A comprehensive review on the effect of plant metabolites on coronaviruses: focusing on their molecular docking score and IC50 values

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Abstract

Coronaviruses such as SARS (severe acute respiratory syndrome), MERS (Middle East respiratory syndrome), and newly emerged SARS-CoV-2, also called 2019-nCoV and COVID 19, have caused worldwide outbreaks in different time periods. There are many studies about chemical and natural drugs to treat these coronaviruses by inhibiting their proteases or their protein receptors through binding to amino acid residues. Plants secondary and primary metabolites are considered as potential drugs to inhibit various types of coronaviruses. IC50 value (the concentration in which there is 50% loss in enzyme activity) and molecular docking score and binding energy are parameters to understand the metabolites ability to inhibit the specific virus. In this study we did review on more than 110 papers on plant metabolites effect on different coronaviruses. Secondary plant metabolites such as polyphenols (flavonoids, coumarins, stilbenes), alkaloids, terpenoids, organosulfur compounds saponins, saikosaponins, lectins, essential oils, nicotianamine and primary metabolites such as vitamins.

Keywords: Coronaviruses, plants metabolites, polyphenols, antiviral-effect

1. Introduction

Coronaviruses are considered as a family of RNA viruses that have helical nucleocapsids and extremely large genomes. Nucleotides in the coronavirus genomic RNA, determines the structural and nonstructural proteins of the virus. Some of the nonstructural proteins have pivotal role in viral RNA synthesis (replicase-transcriptase proteins), and some of them are unnecessary for virus replication but seem to have a selective benefit in vivo (niche-specific proteins). The crown-like spikes present on the viral envelope of coronaviruses help them to bind to cells, and in this way they can get inside them and cause the infection. There are different types of diseases caused by coronaviruses. They can infect numerous animal species, causing different diseases such as neurological, gastrointestinal, cardiovascular, and respiratory diseases. Therefore there are different diseases related to coronaviruses with different target groups such as: porcine transmissible gastroenteritis virus (TGEV, pig), procine respiratory coronavirus (PRCV, pig), porcine epidemic diarrhea virus (PEDV, pig), feline infectious peritonitis virus (F1PV, cat), feline coronavirus (FCoV, cat), canine coronavirus (CCOV, dog), rabbit coronavirus (RaCoV, rabbit), Rat coronavirus (RCoV) or sialodacryoadenitis virus (SDAV, rat and pig), BEV (bovine enteric virus, cattle), Bovine coronavirus (BCoV, livestock), Avian infectious bronchitis virus (IBV, Chicken), Turkey coronavirus (TCoV) or Transmissible gastroenteritis virus (TECoV, turkey), Murine hepatitis virus (MHV, mouse), civet cat CoV (Himalayan palm civet and raccoon dog), and Raccoon dog CoV (Saif et al., 2004). Human coronaviruses (HCoV) are divided into two groups of alpha and beta coronaviruses. HCoV-229E, HCoV-NL63 belong to alpha coronaviruses, and HCoV-OC43, HCoV-HKU1, severe acute respiratory syndrome (SARS-CoV), Middle East respiratory syndrome (MERS-CoV), and SARS-CoV-2 are in the beta coronaviruses genera (Pyrc et al., 2007). Among these, SARS-CoV and COVID-19 are the

most recent types of coronaviruses. SARS-CoV encodes a chymotrypsin-like protease ($3CL_{pro}$), that is also known as the main protease (M_{pro}). This enzyme has an essential role in replication and infection of virus, thus it is an ultimate target for antiviral compounds' designing. Particularly, the main part of the SARS-CoV genome (first 2/3) consists of the genes responsible for the virus replication that encode 16 non-structural proteins (nsPs), which includes the NTPase/helicase (nsP13). The nsP13 helicase is an important component for replication of the virus which is target for many virus inhibitors (Keum et al., 2013). Angiotensin-converting enzyme 2 (ACE2) has been acknowledged as a practical receptor for SARS-CoV (Li et al., 2003). Coronaviruses can enter the host cell and cause infection by S protein (Spike protein). There are lots of studies about this protein and determination of treatments against the SARS-CoV in particular, and other coronaviruses such as MERS (Hofmann et al., 2004b; Prajapat et al., 2020). These studies can help to invent a drug for newly emerged coronavirus SARS-CoV-2, also called Covid-19 or 2019-nCoV, because they have similar active sites and the same enzymatic mechanisms and also there are high similarities between their genome sequences. In comparison to the SARS-CoV that was emerged 2003, SARS-CoV-2 has a greater transmission capacity. SARS-CoV-2 is also stimulated by binding to ACE2 receptor, so ACE2 blocking agents might be effective way to suppress it (Gralinski et al., 2020). Based on the recent reports about the structure of $3CL_{pro}$ from SARS-CoV2 and SARS-CoV, the differences between the two main proteases are only in 12 amino acids (Macchiagodena et al., 2020).

