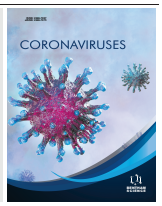
Send Orders for Reprints to reprints@benthamscience.net

Coronaviruses, 2022, *3*, e260522205293

REVIEW ARTICLE

Anti-coronaviral Activity of Plant and Seaweed Secondary Metabolites: A Review



Taha Gökmen Ülger[1,*], Serkan Yılmaz[2], Funda Pınar Çakıroğlu[3] and Aslı Uçar[3]

[1]*Department of Nutrition and Dietetics, Faculty of Health Sciences, Bolu Abant Izzet Baysal University, Bolu, Turkey;* [2]*Department of Midwifery, Faculty of Nursing, Ankara University, Ankara, Turkey;* [3]*Department of Nutrition and Dietetics, Faculty of Health Sciences, Ankara University, Ankara, Turkey*

ARTICLE HISTORY

Received: November 25, 2021
Revised: March 09, 2022
Accepted: March 13, 2022

DOI:
10.2174/2666796703666220526105934

Abstract: ***Background*:** Coronavirus Disease 2019 (COVID-19), one of the greatest challenges facing humanity, continues to affect millions of people worldwide. Vaccines approved and authorized for use are effective against COVID-19, but viral variants of concern may emerge in the near future. The discovery of novel antiviral agents will help humanity overcome COVID-19 and aid in any future viral pandemics.

***Objective*:** This review aimed to evaluate evidence from the plant- and seaweed-derived secondary compound-based interventions for viral diseases caused by coronaviruses.

***Methods*:** A comprehensive search of several databases, including Cochrane Library, Web of Science and PubMed was conducted to identify available studies evaluating the outcomes of plant- and seaweed secondary metabolites in viral diseases such as Severe Acute Respiratory Syndrome, Middle East Respiratory Syndrome and COVID-19.

***Results*:** The volume of existing reports is irrefutable evidence that some plant- and seaweed-derived secondary compounds (*e.g.*, mannose-specific lectins, griffithsin, cyanovirin-N, gallate, curcumin, luteolin, quercetin and betulinic acid) possess a potential antiviral ability against coronaviruses, including SARS-CoV-2.

***Conclusion*:** Plant and seaweed secondary metabolites with antiviral activity show their activity in different metabolic pathways. Besides reducing and preventing the metabolic damage caused by proinflammatory cytokines and oxidative stress, several plants and seaweed secondary metabolites can also be effective in improving some clinical indexes specific to COVID-19. Despite their effectiveness in preclinical studies, plant and seaweed-derived secondary compounds need more pharmacokinetic studies and safety measures concerning their mitogenic and allergenic properties.

Keywords: COVID-19, SARS-CoV-2, phytochemicals, griffithsin, cyanovirin-N, lectins.

1. INTRODUCTION

Coronaviruses (CoVs) are the largest family of viruses that cause diseases in animals and humans [1]. The history of CoVs began in the 1940s, but the identification of the first human CoVs was reported in the 1960s as causative agents for mild respiratory infections [2]. Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) caused by the SARS-CoV-1 and MERS-CoV viruses revealed the lethal effect of coronaviruses for the first time in 2003 and 2012 [3]. However, in 2020, the world faced the lethal effect of coronaviruses so clearly for the first time. The novel and deadly coronavirus strain, named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has infected millions and killed hundreds of thousands of people worldwide in a very short time. Due to the COVID-19 outbreak caused by SARS-CoV-2, the World Health Organization (WHO) declared the outbreak of COVID-19 to be a Public Health Emergency of International Concern. Over 250 million confirmed COVID-19 cases had caused over 5 million deaths worldwide as of 10 November 2021, and these numbers are growing daily [4].

Effective and safe COVID-19 vaccines were developed, but the vaccination rate in low-income countries is still very low. The virus is moving faster than the global distribution of vaccines. In addition, the effectiveness of vaccines against viral variants will always be a matter of concern, although not currently. Thus, it is essential to fight against COVID-19 not only with the vaccine but in all possible ways. Specific nutritional compounds, such as plant and seaweed secondary metabolites, can be essential agents in the fight against COVID-19. As a result, identifying nutritional compounds that can be effective against COVID-19 is of considerable

*Address correspondence to this author at the Department of Nutrition and Dietetics, Faculty of Health Sciences, Bolu Abant Izzet Baysal University, Bolu, Turkey; E-mail: tahagokmenulger@ibu.edu.tr

2666-7975/22 $65.00+.00 © 2022 Bentham Science Publishers

importance for global health. In light of this, this review aimed to evaluate evidence from previous research that studied plant and seaweed secondary metabolites-based interventions for viral diseases (especially SARS, MERS and COVID-19) and summarised our observations.

2. PLANT-DERIVED SECONDARY COMPOUNDS

Plant chemicals are generally divided into primary and secondary metabolites. Primary metabolites, such as proteins, carbohydrates, fats and vitamins, are involved in vital activities (growth, metabolism activity, and reproduction) in human metabolism. Secondary metabolites (phenolic compounds, terpenes steroids, alkaloids, and organosulfur compounds) are produced from primary metabolites by biosynthetic means and are involved in important biological processes like primary metabolites [5]. Plant secondary metabolites (PSMs) have an important role in preventing chronic diseases and acute viral, and bacterial diseases and are of crucial pharmacological importance. Some PSMs may also effectively reduce and prevent the metabolic damage caused by proinflammatory cytokines and oxidative stress, which are increased in viral diseases such as COVID-19.

The experiences in the treatment of SARS or MERS disease, by both conventional medicine and plant-based medicine, also have considerable significance in the treatment of patients infected with SARS-CoV-2. In this context, Traditional Chinese Medicine has an important place in plant-based therapy. In the literature, there are studies in which different plant extracts were tested against MERS, SARS-CoV-1 and SARS-CoV-2 (Table **1**). In one of these studies [6], more than 200 extracts from Chinese medicinal herbs were evaluated for anti-SARS-CoV-1 activity using a cell-based assay, and the findings suggested that six herbal extracts (Dioscoreae Rhizoma, the tuber of *Dioscorea batatas*; Loranthi Ramus, the dried stem, with the leaf of *Taxillus chinensis*; Gentianae Radix, the dried rhizome of *Gentiana scabra*; Cassiae Semen, the dried seed of *Cassia tora*; and two forms of *Rhizoma Cibotii*, the dried rhizome of *Cibotium barometz*) may have a potential as candidates for the future development of anti-SARS therapeutics. On the other hand, extracts from *Lycoris radiata*, *Lindera aggregate, Artemisia annua*, *Pyrrosia lingua* [7], *Isatis indigotica* [8], *Houttuynia cordata* [9], *Laurus nobilis* [10], *Rheum palmatum* [11], *Alnus japonica* [12], *Cinnamomi Cortex* [13] and *Psoralea corylifolia* [14] have been identified to show antiviral activity against SARS-CoV-1 in different studies. However, despite all evidence, it is not currently possible to recommend any herbs and nutraceuticals for therapeutic purposes due to the methodological deficiencies in the studies examined (uncertain composition/combination of herbal products, unstandardized duration of use, shortcomings in the evaluation of measurable laboratory parameters, combined and unknown plant content). However, it should not be ignored that some nutraceuticals or herbs may effectively prevent complications from the cytokine storm caused by COVID-19. In a meta-analysis [15], the effectiveness of Traditional Chinese Medicine administered in addition to pharmacological treatment (*e.g*., lopinavir, alpha-interferon, ribavirin and arbidol) against COVID-19 was evaluated. According to this meta-analysis [15], Traditional Chinese Medicine that is applied in addition to pharmacological treatment has positive effects on COVID-19 symptoms, such as fever, cough, sputum removal, fatigue, chest tightness and anorexia.

