenols against human viral disease *in silico* and *in vitro* screening methods are not validated. Potential regulation of COVID-19 intensity by polyphenols controlling ACE2 *in vivo* has been suggested (Horne and Vohl, 2020; Manoharan *et al.*, 2020) but very few studies have been performed to examine the antiviral activity of polyphenols against SARS-CoV-2 *in vivo*. Pudilan Xiaoyan Oral Liquid (PDL), a traditional Chinese medicine containing four herbs and more than 180 ingredients, showed potent anti-SARSCoV-2 activity in infected hACE2 mice (Deng *et al.*, 2020). It has also been stated that a nebulized formula of quercetin and N-acetylcysteine substantially relieved the respiratory symptoms of SARS-CoV-2 in a patient treated with hydroxychloroquine and antibiotics (Schettig *et al.*, 2020). This reinforces the value of more clinical trials to determine the potential of polyphenol-based nutraceuticals as an adjuvant or key treatment for COVID-19. High-throughput screening methods will speed the *in vitro* development of lead candidates by reducing the number of polyphenol libraries. Screening of polyphenol-rich plant extracts is an alternative, commonly used method, but it has the drawback that extracts contain a multitude of natural products with inherent difficulties of not being able to reliably distinguish active concepts and the potential for pharmacological antagonism. These problems can be solved by integrating classical bioassay-guided fractionation with machine learning approaches that expose the identity of bioactive natural products in extracts without the need for homogeneity purification. In our view, the above hybrid method aims to accelerate research because many antiviral *in vitro* experiments can be conducted without the treatment of live viruses and because the identification of polyphenols (and other natural products) has been made simpler over the past few years thanks to developments in plant metabolism and ever-growing natural product databases such as phenol-explorer (Rothwell *et al.,* 2016), knapsack (Shinbo *et al.,* 2006), and the global natural product social networking database (Wang *et al.,* 2016).

Interestingly, there are no known therapies for CoVs-infection and defensive vaccines are still being discovered even discovered still need extensive evaluation. Thus, the situation illustrates the need for appropriate antivirals and/or immune-enhancers to be produced for prophylaxis CoV-infection. Recently, the antiviral activity of numerous polyphenols from different sources was evaluated against several viruses (Khaerunnisa *et al.,* 2020; Maryam *et al.,* 2020). **Table 3** shows the antiviral activities of polyphenols, their main sources, and mode of action (Khaerunnisa, 2020). In a related study, Sundararajan et al. (2010) evaluated three pomegranate extracts including pomegranate juice, concentrated liquid extract, and dried extract for their anti-influenza activity. He found that the anti-influenza activity of pomegranate polyphenols is substantially modified by changes in covering glycoproteins. Likewise, Vela *et al.* (2010) who utilized isoflavone (genistein) and general kinase inhibitor for treating animals, and reported that general kinase inhibitor genistein may use as an anti-arenavirus component. It was also found that theaflavins, which are the polyphenols of black tea, had antiviral effects on vaccinia virus, influenza virus, poliovirus-1, herpes simplex virus, coxsackievirus, and human rotavirus. Morán-Santibañez *et al.* (2018) reported that polyphenol-rich extracts isolated from Mexican seaweed have *in vitro* significant virucidal effects on the Measles virus. Virucidal activity of these extracts is not only a prophylactic tactic before viral infection but can also be fruitful as a dealing after contagion and for avoiding virus spreading.