Plants are rich sources of metabolites which are valuable compounds for therapeutic purposes. Some of these metabolites possess their antiviral activity by stopping viral proliferations. This can be achieved by different ways such as controlling adsorption of virus, binding to the

receptors of the host cell, inhibiting the virus fusion to the host cell membrane and by regulating intracellular signals as well (Khan et al., 2005; Min et al., 2018, Hudson et al., 2018).

In this study we aimed to do a review on the effect of the metabolites derived from plants, on different kind of coronaviruses. Binding affinity of these compounds to a specific ligand or receptor of a target protein in virus is studied by molecular docking assay in several studies. A compound which has a lower binding energy is considered as a potential drug candidate (Chandel et al., 2020). Also IC50 value of these metabolites which is half maximal inhibitory concentration against virus is determined in different studies. Plant metabolites that are reviewed in this paper for their anti-coronavirus effects, are secondary metabolites including polyphenols (such as flavonoids, coumarins, stilbenes), alkaloids, terpenoids, organosulfur compounds saponins, saikosaponins, lectins, essential oils, nicotianamine and primary metabolites such as vitamins.

2. Method

About 110 accepted and preprint papers on the effect of plants primary and secondary metabolites on various types of coronaviruses and were designated for the review, April 2020. Searching the papers was conducted by the keywords coronaviruses, medicinal plants, plant metabolites, polyphenols, alkaloids, terpenoids, organosulfur compounds, nicotianamine, lectins, essential oils, saponins, herb extracts and vitamins in databases, such as Google Scholar and Science-Direct. Selected papers for this review were the papers published from 1991 to April 2020.

3. Polyphenols

Polyphenols are mostly found in plant kingdom and there are many varieties of them. Flavonoids account for a large part of polyphenolic compounds. These compounds have many health benefits due to their antioxidant activity. There are also some studies on their properties, other than antioxidant activity, such as their antimicrobial, antibacterial, antifungal and antiviral activities (Tapas et al., 2008; Song et al., 2005). In addition, there are various types of flavonoids with inhibitory effect against several enzymes such as alpha-glucosidase, and alpha-amylase (Tadera et al., 2006). In this way these compounds can display their antiviral effect. Molecular docking (MolDock) simulation is used to calculate the binding of flavonoids to these enzymes. In docking studies, the higher negative value of docking score is related to the stronger inhibitory ability of the compound. In a study by Nguyen et al., recombinant 3CL$_{pro}$-a chymotrypsin-like cysteine protease which is vital to virus replication-was expressed in Pichia pastoris GS115 and was used for investigating the effect of seven flavonoids including quercetin, epigallocatechin gallate (EGCG), gallocatechin gallate (GCG), epigallocatechin (EGC), ampelopsin (AMPLS), puerarin, and daidzein on it. Among these flavonoids GCG had the strongest inhibitory effect followed by EGCG, quercetin, AMPLS, diadzein, puerin and EGC. GCG indicated several interaction with amino acid residues in the active site of 3CL$_{pro}$. Also galloyl moiety at the 3-OH position of EGCG and GCG, seems to be responsible for their strong 3CL$_{pro}$ inhibitory effect which is not present in AMPLS and EGC. Molecular docking simulation (affinity of the compounds to bind specific receptor on enzyme) indicated that the substrate-binding pocket of 3CL$_{pro}$ is the site that GCG bounds. Daidzein and puerarin, showed little inhibition of 3CL$_{pro}$. The 3CL$_{pro}$ inhibitory effect of quercetin was 4.96-times higher than AMLSP. The difference between the structures of these polyphenols is the cause for their different inhibition activity. EGC, by having a Hydroxyl group at 5´-position of the B ring, and lacking galloyl moiety and 4