As with herbs and nutraceuticals, PSMs that are effective against SARS-CoV-1 and MERS-CoV may have potential effects against SARS-CoV-2. To date, the effectiveness of PSMs against SARS, MERS, and COVID-19 has been tested with different experimental methods. Wen *et al*. [16] evaluated 221 PSMs for activity against SARS-CoV-1 activity using a cell-based assay measuring SARS-CoV-1 induced cytopathogenic effect on Vero E6 cells. According to this study, betulinic acid, curcumin, savinin, specific abietane-type diterpenoids, and lignoids exhibited strong anti-SARS-CoV-1 effects. In another study, the antiviral activity of resveratrol was assessed in MERS-infected Vero E6 cells, and the findings showed that resveratrol significantly inhibited MERS-CoV infection and prolonged cellular survival after virus infection. It was also found that the expression of nucleocapsid protein essential for MERS-CoV replication decreased after resveratrol treatment, and resveratrol downregulated the apoptosis induced by MERS-CoV *in vitro* [17]. In addition to these compounds, Glycyrrhizin derivatives [18-20] and emodin [21] have also been reported to have antiviral activity against coronaviruses in studies that used Vero E6 cells.

Due to the high cost in time and money of clinical and laboratory trials, as well as the possibility of error, different bioinformatics techniques, such as chemical stability, molecular docking, target point determination, and simulation, are nowadays used in testing the effectiveness of PSMs against viruses and for the design of new drugs. In a bioinformatic study designed by Mohammadi and Shaghaghi [22], the effectiveness of eight different plant-derived secondary metabolites (diallyl Sulfide/garlic, curcumin/turmeric, capsaicin/spicy pepper, limonene/cardamom, thymol/pennyroyal, coumarin/liquorice, verbascoside/hedge nettle, and glucuronic acid/tragacanth) against COVID-19 was evaluated using the molecular docking technique. It was stated that all tested compounds could interact with important amino acids in the enzyme flap to inhibit the novel coronavirus (SARS-CoV-2) protease enzyme. Among these secondary metabolites, curcumin has the strongest interaction with the protease enzyme of SARS-CoV-2. In another similar study [23], 18 dietary molecules, namely, epigallocatechin gallate (EGCG), piperine, beta-glucan, curcumin, phycocyanobilin, apigenin, gingerol-a [6], resveratrol, myricetin, ferulic acid, quercetin, alliin, allicin, genistein, daidzein, sulforaphane , and alpha-lipoic acid, were evaluated by molecular docking, and the effectiveness of the 18 compounds were compared with Food and Drug Administration (FDA) approved drugs (Remdesivir and Chloroquine) that are currently being used in COVID-19. EGCG, quercetin, curcumin, genistein, beta-glucan, myricetin, and daidzein were found as active agents against COVID-19. Among these dietary molecules, epigallocatechin gallate was found as the most active agent against COVID-19, and the computed activity of EGCG was also found to be higher than that of both reference drugs, Remdesivir and chloroquine. Based on these results, a diet consisting of green tea (ECGG), turmeric (curcumin), chamomile tea (apigenin), parsley (apigenin), grain oats, and grain barley (beta-glucan) can provide functional protection

Table 1. Potential plant secondary metabolites for preventing coronaviruses including SARS-CoV-2 and their effectiveness.

References	Virus	PSM	Experimental Model	Main Results
Li *et al*. 2005 [7]	SARS-CoV-1	*Artemisia annua, Lindera aggregata, Lycoris radiata and Pyrrosia lingua.*	Vero E6	The compounds extracted from *L. radiata*, *L. aggregata, A. annua* and *P. lingua* have been identified to show antiviral activity against SARS-CoV in Vero cell-based CPE/MTS screening. In addition, *Lycoris radiata* was the most potent among the four compounds.
Lin *et al*. 2005 [8]	SARS-CoV-1	*Isatis indigotica*, five major compounds of the *I. indigotica* root (beta-sitosterol, indican, indirubin, indigo and sinigrin) and several phenolic compounds (aloeemodin, chrysophanol, daidzein, emodin, hesperetin, quercetin and naringenin)	Vero cells	The results have demonstrated significantly inhibitory effects on SARS-CoV-1 3CLpro by *I. indigotica* root extract, aloeemodin, indigo, hesperetin and sinigrin in the micromolar range. Particularly, the cell-based assay demonstrated that sinigrin and hesperetin could be potential inhibitors of SARS-CoV-1 3C-like protease.
Lau *et al*. 2008 [9]	SARS-CoV-1	*Houttuynia cordata* extract	Balb/c mice, lymphocytes	*Houttuynia cordata* exhibited significant inhibitory effects on SARS-CoV-1 3C-like protease and RNA-dependent RNA polymerase.
Loizzo *et al*. 2008 [10]	SARS-CoV-1	*Cupressus sempervirens ssp. pyramidalis, Juniperus oxycedrus ssp. oxycedrus, Laurus nobilis Satureja thymbra, Salvia officinalis, Thuja orientalis and Pistacia palaestina.*	Vero cells	*L. nobilis* oil exerted an interesting activity against SARS CoV-1 with an IC50 value of 120 µg/mL. It was also reported that anti-herpetic activity of *S. thymbra* and *J. oxycedrus ssp. Oxycedrus* oils providing a potential use of these oils for treatment of viral infectious diseases.
Luo *et al*. 2009 [11]	SARS-CoV-1	Compounds derived from *Rheum palmatum L.*	FRET	Extracts from *Rheum palmatum L*. have a high level of inhibitory activity (inhibition rate was up to 96%) against SARS coronavirus 3C-like protease.
Park *et al*. 2012 [12]	SARS-CoV-1	Diarylheptanoids (isolated from *Alnus japonica*)	FRET	Of the isolated diarylheptanoids, hirsutenone showed the most potent papain-like protease inhibitory activity. The findings demonstrated that the catechol and α,*β-unsaturated carbonyl moieties in d*iarylheptanoid are critical factors affecting SARS-CoV-1 papain-like protease inhibition activity.
Zhuang *et al*. 2009 [13]	SARS-CoV-1	Procyanidins and butanol extract of *Cinnamomi Cortex*	Vero E6 cells	Butanol fraction of *Cinnamomi Cortex* contains inhibitors of SARS virus infection. Among the compounds fractionated from Cinnamomi Cortex, procyanidin B1 and procyanidin A2 showed moderate anti-SARS-CoV-1 activity.
Kim *et al*. 2014 [14]	SARS-CoV-1	Bavachinin, corylifol, isobavachalcone, neobavaisoflavone, 4’ -O-methylbavachalcone and psoralidin (isolated from *Psoralea corylifolia*)	FRET	All isolated flavonoids and extract of the seeds of *Psoralea corylifolia* inhibited papain-like protease in a dose-dependent manner with IC50 ranging between 4.2 and 38.4 µM. Two compounds, psoralidin, and isobavachalcone were the principal contributors to the papain-like protease inhibition.
Wen *et al*. 2007 [16]	SARS-CoV-1	221 different PSMs	Vero E6 cells	20 phytocompounds, including the lupane-type triterpenes, abietanetype and labdane-type diterpenes, curcumin and liganoids were potent inhibitors at concentrations between 3.3 and 10 µM.
Lin *et al*. 2017 [17]	MERS-CoV	Resveratrol	Vero E6 cells	Resveratrol significantly inhibited MERS-CoV infection and prolonged cellular survival after virus infection. In addition, resveratrol down-regulated the apoptosis induced by MERS-CoV *in vitro* and the expression of nucleocapsid protein essential for MERS-CoV replication was decreased after resveratrol treatment.

(Table 1) Contd….