3.4.The role of polyphenols against SARS-CoV, MERS-CoV, and SARS-CoV-2

Regarding SRARS-CoV, saikosaponins, naturally occurring triterpene glycosides derived from medicinal plants such as *Heteromorpha spp.*, *Bupleurum spp.*, and *Scrophularia scorodonia*, showed several biological activities, specifically antihepatoma, anti-hepatitis, antinephritis, anti-inflammation, immunomodulation, and antimicrobial effects. Thus, Cheng *et al.* (2006) recommended the use of saikosaponins as *in vitro* antiviral activity against CoVs-22E9. The extracts of *Cibotium barometz*, *Gentiana scabra*, *Dioscorea batatas, Cassia tora*, and *Taxillus chinensis* inhibited the SARS-CoV replication better than other 200 extracts (Wen *et al.*, 2011). Likewise, the extracts of *Gentianae radix, Dioscoreae rhizoma, Cassiae Semen*, *Loranthi Ramus*, and *Rhizoma Cibotii* in the concentrations from 25 to 200 μg mL^{-1} inhibited SARS-CoV. Bioflavonoids from *Torreya nucifera* inhibited SARS-CoV 3CLpro by 62% at 100 μg mL^{-1} (Ryu, Jeong, *et al.*, 2010), where he identified 8 diterpenoids and 4 bioflavonoids by fluorescence resonance energy transfer analysis. The activity of flavones (apigenin, luteolin, and quercetin) was also investigated with IC_{50}-values of 280.8, 20.2, and 23.8 µM, separately, and the presence of the apigenin moiety at the C-30 position of flavones seems to be more effective. Ethyl acetate fraction of *Houttuynia cordata* Thunb. contribute to the superior antiviral efficacy *in vitro* and *in vivo* presenting the potential for the development of antiviral agents against coronavirus and dengue infections (Chiow *et al.*, 2016) with an IC_{50}-value of 0.98 mg mL^{-1}. The IC_{50}-values for quercetin, epigallocatechin gallate, and galusatechin gallate against SARS-CoV were 73, 73, and 47 µM, respectively, and the galooyl group should be present at 3-OH-position to be more efficient (Nguyen *et al.*, 2012). Quercetin derivatives such as 7-O-arylmethylquercetin and quercetin-3-β-galactoside could combat as anti-SARS-CoV agent (Chen *et al.*, 2006; Park *et al.*, 2012). Flavonoids found in *Galla chinensis* or *Veronica lin rrifolia* extracts may interact with the surface of the spiky protein of the SARS-CoV, avoiding virus particles from powerful the cell (Wang and Liu, 2014). Phlorotannins isolated from brown algae display an inhibitory effect of SARS-CoV-3CLpro, regulating the virus replication. In particular, dieckol showed high inhibitory activity with an IC_{50} value of 2.7 µM (Park *et al.*, 2013). Tetra-O-galoilo-β-d-glucose and luteolin have been confirmed to be active against SARS-CoV (Lin *et al.*, 2005). In particular, *Lycoris radiata* extract showed to be a good entrant against SARS-CoV as it showed the highest efficacy, mainly due to the lycorin component (Lin *et al.*, 2005). In addition, Park *et al.* (2017) isolated 10 polyphenolics from *Broussonetia papyrifera* as CoVs-protease inhibitors against 3-chymotrypsin-like (3CLpro) and-papain-like-CoVs-cysteine-proteases (PLpro). It was also found that all polyphenols have more effectiveness against PLpro than 3CLpro; the results suggested polyphenols of *B. papyrifera* have anti-CoVs activity. Likewise, Ryu *et al.* (2010) examined the capacity for SARS-CoV inhibition of flavonoids from the *Torreya nucifera* leaves. The ethanolic extract of *T. nucifera* leaves-inhibited the SARS-CoV-3CLprotease with inhibition values of 62% at 100 g mL^{-1}. Additionally, this study confirmed that amentoflavone is more effective than the respective flavones (luteolin and apigenin) and bioflavonoids derivatives on SARS-CoV-3CLpro. Thus, amentoflavone may be a good component for development as a natural therapeutic medicine against SARS-CoV infection. Jo *et al.* (2020) studied the antiviral activity of three flavonoids against SARS-CoV. Rhoifolin, herbacetin, and pectolinarin have been found to block SARS-CoV-3CLpro's enzyme activity. The interaction of these bioflavonoids was established using a tryptophan-based fluorescence method, and the three flavonoids were recommended to be templates to strategy functionally developed inhibitors. **Fig 1A**. presented the binding pose of amentoflavone in SARS-CoV 3CLpro cited from the study of Ryu *et al.* (2010). As for MERS-CoV, flavonoids were considered as potential inhibitors of MERS-CoV (Jo *et al.*, 2019), where each of herbacetin, isobavachalcone, quercetin 3-β-d-glucoside, and helichristetine blocked the enzymatic activity of MERS-CoV-3CLpro. It was noted that flavonoid derivatives with hydrophobic or carbohydrate groups devoted to their core structures inhibit MERS-CoV. The computational and experimental study showed that chalcone and flavonol are desired supports to bind with the catalytic site of MERS-CoV-3CLpro. Therefore, this study suggested that flavonoids with these properties can be used as models to develop powerful MERS-CoV-3CLpro inhibitors. Regarding SARS-CoV-2, Negida, and Bahbah (2020) reported that saikosaponins are considered as active substances for SARS-CoV-2 due to their immunomodulatory, anti-inflammatory, and antiviral activities. The water extract from *Isatis indigotica* root, containing a number of phenolic compounds, namely sinigrin (IC_{50}: 217 μM) and hesperetin (IC_{50}: 8.3 μM) showed anti-SARS-CoV-2-3CLpro. Through sequential matching, it has been proven that SARS-CoV-2 major protease has approximately a 96% similarity to SARS-CoV-2-Mpro (Xu *et al.*, 2020). The inhibition of Mpro was ascribed to floronates, flavonoids, and pseudo-opeptides. The most hopeful inhibitors of SARS-CoV-2 were found to be oligomers of phloroglucin (1,3,5-trihydroxybenzene) derived from brown algae *Sergassum spinuligerum*. In turn, the most active inhibitors of SARS-CoV-2 are compounds from the florotannin group (8,8′-Bieckol, 6,6′-Bieckol, Dieckol) isolated from the brown algae *Ecklonia cava* (Gentile *et al.*, 2020). Khalifa, Nawaz, *et al.* (2020) revealed that phacelianin, gentiodelphin, cyanodelphin, and tecophilin authentically interacted with the receptor binding site and catalytic dyad (Cys145 and His41) of SARS-CoV-2-3CLpro. Khalifa, Zhu, *et al.* (2020) also discovered that pedunculagin, tercatain, and castalin intensely interacted with the receptor binding site and catalytic dyad (Cys145 and His41) of SARS□CoV□2-3CLpro. These studies unleashed that anthocyanins and/or tannins with specific structure could be used as effective anti-COVID-19 natural components. Meanwhile, **Fig 1B**. portrayed the interaction between tannins with SARS-CoV-2-3CLpro (Khalifa, Nawaz, *et al.*, 2020; Khalifa, Zhu, *et al.*, 2020). We summarized the antiviral activities from the recent studies of natural polyphenols from several plants and their mode of action against CoVs (**Table 4**).