and 2,3- double bounds, has the lowest inhibitory activity. IC50 of all of the mentioned compounds are shown in (Table. 1). Also inhibitory percentage for AMPLS, EGC, GGC, G, diadzein, puerarin, quercetin, and EGC was 34%, 85%, 91%, 34%, 33%, 82%, and 5.4%, at 200 μM concentration of them, respectively (Table. 2) (Nguyen et al., 2012). Hesperidin (a flavanone glycoside richly found in the citrus and citrus peel), rutin (an essential nutritional compound mostly found in tea and apples), diosmin (flavonoid mostly found in citrus fruit), apiin (flavonoid in parsely), diacetyl curcumin (synthetic derivative of curcumin), were also displayed as potential inhibitors against protease of COVID-19. According to MolDock binding score, hesperidin had the strongest affinity to block the protease of COVID-19, followed by rutin, diosmin, apiin and diacetylcurcumin (Table. 1). However, all of the mentioned compounds had acceptable binding ability which supports the prospective use of these compounds at first steps of treatment for COVID-19. It can be concluded from this study that consumption of citrus fruits, cherries and apples has the potential to increase immunity to fight against COVID-19 infections (Adem et al., 2020). Results of other study in which a virtual screening was conducted to investigate the effect of some drugs including diosmin and hesperidin on the active sites of SARS-CoV-2 (Covid-19) 3CL$_{pro}$ model, indicated that the flavonoid glycosides diosmin and hesperidin present in citrus fruits are very good substances for blocking the substrate binding site and their MolDock scores are shown in Table. 1. Also hesperidin showed numbers of binding modes, displaying not much adverse reactions (Chen et al 2020). Hesperetin, the aglycone of hesperidin is a bioflavonoid compound which is present in high amount in *citrus aurantium* and *Citri Reticulatae Pericarpium*. In a study done by Lin et al, in 2005, seven phenolic compounds, emodin, aloeemodin, chrysophanol (anthraquinones), hesperetin, quercetin (plant flavonol), naringenin (flavanone), and daidzein (isoflavone), were examined for their inhibitory effects on

the SARS- CoV 3CL$_{pro}$. Cell-free and cell-based assays were conducted. Only aloeemodin and hesperetin had inhibitory effect on cleavage activity of the 3CL$_{pro}$ in cell-free and cell-based assays which was dose-dependently. These two compounds have shown to have considerably high inhibitory effects on SARS-CoV 3CL$_{pro}$ with IC50 of 132 and 60 µM in cell-free assay, respectively. In cell based assay the IC50 values were 366 and 8.3 µM, respectively. Also diadzein had IC50 of 105 µM in cell-free assay but its IC50 was not significant in cell-based assay (Table. 1). Aleoemodin had inhibitory percentage of 65% at 100 µM and for hesperetin and daidzein it was around 82% and 72%, respectively (Table. 2) (Lin et al., 2005). In another study, hesperetin (which was investigated to have anti-SARS activity, was studied for its ability to inhibit Angiotensin-converting enzyme 2 (ACE2), and also its anti-2019-nCoV activity. Results indicated that hesperetin has the ability to bind to ACE2 with the binding energy of -8.3 kcal/mol (Table. 1), and binding sites where shown to be TYR-613, SER-611, ARG-482, GLU-479. It was reported that hesperetin can be strong candidate for 2019-nCoV treatment (Chen and Du. 2020). Another study on the effect of flavonoids on ACE 2, showed that flavonoids present in citrus peels are able to prevent the Covid-19 infection. Specifically, simulated molecular docking results indicated that hesperidin, hesperetin (aglycone of hesperidin) and naringin (flavanone) have stronger binding affinity with the ACE2 receptor. In addition, *in vitro* and in vivo experiments displays the ability of naringin to inhibit the cytokine storms syndrome stimulated by the Covid-19, through different pathways. According to the results of this study, nobiletin and neohesperidin which are in lower amounts in citrus fruits, can also have anti-coronavirus effect, however, neohesperidin had the lowest simulated molecular docking score in compare to other flavonoids studied (Table. 1) (Cheng et al., 2020). In other study hesperetin was discovered to have *in vitro* antiviral activity against SARS-CoV, beside several other compounds

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including chloroquine (De Clercq et al., 2006). Other polyphenolic compounds like theaflavins which are extracted from black tea and also their fractionated compounds by HPLC (initial peaks (IP), free theaflavin (TF1), theaflavin-3 monogallate (TF2A), theaflavin-3´ monogallate (TF2B), and theaflavin-3,3´ digallate (TF3)), were tested for their antirotaviral activity. TF1, TF2A, TF2B, and TF3 were the most active compounds having the mean effective concentration (EC50) of 0.125 mg/ml and TF2A had the least effect with an EC50 of 251.39 mg/ml against SARS-CoV (Clark et al., 1998). In a study, anthraquinone, emodin and rhein (anthraquinone compounds), chrysin (a flavonoid compound) which are produced in *Rheum and Polygonum* plants, and promazine which is also a phenolic compound with a similar structure to emodin, were investigated for their inhibitory effect against binding S protein (spike protein) to ACE2. There are several studies on health effects of these compounds (Huang et al., 1991; Chen et al., 2002; Kumar et al., 1998). Results of this study demonstrated that besides disrupting the viral envelope (Sydiskis et al., 1991), emodin and promazine has the potential to block the S protein of SARS-CoV and ACE2 interaction by competing the binding site of S protein with ACE2. On the other hand anthraquinone and 1,4-bis-(1-anthraquinonylamino)-anthraquinone was found to have lower effect on inhibition of the S protein and ACE2 interaction showing that the anthraquinone skeleton don't influence the S protein and ACE2 binding and the side chain has the main role in their inhibitory activity. Chrysin and rhein also had slightly inhibitory effect on mentioned binding with inhibitory percentage of less than 20% at 200 µM concentration. Findings of this study showed that emodin and promazine have the most effect against SARS-COV S protein activity with inhibitory percentage of 50% and 55% at concentration of 200 µM, respectively (Table. 2) (Ho et al., 2006). Baicalein is mainly extracted and purified from the Chinese medicinal plant named *Scutellaria baicalensis Georgi*. The MolDock binding result