References	Virus	PSM	Experimental Model	Main Results
Cinatl *et al*. 2003 [18]	SARS-CoV-1	Glycyrrhizin	Vero cells	Glycyrrhizin was active in inhibiting replication of the SARS-associated virus.
Chen *et al*. 2004 [19]	SARS-CoV-1	Artesunate, baicalin, chlorogenic acid and glycyrrhizin.	Vero E6 cells, FRhK-4 cells	Baicalin and glycyrrhizin showed antiviral activity.
Hoever *et al*. 2005 [20]	SARS-CoV-1	Glycyrrhizin derivatives	Vero cells	Of the 15 glycyrrhizin derivatives tested for anti-SARS-CoV-1 activity, seven derivatives were found to inhibit SARS-CoV replication at lower concentrations compared to glycyrrhizin. The introduction of 2-acetamido- ß -D-glucopyranosylamine into the glycoside chain of glycyrrhizin resulted in 10-fold increased anti-SARS-CoV-1 activity compared to glycyrrhizin.
Ho *et al*. 2007 [21]	SARS-CoV-1	Emodin, promazine, rhein, chrysin, 1,4-bis-(1-anthraquinonylamino)-anthraquinone and anthraquinone	Vero E6 cells	Emodin, an anthraquinone compound derived from *Rheum officinale* and *Polygonum multiflorumThunb.*, significantly blocked the SARS-CoV-1 spike protein and angiotensin-converting enzyme 2 interaction in a dose-dependent manner. It also inhibited the infectivity of SARS-CoV-1 spike protein-pseudotyped retro virus to Vero E6 cells.
Mohammadi and Shaghaghi 2020 [22]	SARS-CoV-2	Capsaicin, curcumin, coumarin, diallyl disulfide, glucuronic acid limonene, thymol and verbascoside.	Molecular docking	The compounds studied can effectively inhibit the virus protease enzyme. Curcumin has a stronger bond and high affinity with SARS-CoV-2 protease among the compounds.
Khan *et al*. 2020 [23]	SARS-CoV-2	Allicin, alliin, apigenin, beta glucan, curcumin, diadzein, epigallocatechin gallate, ferulic acid, genistein, gingerol-(6), glucosamine, myricetin, quercetin, lipoic acid, piperine, phycocyanobillin, resveratrol and sulforaphane.	Molecular docking	Beta-glucan, curcumin, diadzein, epigallocatechin gallate, genistein, myricetin and quercetin were found as active agents against COVID-19. Epigallocatechin gallate exhibited the strongest molecular interactions within pockets at active sites of all the proteins of SARS-CoV-2 including *6vw1, 6y2e, 6lxt, 6vww, 6lu7, 6vsb* and *6lvn.*
Chen *et al*. 2005 [25]	SARS-CoV-1	Extracts from several different types of teas, including oolong tea, green tea, black tea and puer tea.	HPLC assay	Extracts from puer and black tea were more potent than that from green or oolong teas in their inhibitory activities against 3C-like protease. Catechin, epicatechin, caffeine, epigallocatechin, epicatechin gallate, epigallocatechin gallate and theophylline did not inhibit 3C-like protease. Only theaflavin-3,3'-digallate was found to be a 3C-like protease inhibitor.
Khaerunnisa *et al*. 2020 [26]	SARS-CoV-2	Allicin, apigenin-7- glucoside, catechin, curcumin, demethoxycurcumin, epicatechingallate, gingerol, quercetin, kaempferol, luteolin-7- glucoside, oleuropein, naringenin and zingerol.	Molecular docking	Kaempferol, luteolin-7- glucoside, epicatechin-gallate, quercetin, naringenin, curcumin, demethoxycurcumin, oleuropein, apigenin-7-glucoside and catechin appeared to have the best potential to act as COVID-19 chymotrypsin-like protease inhibitors.
Abdel-Mottaleb and Abdel-Mottaleb [27]	SARS-CoV-2	Eriodictyol, menthol, thymoquinone, raspberry-ketone, resveratrol, quercetin and curcumin	Molecular docking	Raspberry-ketone is of comparable binding strength to ivermectin and hydroxychloroquine antiviral drugs. Moreover, raspberry ketone seems to block or at least disturb S protein - ACE2 interactions. Other natural drugs did not show affinity to bind to either S protein or ACE2.
Adem *et al*. 2020 [28]	SARS-CoV-2	26 different PSMs	Molecular docking	Apiin, diacetylcurcumin, diosmin, hesperidin, rutin, (E)-1-(2-Hydroxy-4-methoxyphenyl)-3-[3-[(E)-3-(2-hydroxy-4- methoxyphenyl)-3-oxoprop-1-enyl]phenyl]prop-2-en-1-one, and beta,beta'-(4-Methoxy-1,3- phenylene)bis(2'-hydroxy-4',6'-dimethoxyacrylophenone have been found as more effective on COVID-19 than nelfinavir.

(Table 1) Contd….

References	Virus	PSM	Experimental Model	Main Results
Thuy *et al*. 2020 [29]	SARS-CoV-2	18 secondary metanolites found in garlic essential oil	Molecular docking	17 organosulfur compounds, accounting for 99.4% contents of the garlic essential oil, have strong interactions with the amino acids of the ACE2 protein and the main protease PDB6LU7 of SARS-CoV2. The strongest anticoronavirus activity is expressed in allyl disulfide and allyl trisulfide, which account for the highest content in the garlic essential oil (51.3%).
Park *et al*. 2016 [30]	SARS-CoV-1	9 alkylated chalcones and 4 coumarins (isolated from *Angelica keiskei*)	FRET	Chalcones exhibited competitive inhibition of the SARS-CoV-1 chymotrypsin-like protease, whereas noncompetitive inhibition was observed with SARS-CoV papain-like protease. Alkylated chalcone substituted with a perhydroxyl group (xanthoangelol E) showed the most potent chymotrypsin-like protease and papain-like protease inhibitory activities. This compound has also specific inhibitory activity against cysteine protease specifically.
Utomo *et al*. 2020 [31]	SARS-CoV-2	Curcuminoids, methoxy flavonoids, phenylpropanoid compounds (isolated from *Alpinia galanga*, *Citrus sp., Caesalpinia sappan and Curcuma sp.*)	Molecular docking	The results showed that hesperidin, one of the compounds in *Citrus sp*., has the lowest docking score for all three protein receptors (receptor binding domain of spike glycoprotein; PDB ID:6LXT, receptor at the protease domain Angiotensin Converting Enzyme-2; PDB ID: 6VW1 and SARS-CoV-2 protease; PDB ID:6LU7) representing the highest affinity to bind the receptors. The results of this study indicated that *Citrus sp*. exhibited the best potential as an inhibitor to the development of the SARS-CoV2, followed by galangal, sappan wood, and *Curcuma sp*. that can be consumed in daily life as prophylaxis of COVID-19
Yu *et al*. 2012 [32]	SARS-CoV-1	64 purified natural compounds	FRET	Scutellarein and myricetin and potently inhibited the SARS-CoV-1 helicase protein *in vitro* by affecting the ATPase activity.
Jo *et al*. (2020) [36]	SARS-CoV-1	Sixty four flavonoid compounds	FRET	Rhoifolin, herbacetin, and pectolinarin were found to efficiently block the enzymatic activity of SARS-CoV 3C-like protease.
Nguyen *et al*. 2012 [37]	SARS-CoV-1	Ampelopsin, daidzein, epigallocatechin, epigallocatechin gallate, gallocatechin gallate, quercetin and puerarin.	Molecular docking	Gallocatechin gallate, epigallocatechin gallate and quercetin displayed good inhibition toward the 3C-like protease with IC50 values of 47, 73 and 73 μM, respectively.
Ryu *et al*. 2010 [38]	SARS-CoV-1	*Torreya nucifera* extract, eight diterpenoids and four biflavonoids (isolated from *Torreya nucifera*)	FRET	The ethanol extract of *T. nucifera* leaves exhibited good SARS-CoV-1 chymotrypsin-like protease proinhibitory activity (62% at 100 μg/mL). Luteolin, quercetin and apigenin inhibited 3CLproactivity with IC50values of 20.2, 23.8 and 280.8 μM, respectively. The biflavone amentoflavone (IC50= 8.3 μM) showed most potent 3CLproinhibitory effect.
Schwarz *et al*. 2014 [39]	SARS-CoV-1	Kaempferol, afzelin, juglanine, tiliroside, tiliroside derivatives, kaempferol triglycoside, quercetin, naringenin and genistein	*Xenopus* oocyte	Glycoside juglanin was most the effective one with an IC50 value of 2.3 μM for inhibition of the 3a-mediated current. Kaempferol derivatives with rhamnose residue was also effective.
Chen *et al*. 2006 [40]	SARS-CoV-1	Quercetin-3-beta-galactoside	Molecular docking	Quercetin-3-beta-galactoside was identified as an inhibitor of the SARS-CoV-1 3C-like protease.
Park *et al*. 2012 [41]	SARS-CoV-1	Tanshinones	FRET	All of the isolated tanshinones (cryptotanshinone, dihydrotanshinone I, tanshinone I, tanshinone IIa, tanshinone IIb, methyl tanshinonate and rosmariquinone) are good inhibitors of both cysteine proteases ($3CL^{pro}$ and PL^{pro}). Additionally, the inhibition was selective because these compounds didn't exert significant inhibitory effects against other proteases including chymotrysin, papain, and HIV protease.