4. The underlying mechanism of the antiviral activity of polyphenols

After the outbreak of SARS-CoV-2, there is an abundance of literature on plant-based materials such as traditional Chinese herbs as a possible cure for symptoms related to SARS like fever control and faster chest clearing. Nonetheless, further clinical trials are needed in treating acute respiratory tract infections (Wu *et al.*, 2008). It remains important to recognize new therapeutic and functional agents of infectious diseases using natural sources (Cragg and Newman, 2013). During the last decade, scientists have made significant efforts to classify several polyphenols with anti-SARS-CoV activity. However, because of SARS-CoV and SARS-CoV-2 homology, these earlier findings regard naturally occurring substances could capable of inhibiting SARS-CoV-2. A 3CLpro is essential for virus replication and is thus a potential drug goal for the production of therapeutic materials for SARS-CoV as well as SARS-CoV-2 (Yang *et al.,* 2020). It could be explained that bioactive compounds extracted from herbs were effectively inhibited the enzymatic activity of SARS-3CLpro in a dose-dependent matter. Rhubarb extracts (an IC_{50} of 13.76±0.03 μg mL^{-1}) water extract (Luo *et al.,* 2009), *Houttuynia cordata* water extract (Lau *et al.,* 2008), litchi seeds-flavonoid extracted (Gong *et al.*, 2008), and extracted from *Isatis indigotica* root (Lin *et al.*, 2005) were efficiently effective against CoVs. Further, subsequent herb-derived occurring complexesincludes herbacetin, -rhoifolin, pectolinarin (Jo *et al.*, 2020), sinigrin (IC_{50}: 217 µM), indigo (IC_{50}: 752 µM), -aloe-emodin (IC_{50}: 366 µM), hesperetin- (IC_{50}:8.3-µM) (Lin *et al.*, 2005), quercetin- (IC_{50}: 73 µM), epigallocatechin-gallate- (IC_{50}: 73 µM), and gallocatechin-gallate (IC_{50}: 47 µM) (Nguyen *et al.*, 2012), inhibited SARS 3CLpro effects. In addition, flavonoids, including isobavaschalcone, herbacetin, helichrysetin, and quercetin 3-β-D-glucoside, could inhibit the enzymatic action of MERS-CoV 3CLpro (Jo *et al.*, 2019). Helicase protein is often thought to be a possible focus for the production of anti-HCoV agents. Yu *et al.* stated that myricetin and scutellarein had a strong inhibition of nsP13 (SARS-CoV-helicase-protein) *in vitro* by influencing the function of ATPase (Yu *et al.*, 2012). Wu *et al.* conducted a massive-scale review of emerging medicines, natural products, and synthetic substances (>10000 substances) to classify successful anti-SARS-CoV agents via a cell-based technique of SARS-CoV and Vero-E6-cells. Ginsenoside Rb1 extracted from *Panax-ginseng*, aescin extracted from horse chestnut, reserpine in the eucalyptus, Rauwolfia genus extracts, and *Lonicera japonica* blocked SARS-CoV replication at non-toxic concentrations (Wu *et al.*, 2004). Same as SARS-CoV and HCoV-NL63, SARS-CoV-2-uses the ACE2-host receptor for cellular entry (Letko *et al.*, 2020). Thus, traditional Chinese medicine with ACE_2 goal capability keeps a pledge to avoid SARS-CoV-2 infection. In addition, disruption of the 3a receptor by kaempferol-juglanin derivatives may avoid viral release from contaminated cells (Schwarz *et al.*, 2014). Significantly, in compromised patients with SARS-CoV, MERS-CoV, and SARS-CoV-2 infections, the overpowering inflammatory responses have remarkably occurred. As a consequence, anti-inflammatory drugs are expected to reduce the incidence and mortality risk (Lu, 2020). In addition, a variety of anti-CoV agents have been reported from natural herbs, but the mechanisms of action have not yet been explained. Recently, the Chinese Health Commission has officially confirmed that natural medicinal herbs could be used in combination with traditional medicine for the treatment of COVID-19 patients (Yang *et al.*, 2020). Currently, experimental research on the efficacy of natural and medicinal plants focuses on the therapeutic potential of polyphenols against SARS-CoV-2 (Yang *et al.*, 2020). As the homogeneity of SARS-CoV is closely similar to SARS-CoV-2, many experiments demonstrating the anti-SARS-CoV-2 behavior of polyphenols or are planned to be released in the immediate future. Medicinal plants provide helpful and preventive treatments but are still desperately needed for the care of patients with SARS-CoV-2 infection, and experience with polyphenols is certainly worth researching. More analysis of polyphenols may contribute to the discovery of innovative anti-CoV compounds that could probably prove effective in the treatment of SARS-CoV-2 or other evolving lethal viral diseases as traditional therapeutic agents. Experimental searching with medicinal plant fields still has some risks and needs massive and further experiments. Polyphenols therapies traditionally used to treat the viral respiratory infection can include specific anti-SARS-CoV-2 substances. This research described many medicinal plants labeled as antiviral / pneumonia-effective which could specifically inhibit SARS-CoV-2 (Zhang *et al.*, 2020). Letko *et al.* (2020) confirmed how dissimilar lineage B-viruses can recombine to increase passage into human cells and have agreed that human ACE_2 is the receptor for the recent SARS-CoV-2 development. However, polyphenols including flavonoids as antiviral agents against MERS, SARS-CoV, and SARS-CoV-2 are not hardly investigated and more practical experiments are required. **Fig 2.** illustrated the role of polyphenols against MERS, SARS-CoV, and SARS-CoV-2.