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showed that baicalein have strong binding to the ACE2 enzyme, with binding energy of -8.46 kcal/mol (Table. 1), and the potential binding sites are HIS-505, ASN-149, ARG-273. Based on the anti-SARS activity of this compound and its ability to bind to ACE2, it was stated that baicalein can be a strong candidates for 2019-nCoV treatment (Chen and Du. 2020). Scutellarin is another flavone which indicated wide-ranging pharmacological effects. An in vivo study indicated that this compound is able to reduce the expression and activity of ACE in brain tissue and it was reported that it has IC50 value of 48.13 ± 4.98 μM against ACE (Wang et al., 2016; Wang and Ma, 2018). In other study by conducting a molecular docking it was found that scutellarin is able to bind to ACE2, with binding energy of -14.9 kcal/mol, and the binding sites were GLU-495, UNK-957, ARG-482 (Table. 1). It was stated that this compound can be good candidate for having anti-2019-nCoV activity (Chen and Du. 2020). As mentioned before nsP13, the SARS-CoV helicase, is also vital for viral replication and is regarded as a drug target for SARS-CoV inhibitors. In a study baicalein, scutellarin and myricetin which are natural flavonoids were studied for their inhibitory effect on nsP13. It was shown that baicalein is a strong inhibitor of the ATPase activity of nsP13 protein (with inhibition percentage of 100% at 10 μM (Table. 2)), and its pharmacological activity to inhibit ATPase activity of nsP13 is greater than that of myricetin and scutellarin. IC50 value of baicalein was shown to be 0.47 ± 0.09 μM which was lower than two other flavonoids (Table. 1) (Keum et al., 2013). In another *in vitro* study, the effect of EGCg which is the major active compound of tea polyphenol with different biological activities on inhibition of the bovine coronavirus (BCV) replication in Madin-Darby bovine kidney (MDBK) cells was explored. At concentrations of less than 10 μg/mL, EGCg didn't have any cytotoxicity to MDBK cells. Results of this study showed that EGCg has temperature-dependent effect on BCV and its effect at around 37°C (temperature of intestinal

tract) was better than the temperature of respiratory tract. These results displayed that EGCg has very good anti-BCV activity, it interacts with BCV particles and interferes with the adsorption of BCV to MDBK cells, thus EGCg can be considered as a suitable anti-BCV compound (Matsumoto et al., 2005). In another study, in which secondary metabolites of different medicinal herbs were investigated, results showed that they have inhibitory effects against novel COVID-19 protease. The, dialloyl sulfide from garlic, curcumin in turmeric spices, capsaicin in peppers, limonene and cineol in cardamom, coumarin in liquorice, verbascoside in hedge Nettle, and glucuronic acid in tragacanth were the phenolic compounds in this study that were shown to have inhibitory effect against novel COVID-19 protease. Among these compounds, curcumin had a stronger bond and high affinity with COVID-19 protease (Table. 1) (Mohammadi et al., 2020). In a study by Park et al in 2016, the inhibitory activity of polyphenols from *Broussonetia papyrifera*, was tested against papain-like protease (PL_{pro}) and $3L_{pro}$ of SARS-CoV and MERS-CoV. The polyphenols studied, were broussochalcone B, broussochalcone A, 4-hydroxyisolonchocarpin, papyriflavonol A, 30-(3-methylbut-2-enyl)-30,4,7-trihydroxyflavane, kazinol A, kazinol B, broussoflavan A, kazinol F, and kazinol J. In overall all of the compounds were more effective against PL_{pro} in compare to $3CL_{pro}$. Papyriflavonol A was the most effective inhibitor of SARS-CoV PL_{pro} and its IC50 value was 3.7 µM. Among them 30-(3-methylbut-2-enyl)-30,4,7-trihydroxyflavane was the most effective against MERS-CoV $3CL_{pro}$ with IC50 of 34.7 ± 2.0 µM and Kazinol F had the best inhibitory effect on it with IC50 of 39.5 ± 5.1 µM. Results of this study showed that B. papyrifera ingredients are potential candidates for being anti-coronaviral (SARS-CoV, and MERS-CoV) agents. The IC50 values of all of these polyphenols, were in the low range (Table. 1) (Park et al., 2017). During an investigation lutein (a caretonoid) was found to be an effective component against wild-type SARS-CoV activity by