(Table 1) Contd….

References	Virus	PSM	Experimental Model	Main Results
Jo *et al*. 2019 [43]	MERS-CoV	Herbacetin, isobavachalcone, quercetin 3-β-D-glucoside and helichrysetin	FRET	Isobavachalcone, herbacetin, helichrysetin and quercetin 3-β-D-glucoside were found to block the enzymatic activity of MERS-CoV 3C-like protease.
Yi *et al*. 2004 [44]	SARS-CoV-1	Tetra-*O*-galloyl-β-D-glucose and luteolin	FRET	The results showed that Tetra-*O*-galloyl-β-D-glucose and luteolin could inhibit SARS-CoV-1 activity, in a dose-dependent fashion.
Ryu *et al*. 2010 [45]	SARS-CoV-1	Celastrol, iguesterin, pristimerin and tingenone (isolated from *Triterygium regelii*)	Molecular docking	Celastrol, iguesterin, tingenone and pristimerin showed potent SARS-CoV-1 chymotrypsin-like protease inhibitory activities .
Cho *et al*. 2013 [46]	SARS-CoV-1	Flavonoid derivatives and compounds derived from *P. tomentosa*	FRET	Most compounds inhibited SARS-CoV-1 papain-like proteas in a dose dependent manner with IC50's raging between 5.0 and 14.4 μM.

Abbreviations: FRET; Fluorescence resonance energy transfer, **FRhK-4 cells**; Fetal Rhesus Kidney-4 cells, **Vero cells**; African green monkey kidney epithelial cells, **HPLC**; High performance liquid chromatography.

against COVID-19. Theaflavins, found in abundance in black tea, can also be potential candidates in prophylaxis and treatment of COVID-19 [24, 25]. In addition, it was also stated that molecules having hydroxyl (-OH) and carbonyl (C=O) functionalities (curcumin, piperineare, beta-glucan, flavonoids, such as apigenin, myricetin, and quercetin and isoflavonoids, such as genistein and daidzein) show strong intermolecular interactions with amino acid residues at active sites of proteins through physical forces, such as hydrogen bonds and hydrophobic bonds [23]. Therefore, it may be beneficial to consume vegetables and fruits that are rich in these secondary compounds against COVID-19.

In another molecular docking study, Khaerunnisa *et al*. [26] evaluated several bioactive compounds (epicatechin gallate, zingerol, gingerol, catechin, allicin, quercetin, kaempferol, naringenin, luteolin-7-glucoside, demethoxycurcumin, apigenin-7-glucoside, oleuropein, and curcumin) as potential COVID-19 main protease inhibitors, and they found that curcumin, catechin, epicatechin-gallate, luteolin-7-glucoside, apigenin-7-glucoside, demethoxycurcumin, and oleuropein appeared to have the best potential to act as COVID-19 main protease inhibitors. Abdel-Mottaleb and Abdel-Mottaleb [27] investigated the simulated interactions between several PSMs (raspberry ketone, thymoquinone, eriodictyol, resveratrol, quercetin, and curcumin), the ACE2 enzyme, and specific peptide sequences of the coronavirus spike protein, and they found that raspberry-ketone, eriodictyol, and thymoquinone potentially bind to spike proteins. In addition, it was emphasized that raspberry ketone is of comparable binding strength to hydroxychloroquine and ivermectin antiviral drugs. In another molecular docking study [28], it was found that flavonoids, such as hesperidin and rutin, have a better binding affinity to SARS-CoV-2 main protease than nelfinavir which is used in the treatment of the human immunodeficiency virus. Additionally, organosulfur compounds [29], chalcones [30], hesperidin [31], and myricetin [32] have also been reported to have antiviral activity against coronaviruses in different molecular docking studies.

PSMs with antiviral activity show their activity in different metabolic ways. Glycyrrhizin derivatives show their antiviral activity by inhibiting the replication of SARS-CoV-1. On the other hand, lipophilic terpenoids, which are found in the essential oils of many plants, nonspecifically intercalate into the lipid double layer and disrupt the lipid envelope of viruses [33]. As a result, the fluidity of the membrane is changed, and, at a higher concentration, the membrane is even lysed. On the other hand, phenols and polyphenols (tannins, flavonoids, luteolin, and rosmarinic acid) can bind to viral proteins in the envelope, and, thanks to this effect, these secondary compounds prevent the docking of a virus to its host cell [34]. Additionally, some alkaloids (*e.g*., berberine, ß-carboline, sanguinarine, emetine, dictamine, quinine, skimmianine and cinchonine) are characterized as DNA intercalators, directly target DNA and RNA, stabilize double-stranded nucleic acids, and inhibit the replication, transcription, and translation of genetic material. Chloroquine, one of the alkaloids in this group, has an important role in the pharmacological treatment currently applied against COVID-19. It is assumed that other DNA intercalator alkaloids or the medicinal plants producing them may be important candidates for the development of new antiviral drugs [33]. However, several alkaloids, such as pyrrolizidine alkaloids, aristolochic acid, cycasin, macrozamin, furanocoumarins, and PSMs with aldehyde or epoxide functional groups, are known as DNA-alkylating agents [35], and these compounds can lead to mutations and cell death. Therefore, alkylated PSMs are not used in phytotherapy, even if they may be active against viruses. In addition, the antiviral activity of some flavonoids against coronaviruses is presumed to be directly caused by inhibiting 3C-like protease (3CLpro). Jo *et al*. [36] stated that flavonoids, such as herbacetin, rhoifolin, and pectolinarin can efficiently block the enzymatic activity of SARS-CoV-1 3CLpro. Specifically, epigallocatechin, gallocatechin gallate, epigallocatechin gallate, quercetin, puerarin, daidzein [37], amentoflavone, apigenin, luteolin [38], kaempferol [39], Quercetin-3-beta-galactoside [40] and tanshinones [41] were reported to inhibit the proteolytic activity of SARS-CoV-1 3CLpro.