5. Future needs

This review delivers a comprehensive range of evidence on the utilization of polyphenols extracted from medicinal plants for the reserve of CoVs. The cases obviously demonstrate that the designs with specific components of polyphenols and/or herp extracts that have been established for centuries in traditional medicine can be useful as the basis of anti-SARS-CoV components in the treating and/or deterrence of COVID-19. Natural polyphenols can act as anti-enzymes, antioxidants, and through binding-blocking virus exterior protein receptors. Different plants can be utilized as a source of polyphenols with a wide range of biological activity. These components offer hope that polyphenol extracts accessible in this review may have antiviral activity, also against CoVs-family. The wide range of natural polyphenols presented in different sources, which are undervalued in conformist medicine, may establish a nearly infinite source of remedies. The latest tendencies in medicine and biotechnology have allowed the usage of polyphenols to a greater level, than in the earlier decades, mainly as nutritional complements and nutraceuticals. Their toxicity altogether with ingesting time is yet to be explored by aims of multidisciplinary tactics (proteomics, omics science-genomics, and metabolomics). New formulation technologies and processing might aid to improve the antiviral polyphenols solubility, delivery tactics, and therapeutic effects to adjust them as antiviral functional foods and remedies. The research achieved so far have added to the information of the chemical structure of antiviral polyphenols. Bioinformatic studies of the polyphenols-pharmacophores structures can chief to scheming new antiviral polyphenols drugs. The usage of plant extracts might deliver synergistic health useful effects i.e., anti-inflammation, antioxidant, antimutagenic, and antiviral among occurring polyphenol blends, which should be considered and must be intensely discovered.

6. Conclusion

Numerous instances display that nature proposes the greatest solutions. Many plant species hold biologically active polyphenols, which in synergistic blends are active in battling many diseases. They already have been discovered by ancient medicine and/or folk. Recognizing individual components and revealing the underlying mechanisms is a challenge. This delays the product’s standardization, namely since plant extracts hold a wide variety of different components, happening in fluctuating concentrations, with seemingly synergistic effects. Despite several unknowns, studies decidedly show that polyphenols inhibit the life cycle of CoVs. This review indicates the huge possibility of polyphenols in the expansion of functional foods and/or pharmaceutical preparations. Laboratory model trials are required to verify their efficiency in inhibiting CoVs-replication. The upcoming phase should be to conduct clinical trials on COVID-19-patients and remarking the possibility to decrease virus multiplication in the patient's organism and thus recover clinical signs. It appears that the addition of polyphenols into food and clinical practice should be fairly fast because those are mixtures of natural origin, attained from plants approved for use as herbs and food. It is worth stating that the advantage of using polyphenols is related to the high-safety profile without causing major side effects.

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Declaration of competing interest

The authors declared that there is no conflict of interest.

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Table 1. The Japanese "FOSHU" criteria for functional foods, (Iwatani and Yamamoto, 2019).

1. They can or should be consumed as a portion of a normal diet.
2. They are foods: not capsules, pills, or powder-based on natural food components.
3. They have a clear function on the human organism such as:
3.1. Improving the immunity function.
3.2.Supporting recovery from specific diseases.
3.3.Preventing specific diseases.
3.4.Slowing down the aging process.
3.5.Controlling physical complaints.

Table 2. Overview of vital functional food components (non-polyphenols) in boosting up the immune response, virus targeted, and functions related, quoted from (London, 2010; Maggini *et al.*, 2018; Zhang and Liu, 2020).

Food components	Health properties	Virus targeted and related functions
Ʊ-3 fatty acids	• Stimulation of the immune system.	Influenza and human immunodeficiency virus.
Vitamin C	• Stimulates production, function, and movement of leukocytes (e.g., lymphocytes, neutrophils, and phagocytes). Antimicrobial, natural killer cell activities, and chemotaxis. Regenerates other important antioxidants such as glutathione and vitamin E to their active state. Promotes collagen synthesis. Increases serum levels of complement proteins. Involved in apoptosis and clearance of spent neutrophils from sites of infection by macrophages.	Avian coronavirus.
Vitamin D	• Stimulates immune cell proliferation and cytokine production and helps protect against infection caused by pathogens. Expressed in innate immune cells (e.g., monocytes, macrophages, dendritic cells).	Bovine coronavirus.
Vitamin A	• Maintains the structural and functional integrity of mucosal cells in innate barriers (e.g., skin, and respiratory tract).	Measles virus, human immunodeficiency virus, and avian coronavirus.
Vitamin B	• Boosting the immune response of the host.	MERS□CoV.