binding to its S protein with effective concentration (EC50) of 10.6 µM (Yi et al., 2004). In a study by Chen et al., the inhibitory activity of quercetin-3-β-galactoside was investigated against SARS-CoV and it showed IC50 of 42.79 ± 4.97 µM (Table. 1). In this study the binding position of quercetin-3-β-galactoside for two types of SARS-CoV 3CLpro (the wild-type 3CLpro and its mutated type (3CLpro Q189A)), was also compared and the IC50 of quercetin-3-β-galactoside on SARS-CoV 3CLpro Q189A was considerably decreased to 127.89 ± 10.06 µM because of the decrease in binding affinity (Table. 1). Moreover, the inhibition percentage of this compound against SARS-CoV 3CLpro, was 41.8% at 50 µM concentraion (Table. 2). Also new derivatives of the quercetin-3-b-galactoside with some chemical variations to the binding components were devised and the results were like this: 1. Detaching the hydroxy groups of the quercetin moiety which considerably decreases the inhibitory activity 2. Addition of a large sugar on 7-hydroxy of quercetin which can be tolerated 3. Acetoxylation of sugar moiety which stops the inhibitory activity, and 4. Substitution of the galactose moiety with sugars, such as fucose which increased the inhibitory activity (2-fold), arabinose, and glucose, that had no remarkable effect on inhibitory activity (Chen et al., 2006). In other study bioflavonoids extracted from the *Torreya nucifera* leaves were investigated as possible anti-SARS-CoV 3CLpro. Of the isolated components, amentoflavone was documented as strong inhibitor, showing IC50 value of 8.3 µM. Also the three flavones (apigenin, luteolin, and quercetin) used as positive control for bioflavonoids and indicated IC50 value of 280.8, 20.2, and 23.8 µM, respectively (Table. 1). It was shown that there are interactions between the C5 hydroxyl group of amentoflavone with the nitrogen atom of the imidazole group of His163 and OH group of Leu14, with two hydrogen bonds. These groups belong to S1 site of 3CLpro. In addition, there are hydrogen bonds between the hydroxyl group in the B ring of amentoflavone and Gln189 which belongs to S2 site of

$3CL_{pro}$. Also interactions with Val186 and Gln192 can be considered as one of the major bindings with the target site. inhibition percentage results are present in Table. 2 (Ryu et al. 2010). In a study, 720 natural compounds was investigated for their inhibitory effect against $3CL_{pro}$. Also the $3CL_{pro}$-inhibitory effect of extracts from different kinds of teas, such as black tea, oolong tea, Puer tea and green tea was investigated. Results showed that their inhibitory activities against $3CL_{pro}$ of Puer and black tea extracts were greater than that of green or oolong tea extracts. Also it was indicated that (-)-epigallocatechin gallte (EGCg), catechin (C), epicatechin gallate (ECg), epicatechin (EC), theophylline (TP), epigallocatechin (EGC), and caffeine are not able to have $3CL_{pro}$ inhibitory activity. Black tea polyphenols (TF1, TF2 and TF3) also displayed inhibitory activity against $3CL_{pro}$. TF3 was the most abundant polyphenol in black tea, followed by TF2A ,TF2B, and TF1. This study has discovered that TF2B, TF3 and tannic acid are effective three compounds to inhibit $3CL_{pro}$ and their IC50 are less than 10 μM, but TF2A was not investigated due to its unavailability (Table. 1). These components are presents at high amounts in the extract of black tea. It is difficult to quantify tannic acid's level in green or black tea because it constitutes a wide variety of polymers with mol.wts of 500–3000 Da (Chen et al., 2005). In another study, inhibitory activities of alkylated chalcones and coumarins (flavonoids) which were isolated from *Angelica keiskei*, were investigated against $3CL_{pro}$ and PL_{pro} of SARS-CoV in cell-free and cell-based form. Chalcones are abundant in various plants and these compounds are precursors for other components such as flavonoids and alkylated chalcones are the most principal derivatives of them. Of the isolated alkylated chalcones, xanthoangelol E, which has the perhydroxyl group, showed the most possible inhibitory activity against $3CL_{pro}$ and PL_{pro} with IC50 values of 11.4 and 1.2 μM, respectively (Table. 1). Moreover, the active chalcones were 2-fold more effective when tested with cell-