As a result, the current literature carries strong evidence in support of PSMs as potential effective antivirals against

coronavirus species, such as SARS-CoV-1, MERS-CoV and SARS-CoV-2. Besides reducing and preventing the metabolic damage caused by proinflammatory cytokines and oxidative stress, PSMs can also be effective in improving some clinical indexes specific to COVID-19 (oxyhemoglobin saturation, lymphocyte percentage, and lactate dehydrogenase), enhancing immunity, alleviating the adverse drug reactions induced by anti-virus drugs and corticosteroids, shortening the rehabilitation period, and decreasing the transfer rate from mild to severe or critical cases [42]. Studies evaluating the effectiveness of plant secondary metabolites against COVID-19 are ongoing. The activities of PSMs and herbal products that can potentially affect COVID-19 need to be tested in clinical studies with different methodological features. After extensive studies with PSMs regarding their activity, bioavailability, specificity and safety, there should be consideration concerning their use in the treatment of COVID-19 [43-46].

3. PLANT AND SEAWEED LECTINS

Lectins comprise a unique and heterologous class of proteins sharing the ability to recognize specific types of carbohydrate residues [47]. Lectins are found in many organisms, such as plants, bacteria, animals, viruses, and single-cell organisms. All plant proteins possessing at least one noncatalytic domain that binds reversibly to a specific mono- or oligosaccharide are considered lectins. Proteins, which are structurally and evolutionarily related to lectins but lack active carbohydrate-binding sites, do not meet this criterion and hence are not regarded as lectins but as lectin-related proteins [48]. The sugar content in lectin varies from 0% to 18%, and the carbohydrate specificity could be simple sugars or glycoprotein [49]. Raw legumes (beans, peas, lentils, peanuts, and soybeans) and whole grains like wheat contain the highest amounts of plant lectins. To date, more than 500 different plant lectins have been isolated and characterized [50]. Apart from plant sources, different types of lectins have also been isolated from different microorganisms (*Acinetobacter baumannii, Escherichia coli, Microcystic aeruginosa, Photorhabdus asymbiotica*) [51] and animals (*Marsupenaeus japonicas, Branchiostoma japonicum, Ictalurus punctatus, Marsupenaeus japonicas, Eriocheir sinensis, Homo sapiens, Mus musculus*) [52]. Around 800 marine algae produce antiviral lectins [53], and some of the lectins isolated from seaweed are known to be effective against viruses.

Lectins have diverse potencies, such as potent antiviral, antimicrobial, antimitogenic, antiproliferative, and antioxidant effects. The significant differences in molecular and physiological characteristics, molecular size/structure and carbohydrate specificity lead to varied therapeutic uses and applications. Thanks to their potential activities, plant and seaweed lectins can act as immunologic receptors and defence proteins. Lectins also have important biological functions in the corresponding organisms, including cell-cell interactions, protection from pathogens, cell adhesion, and intracellular translocation of glycoproteins, also acting as storage proteins [54]. Among the natural substances that have antiviral activities, plant and seaweed lectins are thought to have the ability to bind to several virus species, including coronaviruses, through a sugar-lectin binding model.

The envelope of SARS-CoV-2 exhibits glycoproteins, such as spikes and membrane proteins, and these structural proteins have been identified as important targets for vaccine drug design and neutralizing antibodies [47]. The SARS-CoV-2 infectivity can be inhibited by lectins like other carbohydrate-binding agents that are specific to glycans. Because the sugar content of glycoproteins is critical for the effective replication of the virus, viral protein glycosylation plays an important role during virus infection, replication, and virus-host interactions [55]. Many lectins inhibit the replication of viruses by interacting with viral envelope glycoproteins [56]. The lectins interfere with the glycans on the spike protein like other carbohydrate-binding agents during virus entry and virus release.

To date, the antiviral effects of several lectins isolated from different plants, microorganisms, and animals have been investigated (Table **2**). Among plant-based lectins, *Urtica dioica* agglutinin (UDA) has an important place, as this monomeric lectin has been reported to have significant activity against Nidovirales. Kumaki *et al*. [57] stated that UDA reduced SARS-related mortality and weight loss. Keyaerts *et al*. [58] also emphasized the importance of mannose-specific lectins against coronaviruses. In the study by Keyaerts *et al*. [58], the antiviral activities of 33 plant lectins with different specificities were evaluated against SARS-CoV-1 and feline infectious peritonitis virus (FIPV) using Vero E6 cells. They found that mannose-binding lectins showed the strongest anti-coronavirus activity. In addition, it was also stated that many galactose-, N-acetylgalactosamine-, glucose-, and N-acetylglucosamine-specific plant agglutinins exhibited anti-coronaviral activity. In another study [59], it was reported that a glucose/mannose lectin isolated from hyacinth beans (*Lablab purpureus*) effectively neutralized SARS-CoV-2, preventing viral protein production and cytopathic effects in host cells, and this lectin has been reported as an antiviral agent against SARS-CoV-2. It was also stated that the soluble serum protein mannose-binding lectins, which decline with age, could be involved in recognition of oligomannose-type glycans exposed to the SARS-CoV-2 spike protein, representing a susceptibility factor for the acquisition of this viral infection [60, 61]. Reduced soluble serum protein mannose-binding lectin concentrations in elders coincide with higher SARS CoV-2 susceptibility, suggesting a protagonist role in antiviral defense [60]. A different study has similarly stated that mannose-binding lectins contribute to the first-line host defense against SARS-CoV-1 and that serum mannose-binding lectin deficiency is a susceptibility factor for the acquisition of SARS [62].

Different mechanisms for the effectiveness of lectins against coronaviruses have also been determined. Lectins, such as *Maackia amurensis* seed lectin target the Angiotensin-converting enzyme 2 (ACE2), established as the functional host receptor for SARS-CoV-2. Sheehan *et al*. [63] reported that *Maackia amurensis* seed lectin inhibits SARS-CoV-2 spike binding and decreases the expression of ACE2, sialic acid glycosylase, furin, and inflammatory cytokines in human oral squamous cell carcinoma cells. These agents with similar effects may benefit SARS-CoV-2 infection and

Table 2. Potential plant and seaweed lectins for preventing coronaviruses including SARS-CoV-2 and their effectiveness.

References	Virus	PSM	Experimental Model	Main Results
Kumaki *et al*. 2011 [57]	SARS-CoV-1	UDA	Vero 76 cells, Balb/c mice	UDA inhibited virus replication in a dose-dependent manner and reduced virus yields by 90% at Vero 76 cells. UDA treatment of SARS infection in mice leads to a substantial therapeutic effect that protects mice against death and weight loss. UDA likely inhibits SARS-CoV-1 infection by targeting early stages of the replication cycle, namely, adsorption or penetration. UDA neutralizes the virus infectivity, presumably by binding to the SARS-CoV-1 spike glycoprotein.
Keyaerts *et al*. 2007 [58]	SARS-CoV-1	Plant lectins (Collection of 33 plant lectins)	Vero E6 cells	The strongest anti-coronavirus activity was found predominantly among the mannose-binding lectins. In addition, a number of galactose-, glucose-, *N*-acetylgalactosamine-, and *N*-acetylglucosamine-specific plant agglutinines exhibited anti-coronaviral activity.
Liu *et al*. 2020 [59]	SARS-CoV-2	*Lablab purpureus* lectin	Balb/c mice	A glucose/mannose lectin isolated from *Lablab purpureus* effectively neutralized SARS-CoV-2, preventing viral protein production and cytopathic effect in host cells and this lectin has been reported as an antiviral agent against SARS-CoV-2.
Sheehan *et al*. 2021 [63]	SARS-CoV-2	*Maackia amurensis* seed lectin	HSC-2 cells	*Maackia amurensis* seed lectin targets the ACE2 receptor, inhibits SARS-CoV-2 spike binding, and decreases the expression of ACE2, sialic acid glycosylases, furin, and inflammatory cytokines in human oral squamous cell carcinoma cell lines. In addition, *Maackia amurensis* seed lectin also inhibited SARS-CoV-2 infection of mammalian kidney epithelial cells.
O'Keefe *et al*. [64]	SARS-CoV-1	Griffithsin	Vero 76 cells, Balb/c mice	Griffithsin binds to the SARS-CoV-1 spike glycoprotein and inhibits viral entry. Griffithsin treatment specifically inhibits deleterious aspects of the host immunological response to SARS infection in mammals and has a positive effect on mortality and morbidity in a lethal infection model using a mouse-adapted SARS-CoV.
Millet *et al*. [65]	MERS-CoV	Griffithsin	Vero-81 cells	Griffithsin inhibits entry into host cells of particles pseudotyped with the MERS-CoV spike protein, suggesting that griffithsin inhibits spike protein function during entry. Griffithsin can be a potent inhibitor of MERS-CoV infection at the entry step.