Vitamin E	• Impairs humoral and cell-mediated aspects of adaptive immunity, i.e., B and T cell function.	Coxsackievirus and bovine coronavirus.
Se	• Important for the antioxidant host defense system affecting leukocyte.	Influenza virus and avian coronavirus.
Fe	• Stimulation of the immune system.	Viral mutations.
Zn	• Stimulation of the immune system.	Measles and SARS□CoV.

Table 3. The antiviral activities of polyphenols, some examples from the available studies.

Polyphenols	Main sources	Conclusion	References
Theaflavins	Black tea	Theaflavins inhibited the Sindbis Virus infection by 99% at a concentration of 14.6mM.	Villagomez (2017)
		Act directly on HCV-viral particles and inhibit the ability to bind to the receptor surface.	Chowdhury *et al.* (2018)
Epigallocatechin gallate, epicatechingallate and gallocatechin-3-gallate	Green tea	EGCG effectively inhibits porcine reproductive and respiratory syndrome virus infection and replication in porcine alveolar macrophages. It prevents MARC-145 cells.	Ge *et al.* (2018)
		EGCG directly interacts with the Dengue virus molecule causing virus deformation and thus preventing the virus from infecting further cells.	Raekiansyah *et al.* (2018)
Different polyphenols	*Radix Sophorae*, *rhrizome Acanthopanacis*, *radix Sanguisorbae* and extract	Inhibits the effects on replication stages and/or their influence on cellular signal pathways of Mouse hepatitis virus.	(Kim *et al.*, 2010)

	Torilis fructus		
Quercetin and rutin	*Houttuynia cordata Thunb*	Inhibitory effects on the ATPase of mouse hepatitis and DENV type 2 virus.	(Chiow *et al.*, 2016)
(+)-Catechin	Teas and pome fruits	Inhibiting effect on transmissible gastroenteritis virus proliferation *in vitro* and associated with its anti-oxidation.	(Liang *et al.*, 2015)
Caffeic, chlorogenic, and gallic acids	*Sambucus Formosana Nakai*	Inhibition of the replication of HCoV NL63 in a cell-type independent manner.	(Weng *et al.*, 2019)
Anthocyanins	*Sambucus nigra*	Inhibition of avian infectious bronchitis virus replication	(Chen *et al.*, 2014)
Resveratrol	Skins of red fruits	Resveratrol inhibits the binding of Zika virus particles to cells and reduces circulating Zika virus particles, which underlines its potential of limiting disease severity during the viraemic phase.	(Mohd *et al.*, 2019)
Resveratrol	Skins of red fruits	Resveratrol exhibited potent inhibitory effects against influenza in MDCK cells via the blockade of nuclear-cytoplasmic translocation of viral ribonucleoprotein complexes,	(Palamara *et al.*, 2019)

		the decrease in the expression of late viral proteins, and the inhibition of cellular protein kinase C activity and its dependent pathways.	
Flavonoids	Elderberry and blueberry	Several blueberry varieties exert anti□influenza viral activities, especially viral adsorption, which positively correlated with the total polyphenol content in Madin-Darby canine kidney cells.	(Sekizawa *et al.*, 2019)

Table 4. The role of polyphenols against SARS-CoV, MERS-CoV, and SARS-CoV-2.

Polyphenols	Representative	Form/Source	Virus	Mechanism	Reference
		Phenolic acids			
Hydrobenzoic acids	Gallic acid	Tetra-*O*-galloyl-β-D glucose from *Galla chinensis*	SARS-CoV	Avidly binds with surface spike protein of SARS-CoV.	(Yi *et al.*, 2004)
	Hydrobenzoic acid	Desmethoxyreserpine	SARS-CoV-2	Inhibit replication of 3CLpro, and entry.	(Kesel, 2005)
		Flavonoids			
Flavonols	Kaempferol	Kaempferol derivatives, Kaempferol	SARS-CoV	Inhibit 3a ion channel of CoVs.	(Schwarz *et al.*, 2014)
			MERS-CoV, SARS-CoV	Inhibit PLpro. Inhibit SARS-3CLpro activity.	(Park *et al.*, 2017)
	Quercetin	Quercetin, Quercetin 3□β□D□glucoside,	MERS	Inhibit cleavage activity of MERS-3CLpro	(Jo *et al.*, 2019)