based cis-cleavage assay in compare to the cell-free trans-cleavage assay. Inhibition percentage results are present in Table. 2 (Park et al., 2015). The open-reading-frame 3a of SARS coronavirus has been shown to code a protein which forms a channel with cation-selective ability that can be expressed in the infected cell. The mechanism of virus release is related to the activity of the channel. In a study the flavanols such as kaempferol, kaempferol glycosides, and acylated kaempferol glucoside derivatives were examined for their ability to block the 3a channel. Glycoside juglanin (with an arabinose residue) was found to be the most effective component to block 3a channel which had an IC50 value of 2.3 µM (Table. 1). Kaempferol derivatives which had a rhamnose residue also was likely to be quite effective in blocking 3a channel. As a conclusion, this study found out that more bioavailable compounds such as emodin and kaempferol (specifically, the glycosides of kaempferol) could be a foundation for the new antiviral drugs exploration. These compounds not only can block the 3a channel, but also they can interfere with other stages of the viral life cycle (Kaul et al., 1985) and this is an important feature to consider them as a potent antiviral agent (Schwarz et al., 2014). In another *in vitro* study the inhibitory activities of 64 different natural compounds were investigated against SARS helicase (nsP13). Scutellarin and myricetin showed to restrain the SARS-CoV helicase protein by influencing the ATPase activity, but they didn't have any effect on unwinding activity (inhibition of helicase activity). The IC50 values of myricetin and scutellarein were 2.71 ± 0.19 µM and 0.86 ± 0.48 µM, respectively. Moreover, the inhibitory percentage of these compounds is 100% at approximately 10 µM concentration of them (Table. 2) (Yu et al., 2012). Stilbene compounds can also be classified as polyphenols and they have a lot of biological activities. These derivatives are assumed to be phytoalexins. In a study (E)-stilbene derivatives with hydroxyl groups were synthesized and in some of them pyridine ring was used in place of one

benzene ring. Two of these compounds exhibited antiviral effect against SARS *in vitro* (Li et al., 2006). In a study researchers aimed to show the potential anti SARS-CoV-2 from *Citrus sp.*, *Alpinia galangal, Curcuma sp.*, and *Caesalpinia sappan* herbs through their binding to 3 protein receptors, by molecular docking study. The studied protein receptors were SARS-CoV-2 protease (PDB ID:6LU7), PD-ACE2 (PDB ID:6VW1), and RBD-S (PDB ID:6LXT). The results indicated that among the compounds present in *Citrus sp.*, hesperidin had the least docking score for all of the protein receptors showing its high affinity to bind to these receptors. Other compounds' inhibitory effects are present in Table. 1. Generally, the results of this study showed that *Citrus sp.* can be a very good inhibitor of SARS-CoV-2, followed by *A. galanga*, *sappan wood*, and *Curcuma sp*. Also other citrus flavonoids which are present in lemon peel and orange, such as nobiletin, tangeretin, hesperetin, and naringenin, indicated very good affinity to the mentioned receptors, it means that these citrus flavonoids may be able to have antiviral effect (Utomo et al., 2020). In other study the binding energies of different phenolic compounds were studied and among them apigenin-7-glucoside, oleuropein, catechin, curcumin, luteolin-7-glucoside, demethoxycurcumin, and epicatechin-gallate showed to have the best activity to consider as COVID-19 M_{pro} inhibitors (Table. 1). Nevertheless, it was mentioned that more researches are needed to know their potential medicinal use (Khaerunnisa et al., 2020). In other study researchers predicted the SARS-CoV-2 (COVID-19) $3CL_{pro}$ enzyme and their results showed that in spite of similarities between $3CL_{pro}$ of SARS-CoV-2 and SARS-CoV, there are some principal differences (Chen et al., 2020) . Thus, researchers are still seeking for a suitable drug to treat Covid-19. In a study nine anitiviral phytochemicals were selected from a broad variety of plant based antiviral agents database, which had shown to have high inhibitory activity against SARS-CoV-2 $3CL_{pro}$. Nelfinavir (a nocleoside), colistin and prulifloxacin that were

suggested as natural drugs to be effective against SARS-CoV-2 3CL$_{pro}$, were considered as controls (Xu et al., 2020; Li et al., 2020). Docking results (Table. 1) showed that 5,7,3',4'-tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone which is extracted from the herb named *Psorothamnus arborescens,* had the highest docking score (-16.35) and also the highest binding affinity (-29.57 kcal/mol). Generally all of the phenolic compounds they studied, including myricetin, licoleafol (prenylated flavanone), myricetin 3-O-beta-D-glucopyranoside (flavonoid glycoside), (2S)-Eriodictyol 7-O-(6''-O-galloyl)-beta-D-glucopyranoside, and 3,5,7,3',4',5'-hexahydroxy flavanone-3-O-beta-D-glucopyranoside (flavonone glycosides), and other phytochemicals such as, amaranthin, methyl rosmarinate, and calceolarioside B (carbohydrate) had higher docking score and binding energies to receptor-binding site of SARS-CoV-2 3CL$_{pro}$ in compare to the control compounds (ul Qamar et al., 2020). In another study, in order to find a potent FDA-approved drug to inhibit COVID-19 M$_{pro}$, 19 potent inhibitors were selected from the library of numbers of plant based compounds and results of MolDock analysis of these compounds against COVID-19 Major Protease (6LU7) (Table. 1) showed that phenolic phytochemicals such as aloe-emodin, rhein, withaferin A, enoxacin, and non-phenolics such as withanolide D a naturally occurring steroid, nelfinavir, are considerably suitable inhibitors against COVID-19 M$_{pro}$. Results indicated that the binding affinity for nelfinavir, withanolide D and withaferin A were -8.4, -7.8 and -7.7 kcal/mol, respectively and these compounds can be used as potential inhibitors against COVID-19 M$_{pro}$, which can be further explored to test against Coronavirus (COVID-19) in pre-clinical and clinical settings (Chandel et al., 2020). There are also some recent *in silico* studies about the developing a drug for COVID-19 treatment. In one *in silico* study MolDocking was performed to study 10 potential naturally occurring flavonoids and nonflavonoid compounds against the SARS-CoV-2 S protein and also the results were compared