Abbreviations: Vero-E6; African green monkey, *Cercopithecus aethiops*, kidney epithelial cells, **UDA**; *Urtica dioica* agglutinin, **HSC-2 cells**; *human* oral *squamous cell carcinoma cells,* **Vero cells**; African green monkey kidney epithelial cells.

COVID-19 progression when administered orally to epithelial cells.

There are studies suggesting that lectins isolated from sources other than plants may also be effective against coronaviruses. Griffithsin and cyanovirin-N, are lectins isolated from red algae and cyanobacterium [49], and have antiviral activity against coronaviruses, including SARS-CoV-1 [64] and MERS-CoV [65]. Griffithsin reduced the mortality and the severity of lethal pulmonary infection induced by SARS-CoV-1 in mice by decreasing the proinflammatory cytokines in infected lung tissue [64]. It is not yet clear whether griffithsin or cyanovirin-N inactivates SARS-CoV-2, but the surface-exposed spike proteins of SARS-CoV-1 and SARS CoV-2 are highly conserved, with some conserved and some unique glycan positions [66]. In other words, among seaweed lectins, griffithsin and cyanovirin-N can have potent antiviral activity against SARS-CoV-2. On the other hand, it was suggested that galectin-3, an animal lectin, may be beneficial in treating COVID-19 by suppressing the host inflammatory response and impeding viral attachment to host cells [67].

Consequently, coronaviruses, including SARS-CoV-2, carry glycoproteins on their surface. These glycoproteins are mainly responsible for the infection processes [53]. Many studies have claimed that this novel coronavirus infection can be prevented by lectins specific to glycans. Lectins could inhibit the SARS-CoV-2 activity through binding to the virus surface glycoprotein, blocking the host receptor, or inhibiting the viral polymerase enzyme by binding to its active site. Based on previous studies on coronaviruses, mannose-specific plant lectins, griffithsin, and cyanovirin-N have potential effects on coronaviruses, including SARS-CoV-2. However, it is currently not possible to recommend the therapeutic use of these natural compounds against COVID-19 in nutraceutical and drug forms. On the other hand, it should not be ignored that, for lectins to be used as nutraceuticals or drugs, they must comply with three main physiological conditions. Firstly, they must not be toxic or cause immunogenicity. Secondly, they must not be degraded by proteolytic enzymes [68]. Finally, many lectins are still waiting for new discoveries, and further studies are needed on this topic.

CONCLUSION

In the light of the recent pandemic, an important question was raised concerning which therapeutic agents can prevent or kill SARS-CoV-2. For the answer, we have reviewed the literature and evaluated all nutritional components that may potentially affect this virus. According to the results obtained from the literature, many PSMs and plant lectins have potential effects against coronaviruses, including SARS-CoV-2. These PSMs may have potential as candidates for future development of anti-SARS-CoV-2 therapeutics. However, further studies should be conducted to validate these PSMs,

using *in vitro* and *in vivo* models to pave the way for these compounds in drug discovery. Last of all, the findings suggest that plants provide an ultimate, natural source of enzymes and viral propagation inhibitors to be explored as treatment methods for disorders caused by SARS-CoV-2.

AUTHORS' CONTRIBUTIONS

TGÜ and SY: Conceptualization, literature search, and manuscript writing; FPÇ and AU review and edited the manuscript.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Pal M, Berhanu G, Desalegn C, Kandi V. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): An update. Cureus 2020; 12(3): e7423. http://dx.doi.org/10.7759/cureus.7423 PMID: 32337143

[2] Pillaiyar T, Meenakshisundaram S, Manickam M. Recent discovery and development of inhibitors targeting coronaviruses. Drug Discov Today 2020; 25(4): 668-88. http://dx.doi.org/10.1016/j.drudis.2020.01.015 PMID: 32006468

[3] Hui DS. Epidemic and Emerging coronaviruses severe acute respiratory syndrome and middle east respiratory syndrome. Clin Chest Med 2017; 38(1): 71-86. http://dx.doi.org/10.1016/j.ccm.2016.11.007 PMID: 28159163

[4] WHO. Coronavirus disease (COVID-19) pandemic. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 [cited: 9th Nov 2021].

[5] Ülger TG, Ayhan NY. Functional effects of plant secondary metabolites on health. Acıbadem Univ Health Sci J 2020; 3: 384-90.

[6] Wen CC, Shyur LF, Jan JT, *et al*. Traditional Chinese medicine herbal extracts of *Cibotium barometz*, *Gentiana scabra*, *Dioscorea batatas*, *Cassia tora*, and *Taxillus chinensis* inhibit SARS-CoV replication. J Tradit Complement Med 2011; 1(1): 41-50. http://dx.doi.org/10.1016/S2225-4110(16)30055-4 PMID: 24716104

[7] Li SY, Chen C, Zhang HQ, *et al*. Identification of natural compounds with antiviral activities against SARS-associated coronavirus. Antiviral Res 2005; 67(1): 18-23. http://dx.doi.org/10.1016/j.antiviral.2005.02.007 PMID: 15885816

[8] Lin CW, Tsai FJ, Tsai CH, *et al*. Anti-SARS coronavirus 3C-like protease effects of *Isatis indigotica* root and plant-derived phenolic compounds. Antiviral Res 2005; 68(1): 36-42. http://dx.doi.org/10.1016/j.antiviral.2005.07.002 PMID: 16115693

[9] Lau KM, Lee KM, Koon CM, *et al*. Immunomodulatory and anti-SARS activities of *Houttuynia cordata*. J Ethnopharmacol 2008; 118(1): 79-85. http://dx.doi.org/10.1016/j.jep.2008.03.018 PMID: 18479853

[10] Loizzo MR, Saab AM, Tundis R, *et al*. Phytochemical analysis and *in vitro* antiviral activities of the essential oils of seven Lebanon species. Chem Biodivers 2008; 5(3): 461-70. http://dx.doi.org/10.1002/cbdv.200890045 PMID: 18357554

[11] Luo W, Su X, Gong S, *et al*. Anti-SARS coronavirus 3C-like protease effects of *Rheum palmatum* L. extracts. Biosci Trends 2009; 3(4): 124-6. PMID: 20103835

[12] Park JY, Jeong HJ, Kim JH, *et al*. Diarylheptanoids from *Alnus japonica* inhibit papain-like protease of severe acute respiratory syndrome coronavirus. Biol Pharm Bull 2012; 35(11): 2036-42. http://dx.doi.org/10.1248/bpb.b12-00623 PMID: 22971649

[13] Zhuang M, Jiang H, Suzuki Y, *et al*. Procyanidins and butanol extract of *Cinnamomi cortex* inhibit SARS-CoV infection. Antiviral Res 2009; 82(1): 73-81. http://dx.doi.org/10.1016/j.antiviral.2009.02.001 PMID: 19428598