	isobavachalcone, and helichrysetin		enzyme.	
	Quercetin, Quercetin-β-galactoside	MERS-CoV, SARS-CoV	Inhibit PLpro. Inhibit SARS-3CLpro activity.	(Park *et al.*, 2017)
	Quercetin and TSL-1 from *Toona sinensis* Roem	SARS-CoV	Inhibit the cellular entry of SARS-CoV.	(Chen *et al.*, 2008)
	Quercetin	SARS-CoV-2	PLpro and 3CLpro enzyme.	(Park *et al.*, 2013)
Myricetin	Myricetin	SARS-CoV	Inhibit nsP13 by affecting the ATPase activity. SARS-CoV helicase inhibitor.	(Yu *et al.*, 2012)
Herbacetin	Herbacetin	MERS	Inhibit cleavage activity of MERS-3CLpro	(Jo *et al.*, 2019)

			enzyme.	
		SARS-CoV	block the enzymatic activity of SARS-CoV 3CLpro.	(Jo *et al.*, 2020)
Papyriflavonol A	*Broussonetia papyrifera*	MERS-CoV, SARS-CoV	Inhibit PLpro. Inhibit SARS-3CLpro activity.	(Park *et al.*, 2017)
Kazinol A, B, F and J, and broussoflavan A				
Amentoflavone,	*Torreya nucifera* leaves	SARS-CoV 3CL pro inhibitor		(Ryu, Park, *et al.*, 2010)
Kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin,	Traditional herbs	Inhibitors of SARS-CoV-2-Mpro	block the enzymatic activity of SARS-CoV 3CLpro.	(Khaerunnisa *et al.*, 2020)

	epicatechingallate, zingerol, gingerol, and allicin				
Flavones	Apigenin	*Ocimum basilicum*	SARS-CoV	Inhibit PLpro. Inhibit SARS-CoVpro activity.	(Pandey *et al.*, 2020)
	Baicalin	*Scutellaria baicalensis*	SARS-CoV	Inhibit Angiotensin-converting enzyme.	(Chen and Nakamura, 2004)
	Scutellarein	*Scutellaria lateriflora*	SARS-CoV	Inhibit nsP13 by affecting the ATPase activity.	(Yu *et al.*, 2012)
	Rhoifolin	*Rhus succedanea.*	SARS-CoV	Inhibit SARS-3CLpro activity.	(Gong *et al.*, 2008; Nguyen *et al.*, 2012)

	Luteolin	luteolin, from *Veronicalina riifolia*	SARS-CoV	Avidly binds with surface spike protein of SARS-CoV.	(Yi *et al.*, 2004)
	Daidzein	Plant-derived phenolic compounds and Root extract of *Isatis indigotica*	SARS-CoV	Not active.	(Lin *et al.*, 2005)
	30-(3-methylbut-2-enyl)-30,4,7-trihydroxyflavone	*Broussonetia papyrifera*	MERS-CoV, SARS-CoV	Inhibition of cysteine proteases CoV	(Park *et al.*, 2017)
	neobavaisoflavone	*Psoralea corylifolia*	SARS-CoV	Inhibitory activity toward SARS-CoV PLpro.	(Kim *et al.*, 2014)
Flavanones	Herbacetin, Rhoifolin pectolinarin Tetra-O-galoyl-β-d-glucose (TGG)	Plant-derived phenolic compounds and Root extract of *Isatis indigotica*,	SARS-CoV	Inhibit the cleavage activity of the SARS-3CLpro enzyme.	(Jo *et al.*, 2020; Lin *et al.*, 2005)

	luteoline				
	Pelargonidin	*Pimpinella anisum*	SARS-CoV-2	Binding affinities to 3C-like protease of SARS-CoV-2	(Hasan *et al.*, 2020)
	Bavachinin	*Psoralea corylifolia*	SARS-CoV	Inhibitory activity toward SARS-CoV PLpro.	(Kim *et al.*, 2014)
Anthocyanidins	10 polyacylated and monomeric anthocyanins	Bure components	SARS-CoV-2	Constructively network with catalytic dyad residues of 3CLpro of SARS-CoV-2.	(Khalifa, Nawaz, *et al.*, 2020)
Flavanols	Epigallocatechin gallate	Green tea	SARS-CoV	Inhibit SARS-3CLpro activity.	(Gong *et al.*, 2008; Nguyen *et al.*, 2012)
	Gallocatechin gallate	Green tea	SARS-CoV	Inhibit SARS-3CLpro	(Gong *et al.*,

	and epicatechingallate			activity.	2008; Nguyen *et al.*, 2012)
	gallocatechin-3-gallate	Green tea	SARS-CoV	Inhibit SARS-3CLpro activity.	(Ghosh *et al.*, 2020)
Chalcone	Isoliquiritigenin	*Glycyrrhiza glabra*	MERS-CoV, SARS-CoV	Inhibit PLpro. Inhibit SARS-3CLpro activity.	(Park *et al.*, 2017)
	Broussochalcone B, broussochalcone A, and 4-hydroxyisolonchocarpin	*Broussonetia papyrifera*	MERS-CoV, SARS-CoV	Inhibit PLpro. Inhibit SARS-3CLpro activity.	(Park *et al.*, 2017)
	isobavachalcone	*Psoralea corylifolia*	SARS-CoV	inhibitory activity toward SARS-CoV PLpro.	(Kim *et al.*, 2014)
	4' -O-	*Broussonetia papyrifera*	MERS-CoV,	Inhibit PLpro.	(Park *et al.*,

	methylbavachalcone		SARS-CoV	Inhibit SARS-3CLpro activity.	2017)
Tannins	19 hydrolysable tannins	Bure components	SARS-CoV-2	Efficacious and selective anti-COVID-19 therapeutic compounds.	(Khalifa, Zhu, *et al.*, 2020)

Figures legends:

Fig 1. The binding poses of amentoflavone in SARS-CoV 3CLpro. Ribbon plot of amentoflavone complexed to 3CLpro with hydrogen bonding (A). Fig B. represented the binding between tannins and 3CLpro of SARS-CoV-2, adopted from Khalifa *et al.* (2020) and Khalifa *et al.* (2020).