with hydroxychloroquine (HCQ) which is an approved drug by FDA. Docking analysis showed that C- terminal of S1 and S2 domain of the S protein play a key role in binding with these natural compounds. Pterostilbene, kamferol, curcumin, which are phenolic compounds, and HCQ were shown to bind to the C-terminal of S1 domain and the binding energies were -6.7, -7.4, -7.1, and -5.6 Kcal/mol, respectively. On the other hand the compounds which could bind to the S2 domain of spike protein were resveratrol, apigenin, isorhamnetin, fisetin, quercetin, genistein, luteolin, and their binding energies were -7.9, -7.7, -8.3, -8.5, -8.5, -8.2, and -8.2, Kcal/mol, respectively. These phenolic compounds were shown to have considerably high binding affinity for S1 and S2 domain of the S protein which are two main important target domains for virus attachment in the host cell and their binding affinities were significantly higher than that of HCQ (Subhash Rane et al., 2020). In another study 15 natural phenolic compounds with antiviral activity was docked with nCov-2019 M_{pro}. Lopinavir, nelfinavir, and ritonavir were used as positive controls which have been stated to treat the nCov-2019 patients. MolDock score results showed the potentials of these compounds. Bavachinin had the highest docking score with binding energy of -7.74+/-0.152 Kcal/mol. The next compound with higher docking score (7.68 ± 0.021 Kcal/mol) was kaempferol followed by luteolin with docking score of -7.58 ± 0.112 Kcal/mol, hinokinin with docking score of -7.51 ± 0.021 and sinigrin with docking score of -7.49 ± 0.152 Kcal/mol. Nelfinavir which was used as a positive control had higher docking score (-7.9 ± 0.057 Kcal/mol), than bavachinin. The docking score of the two other positive controls (Lopinavir and Ritonavir) were lower than bavachinin and kaempferol being -7.52 ± 0.022 Kcal/mol, and -7.42 ± 0.68 Kcal/mol, respectively (Table. 1) (Ranjan et al., 2020).

In a study a library of flavonoids were applied against SARS-CoV $3CL_{pro}$. Among these flavonoids herbacetin, pectolinarin, and rhoifolin could block the activity of SARS-CoV $3CL_{pro}$,

effectively. Docking analysis showed that there are three sites for binding with flavonoids such as S1, S2 and S3´ sites. Among the flavonoids, herbacetin (a flavonol), and rhoifolin and pectolinarin (flavones) were found to have noticeable inhibitory activity. The IC50 values of these compounds were 33.17, 27.45 and 37.78 µM, respectively. Induce-fit docking were done for these compounds and glide scores results for herbacetin, rhoifolin, and pectolinarin were -9.263, -9.565 and -8.054, respectively. Herbacetin had high binding affinity around the S1 and S2 sites and this was found to be due to the presence of additional 8- hydroxyl group. Moreover, carbohydrate groups present in rhoifolin and pectolinarin compounds were found to occupy the S1 and S2 sites and this was shown to be another cause of high affinity of these glycosylated flavonoids to SARS-CoV 3CL$_{pro}$ (Jo et al., 2020).

4. Alkaloids

Plants produce around 12,000 alkaloids, which can be classified into different groups based on the structures of their carbon skeletal. There are several studies about the antiviral activity of different alkaloids (Özçelik et al., 2011; Peng et al., 2013; Moradi et al., 2017).

In a study researchers aimed to study the antiviral activities of alkaloids such as tetrandrine (TET), fangchinoline (FAN), and cepharanthine (CEP) against HCoV-OC43. These compounds considerably inhibited cell death caused by the virus at the early phases of infection. They had a considerable effect on suppressing the replication of HCoV-OC43 and also they are able to inhibit the viral S and N protein expression (Kim et al., 2019).