[14] Kim DW, Seo KH, Curtis-Long MJ, *et al*. Phenolic phytochemical displaying SARS-CoV papain-like protease inhibition from the seeds of *Psoralea corylifolia*. J Enzyme Inhib Med Chem 2014; 29(1): 59-63. http://dx.doi.org/10.3109/14756366.2012.753591 PMID: 23323951

[15] Liu M, Gao Y, Yuan Y, *et al*. Efficacy and safety of integrated traditional Chinese and western medicine for corona virus disease 2019 (COVID-19): A systematic review and meta-analysis. Pharmacol Res 2020; 158: 104896. http://dx.doi.org/10.1016/j.phrs.2020.104896 PMID: 32438037

[16] Wen CC, Kuo YH, Jan JT, *et al*. Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. J Med Chem 2007; 50(17): 4087-95. http://dx.doi.org/10.1021/jm070295s PMID: 17663539

[17] Lin SC, Ho CT, Chuo WH, Li S, Wang TT, Lin CC. Effective inhibition of MERS-CoV infection by resveratrol. BMC Infect Dis 2017; 17(1): 144. http://dx.doi.org/10.1186/s12879-017-2253-8 PMID: 28193191

[18] Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet 2003; 361(9374): 2045-6. http://dx.doi.org/10.1016/S0140-6736(03)13615-X PMID: 12814717

[19] Chen F, Chan KH, Jiang Y, *et al*. *In vitro* susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol 2004; 31(1): 69-75. http://dx.doi.org/10.1016/j.jcv.2004.03.003 PMID: 15288617

[20] Hoever G, Baltina L, Michaelis M, *et al*. Antiviral activity of glycyrrhizic acid derivatives against SARS-coronavirus. J Med Chem 2005; 48(4): 1256-9. http://dx.doi.org/10.1021/jm0493008 PMID: 15715493

[21] Ho TY, Wu SL, Chen JC, Li CC, Hsiang CY. Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. Antiviral Res 2007; 74(2): 92-101. http://dx.doi.org/10.1016/j.antiviral.2006.04.014 PMID: 16730806

[22] Mohammadi N, Shaghaghi N. Inhibitory effect of eight secondary metabolites from conventional medicinal plants on COVID-19 virus protease by molecular docking analysis. Chemrxiv 2020. http://dx.doi.org/10.26434/chemrxiv.11987475.v1

[23] Khan MF, Khan MA, Khan ZA, Ahamad T, Ansari WA. Identification of dietary molecules as therapeutic agents to combat covid-19 using molecular docking studies. Researchsquare 2020. http://dx.doi.org/10.21203/rs.3.rs-19560/v1

[24] Mhatre S, Srivastava T, Naik S, Patravale V. Antiviral activity of green tea and black tea polyphenols in prophylaxis and treatment of COVID-19: A review. Phytomedicine 2021; 85: 153286. http://dx.doi.org/10.1016/j.phymed.2020.153286 PMID: 32741697

[25] Chen CN, Lin CP, Huang KK, *et al*. Inhibition of SARS-CoV 3C-like protease activity by theaflavin-3, 3'-digallate (TF3). Evid Based Complement Alternat Med 2005; 2(2): 209-15. http://dx.doi.org/10.1093/ecam/neh081 PMID: 15937562

[26] Khaerunnisa S, Kurniawan H, Awaluddin R, Suhartati S, Soetjipto S. Potential inhibitor of COVID-19 main protease (Mpro) from several medicinal plant compounds by molecular docking study. Preprints 2020. http://dx.doi.org/10.20944/preprints202003.0226.v1

[27] Abdel-Mottaleb MS, Abdel-Mottaleb Y. In search for effective and safe drugs against SARS-CoV-2: Part I] simulated interactions between selected nutraceuticals, ACE2 enzyme and S Protein simple peptide sequences. Chemrxiv 2020.

http://dx.doi.org/10.26434/chemrxiv.12155235.v1

[28] Adem S, Eyupoglu V, Sarfraz I, Rasul A, Ali M. Identification of potent COVID-19 main protease (Mpro) inhibitors from natural polyphenols: An *in silico* strategy unveils a hope against CORONA. Preprints 2020. http://dx.doi.org/10.20944/preprints202003.0333.v1

[29] Thuy BTP, My TTA, Hai NTT, *et al*. Investigation into SARS-CoV-2 resistance of compounds in garlic essential oil. ACS Omega 2020; 5(14): 8312-20. http://dx.doi.org/10.1021/acsomega.0c00772 PMID: 32363255

[30] Park JY, Ko JA, Kim DW, *et al*. Chalcones isolated from Angelica keiskei inhibit cysteine proteases of SARS-CoV. J Enzyme Inhib Med Chem 2016; 31(1): 23-30. http://dx.doi.org/10.3109/14756366.2014.1003215 PMID: 25683083

[31] Utomo RY, Meiyanto E. Revealing the potency of citrus and galangal constituents to halt SARS-CoV-2 infection. Preprints 2020. http://dx.doi.org/10.20944/preprints202003.0214.v1

[32] Yu MS, Lee J, Lee JM, *et al*. Identification of myricetin and scutellarein as novel chemical inhibitors of the SARS coronavirus helicase, nsP13. Bioorg Med Chem Lett 2012; 22(12): 4049-54. http://dx.doi.org/10.1016/j.bmcl.2012.04.081 PMID: 22578462

[33] Wink M. Potential of DNA intercalating alkaloids and other plant secondary metabolites against SARS-CoV-2 causing COVID-19. Diversity (Basel) 2020; 12: 175. http://dx.doi.org/10.3390/d12050175

[34] Bhuiyan FR, Howlader S, Raihan T, Hasan M. Plants metabolites: Possibility of natural therapeutics against the COVID-19 pandemic. Front Med (Lausanne) 2020; 7: 444. http://dx.doi.org/10.3389/fmed.2020.00444 PMID: 32850918

[35] Wyk BE, Wink M. Medicinal plants of the world. CABI 2018. Available from: https://www.springer.com/gp/book/9781588291295 [cited: 9th Nov 2021].

[36] Jo S, Kim S, Shin DH, Kim MS. Inhibition of SARS-CoV 3CL protease by flavonoids. J Enzyme Inhib Med Chem 2020; 35(1): 145-51. http://dx.doi.org/10.1080/14756366.2019.1690480 PMID: 31724441

[37] Nguyen TTH, Woo HJ, Kang HK, *et al*. Flavonoid-mediated inhibition of SARS coronavirus 3C-like protease expressed in *Pichia pastoris*. Biotechnol Lett 2012; 34(5): 831-8. http://dx.doi.org/10.1007/s10529-011-0845-8 PMID: 22350287

[38] Ryu YB, Jeong HJ, Kim JH, *et al*. Biflavonoids from *Torreya nucifera* displaying SARS-CoV 3CL(pro) inhibition. Bioorg Med Chem 2010; 18(22): 7940-7. http://dx.doi.org/10.1016/j.bmc.2010.09.035 PMID: 20934345

[39] Schwarz S, Sauter D, Wang K, *et al*. Kaempferol derivatives as antiviral drugs against the 3a channel protein of coronavirus. Planta Med 2014; 80(2-3): 177-82. http://dx.doi.org/10.1055/s-0033-1360277 PMID: 24458263

[40] Chen L, Li J, Luo C, *et al*. Binding interaction of quercetin-3-β-galactoside and its synthetic derivatives with SARS-CoV 3CL(pro): Structure-activity relationship studies reveal salient pharmacophore features. Bioorg Med Chem 2006; 14(24): 8295-306. http://dx.doi.org/10.1016/j.bmc.2006.09.014 PMID: 17046271

[41] Park JY, Kim JH, Kim YM, *et al*. Tanshinones as selective and slow-binding inhibitors for SARS-CoV cysteine proteases. Bioorg Med Chem 2012; 20(19): 5928-35. http://dx.doi.org/10.1016/j.bmc.2012.07.038 PMID: 22884354