Fig 2. Underlying of the most important structural proteins of CoV are spike protein (S), membrane protein (M), envelop protein (E), and the nucleocapsid protein (N), the RNA genome of CoV is packed in the nucleocapsid protein and further covered with envelope. The hydroxyl group of flavonoids at 7□position looks important to bind at the binding site against 3-chymotrypsin-like protease (3CLpro), and papain-like protease (PLpro). Flavonoids as a vast reservoir of therapeutically active constituents as antiviral candidates against RNA viruses, adopted from Rasouli *et al.* (2017), Solnier *et al.* (2020), and Pillaiyar *et al.* (2020).

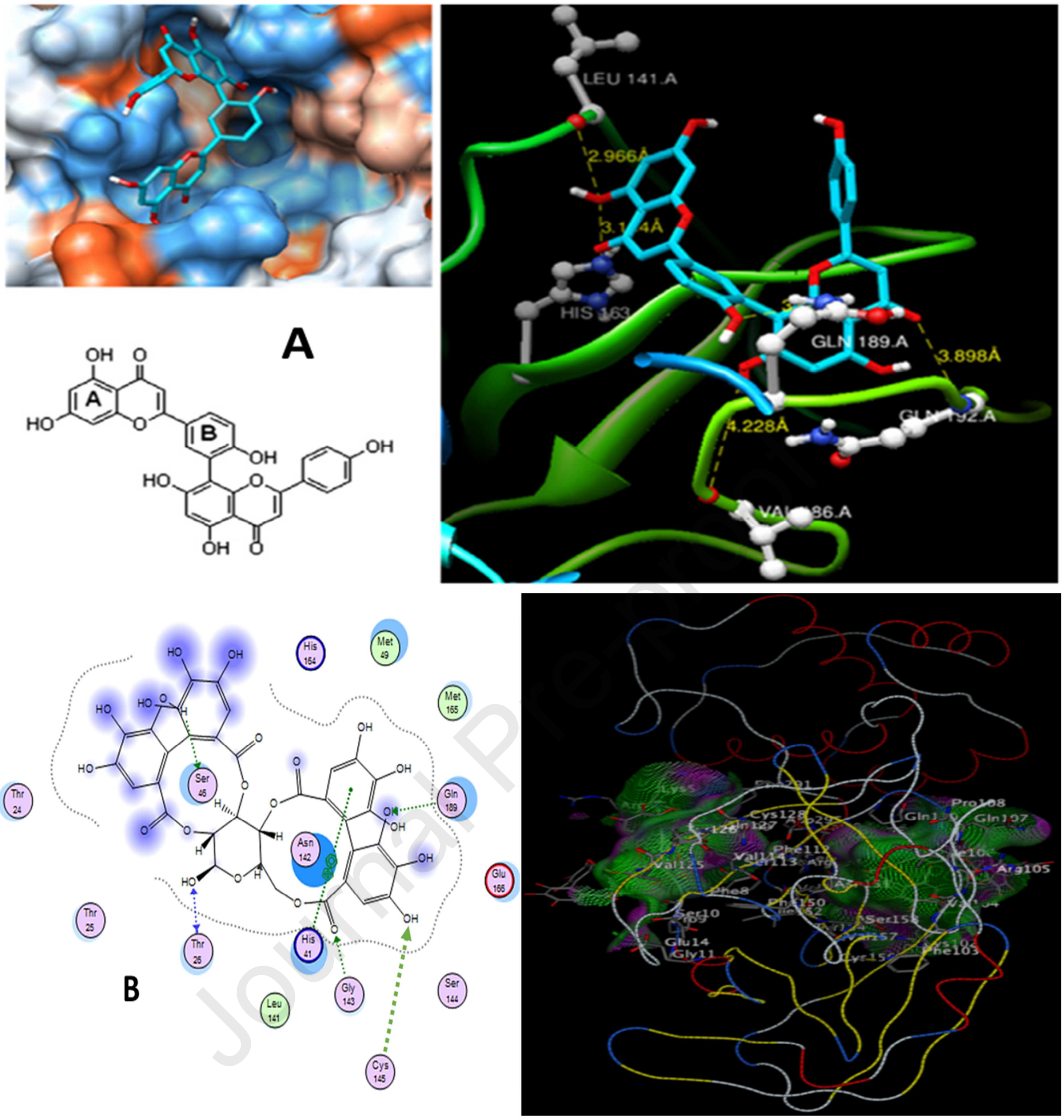
A
B
LEU 141.A
2.966Å
HIS 163
GLN 189.A
3.898Å
4.228Å
Thr 24
Thr 25
Thr 26
His 164
Met 49
Met 165
Ser 46
Asn 142
Gln 189
Glu 166
His 41
Gly 143
Leu 141
Ser 144
Cys 145

Fig 1.

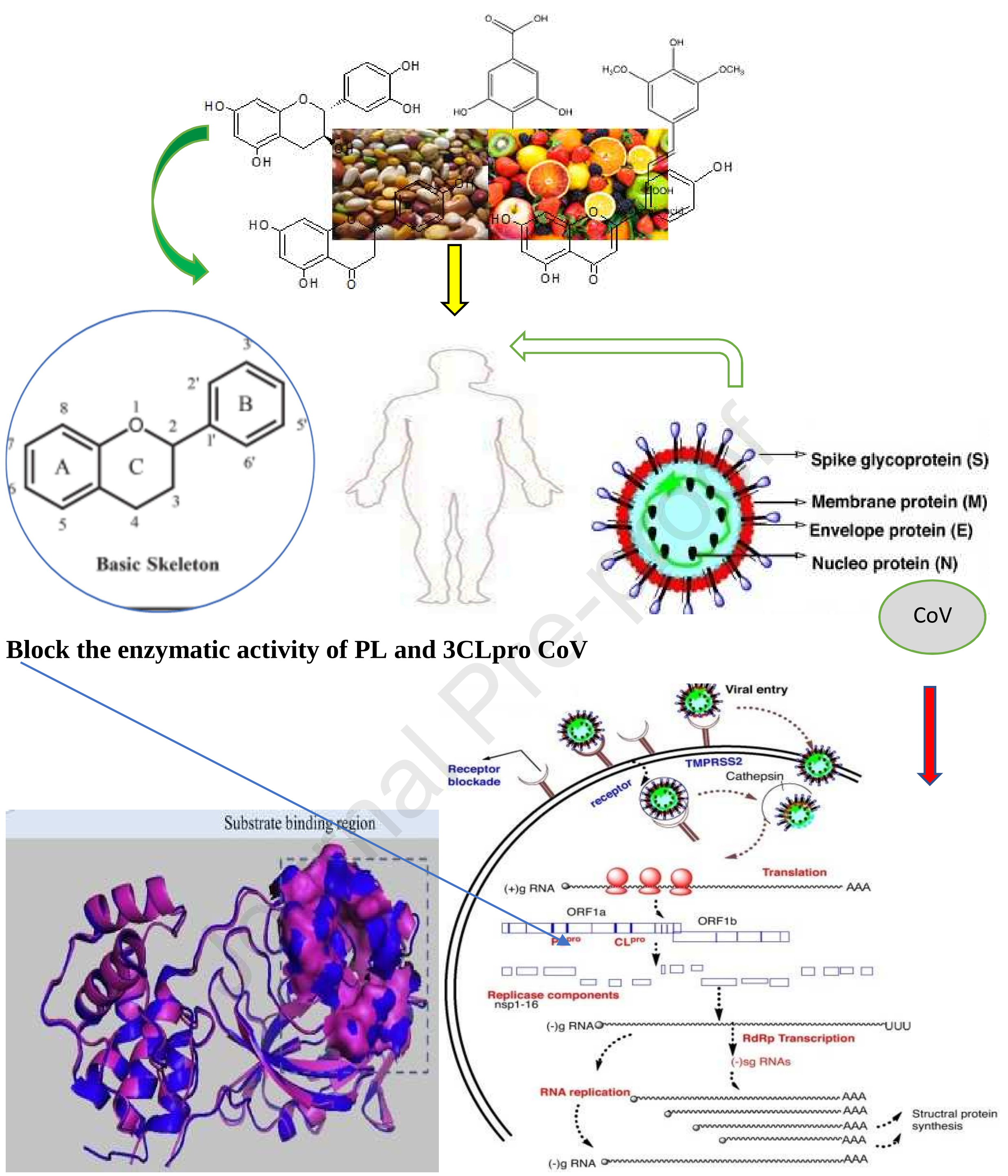
HO
OH
O
Basic Skeleton
A
B
C
Spike glycoprotein (S)
Membrane protein (M)
Envelope protein (E)
Nucleo protein (N)
CoV
Block the enzymatic activity of PL and 3CLpro CoV
Viral entry
Receptor blockade
TMPRSS2
Cathepsin
receptor
Substrate binding region
Translation
(+)g RNA
AAA
ORF1a
ORF1b
CLpro
Replicase components
nsp1-16
(-)g RNA
UUU
RdRp Transcription
(-)sg RNAs
RNA replication
Structral protein synthesis

Fig 2.

Highlights

Polyphenols possess many potential health benefits, including antiviral effects.

Polyphenols consider promising bioactive substances for COVID-19 prevention.

Polyphenol-rich foods will be helpful during the COVID-19's treatment.

Polyphenols assist as blocking agent for protease's enzymatic activity of COVID-19.

Conflict of interest

No conflict of interest among authors.