[42] Wang WY, Xie Y, Zhou H, Liu L. Contribution of traditional Chinese medicine to the treatment of COVID-19. Phytomedicine 2021; 85: 153279. http://dx.doi.org/10.1016/j.phymed.2020.153279 PMID: 32675044

[43] Jo S, Kim H, Kim S, Shin DH, Kim MS. Characteristics of flavonoids as potent MERS-CoV 3C-like protease inhibitors. Chem Biol Drug Des 2019; 94(6): 2023-30. http://dx.doi.org/10.1111/cbdd.13604 PMID: 31436895

[44] Yi L, Li Z, Yuan K, *et al*. Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. J Virol 2004; 78(20): 11334-9. http://dx.doi.org/10.1128/JVI.78.20.11334-11339.2004 PMID: 15452254

[45] Ryu YB, Park SJ, Kim YM, *et al*. SARS-CoV 3CLpro inhibitory effects of quinone-methide triterpenes from *Tripterygium regelii*. Bioorg Med Chem Lett 2010; 20(6): 1873-6. http://dx.doi.org/10.1016/j.bmcl.2010.01.152 PMID: 20167482

[46] Cho JK, Curtis-Long MJ, Lee KH, *et al*. Geranylated flavonoids displaying SARS-CoV papain-like protease inhibition from the fruits of *Paulownia tomentosa*. Bioorg Med Chem 2013; 21(11): 3051-7. http://dx.doi.org/10.1016/j.bmc.2013.03.027 PMID: 23623680

[47] Nascimento da Silva LC, Mendonça JSP, de Oliveira WF, *et al*. Exploring lectin-glycan interactions to combat COVID-19: Lessons acquired from other enveloped viruses. Glycobiology 2021; 31(4): 358-71. http://dx.doi.org/10.1093/glycob/cwaa099 PMID: 33094324

[48] Wu AM. The molecular immunology of complex carbohydrates—2. Springer Science & Business Media 2012. Available from: https://www.springer.com/gp/book/9780306465321 [cited: 9th Nov 2021].

[49] El-Maradny YA, El-Fakharany EM, Abu-Serie MM, Hashish MH, Selim HS. Lectins purified from medicinal and edible mushrooms: Insights into their antiviral activity against pathogenic viruses. Int J Biol Macromol 2021; 179: 239-58. http://dx.doi.org/10.1016/j.ijbiomac.2021.03.015 PMID: 33676978

[50] Peumans WJ, Van Damme EJ, Barre A, Rougé P. Classification of plant lectins in families of structurally and evolutionary related proteins. Adv Exp Med Biol 2001; 491: 27-54. http://dx.doi.org/10.1007/978-1-4615-1267-7_3 PMID: 14533788

[51] Kotecha H, Poduval PB. Microbial lectins: Roles and applications. Adv Biol Sci Res 2019; 135-47.

[52] Dias RdeO, Machado LdosS, Migliolo L, Franco OL. Insights into animal and plant lectins with antimicrobial activities. Molecules 2015; 20(1): 519-41. http://dx.doi.org/10.3390/molecules20010519 PMID: 25569512

[53] Bhattacharyya M, Patni B. Plant lectins have antagonistic effects against Coronavirus family: Natural products can control Coronaviral infections: A review. Agric Technol Thail 2020; 16: 1077-88.

[54] Mazalovska M, Kouokam JC. Lectins as promising therapeutics for the prevention and treatment of HIV and other potential coinfections. BioMed Res Int 2018; 2018: 3750646. http://dx.doi.org/10.1155/2018/3750646 PMID: 29854749

[55] van der Meer FJUM, de Haan CAM, Schuurman NMP, *et al*. The carbohydrate-binding plant lectins and the non-peptidic antibiotic pradimicin A target the glycans of the coronavirus envelope glycoproteins. J Antimicrob Chemother 2007; 60(4): 741-9. http://dx.doi.org/10.1093/jac/dkm301 PMID: 17704516

[56] Mitchell CA, Ramessar K, O'Keefe BR. Antiviral lectins: Selective inhibitors of viral entry. Antiviral Res 2017; 142: 37-54. http://dx.doi.org/10.1016/j.antiviral.2017.03.007 PMID: 28322922

[57] Kumaki Y, Wandersee MK, Smith AJ, *et al*. Inhibition of severe acute respiratory syndrome coronavirus replication in a lethal SARS-CoV BALB/c mouse model by stinging nettle lectin, Urtica dioica agglutinin. Antiviral Res 2011; 90(1): 22-32. http://dx.doi.org/10.1016/j.antiviral.2011.02.003 PMID: 21338626

[58] Keyaerts E, Vijgen L, Pannecouque C, *et al*. Plant lectins are potent inhibitors of coronaviruses by interfering with two targets in the viral replication cycle. Antiviral Res 2007; 75(3): 179-87. http://dx.doi.org/10.1016/j.antiviral.2007.03.003 PMID: 17428553

[59] Liu YM, Shahed-Al-Mahmud M, Chen X, *et al*. A carbohydrate-binding protein from the edible Lablab beans effectively blocks the infections of influenza viruses and SARS-CoV-2. Cell Rep 2020; 32(6): 108016. http://dx.doi.org/10.1016/j.celrep.2020.108016 PMID: 32755598

[60] Lardone RD, Garay YC, Parodi P, *et al*. How glycobiology can help us treat and beat the COVID-19 pandemic. J Biol Chem 2021; 296: 100375. http://dx.doi.org/10.1016/j.jbc.2021.100375 PMID: 33548227

[61] Gao A, Zeng J, Jia N, *et al*. SARS-CoV-2 spike protein interacts with multiple innate immune receptors. BioRxiv 2020. http://dx.doi.org/10.1101/2020.07.29.227462

[62] Ip WK, Chan KH, Law HKW, *et al*. Mannose-binding lectin in severe acute respiratory syndrome coronavirus infection. J Infect Dis 2005; 191(10): 1697-704. http://dx.doi.org/10.1086/429631 PMID: 15838797

[63] Sheehan SA, Hamilton KL, Retzbach EP, *et al*. Evidence that *Maackia amurensis* seed lectin (MASL) exerts pleiotropic actions on oral squamous cells with potential to inhibit SARS-CoV-2 infection and COVID-19 disease progression. Exp Cell Res 2021.

[64] O'Keefe BR, Giomarelli B, Barnard DL, *et al*. Broad-spectrum *in vitro* activity and *in vivo* efficacy of the antiviral protein griffithsin against emerging viruses of the family Coronaviridae. J Virol 2010; 84(5): 2511-21.
http://dx.doi.org/10.1128/JVI.02322-09 PMID: 20032190

[65] Millet JK, Séron K, Labitt RN, *et al*. Middle East respiratory syndrome coronavirus infection is inhibited by griffithsin. Antiviral Res 2016; 133: 1-8.
http://dx.doi.org/10.1016/j.antiviral.2016.07.011 PMID: 27424494

[66] Capell T, Twyman RM, Armario-Najera V, Ma JKC, Schillberg S, Christou P. Potential applications of plant biotechnology against SARS-CoV-2. Trends Plant Sci 2020; 25(7): 635-43.
http://dx.doi.org/10.1016/j.tplants.2020.04.009 PMID: 32371057

[67] Caniglia JL, Guda MR, Asuthkar S, Tsung AJ, Velpula KK. A potential role for Galectin-3 inhibitors in the treatment of COVID-19. PeerJ 2020; 8: e9392.
http://dx.doi.org/10.7717/peerj.9392 PMID: 32587806

[68] Fouad A. Lectin therapy: A way to explore in order to inhibit the binding of COVID-19 to these host cells. Int J Innov Sci Res Technol 2020; 5: 1280-6.