Emotin is one of the major alkaloids that is found in ipecacuanha or ipecac root. In other study emetin, was studied to cure COVID-19. Among 290 anti-MERS and anti-SARS agents, emetine had stated to have the lowest half-maximal effective concentration (EC50). Also, it was stated

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that due to the lower EC50s of emetine against coronaviruses, in compare to *Entamoeba histolytica*, it can be considered as an anti-coronavirus agent. Investigations about emetine indicated that this compound can reach therapeutic concentrations inside the lungs so ipecac, emetine, and other analogues can be considered as possible treatment options, especially if *in vitro* studies approve viral sensitivity (Bleasel et al., 2020).

Mongolia, is a traditional Mongolian medicine generally used for treating tumor and cancer. Main compounds in *Agsirga* are alkaloids, organic acids, stilbenes, flavonoids saponins , etc, and among these compounds steroidal alkaloids are the major active components. Molecular docking technology results showed that these compounds have the ability to block the binding between S-protein of 2019-nCoV and middle bridge, namely D30, H34 of ACE2 protein (Table. 1). This research provided a theoretical and methodological reference for future researches about using Mongolian medicine for 2019-nCoV treatment (Cheng et al., 2020).

In a study it was indicated that tryptanthrin (a plant alkaloid) which is among the major active compounds in *S. cusia* leaf is able to inhibit HCoV-NL63 replication independently. Findings showed that tryptanthrin has a greater antiviral activity against HCoV-NL63 in compare to indigodole B which has an extra ethyl moiety at C5a in the place of double bond in tryptanthrin. In addition, in particular, tryptanthrin changes the antigenic configuration of viral S proteins and in this way it inhibits the PLP2's cleavage activity (with IC50 of less than 0.1 μM). Therefore, tryptanthrin can be used as one of the successful compounds against human coronaviruses. Notably, tryptanthrin and indigodole B demonstrated strong virucidal activity with IC50 of 0.06 μM and 2.09 μM, respectively (Tsai et al., 2020).

5. **Terpenoids**

Terpenoids, which are also called isoprenoids, are the most abundant natural products with various structures that are found in many plants and have a many pharmacological properties (Ludwiczuk et al., 2017).

In a cell-based study 20 phytocompounds were selected to investigate their inhibitory activity against 3Cl$_{pro}$ of SARS- CoV. Curcumin, betulinic acid, and savinin exhibited inhibitory activities on 3CL$_{pro}$ and their IC50 values were 40, 10, and 25, respectively. Contrarily, betulonic acid and hinokinin, analogues of betulinic acid and savinin, had IC50 values of more than 100 μM. Betulinic acid and savinin had competitive inhibitory activity on 3CL$_{pro}$ because of the multiple hydrogen bonds that they form with specific amino acid residues present at the active site of the enzyme (Wen et al., 2007). In other study the activity of 23 compounds from the ethanolic extract of *E. neriifolia* leaves, were studied against HCoV. Among these compounds, 22 of them were triterpenoids and one of them was flavonoid glycoside. of these compounds, 3β-Friedelanol exhibited stronger antiviral activity in compare to actinomycin D which was the positive control, and this suggests the significance of the friedelane skeleton as a possible stage for evolving new anti-HCoV-229E drugs (Chang et al., 2012). In an *in silico* study, a library of plant based compounds with antiviral activity was studied for their activity against S glycoprotein 6vsb and M$_{pro}$ 6lu7 targets of SARS-CoV-2 with the PyRX software. Six top compounds such as scopadulcic acid (a diterpenoid), dammarenolic acid (a triterpenoid), baicalin, sylibinin or silymarin (a flavonolignan), solanidin (steroidal glycoalkaloid), naringenin, oleanane with binding energies between -9 to -9.6 Kcal/mol were selected for molecular docking analyses against 6lu7. Generally, the two diterpenoid and triterpenoid compounds, scopadulcic acid and dammarenolic acid exhibited the strongest activity against SARS-CoV-2 S glycoprotein

6vsb and M_{pro} 6lu7 targets, respectively, followed by solanidin and sylibinin (Table. 1) (Ubani et al., 2020).

Resveratrol which is a stilbene and belong to phenolic compounds family, was studied for its activity against MERS-CoV and was shown to be effective at both entry and post entry step of infection. Their investigations demonstrated that resveratrol is able to inhibit nucleocapsid expression of MERS-CoV also it can reduce the vero E6 cell death as a result of MERS-CoV infection at concentration range from 125–250 µM. Moreover, this compound could reduce the MERS-CoV RNA expression and it can suppress this RNA replication, however for this purpose high concentrations of resveratrol is required. Generally, the could firmly confirm resveratrols' anti-MERS activity (Lin et al., 2017).

6. Saponins and saikosaponins

Glycyrrhizin is another phytochemical belong to saponins, which is derived from Chinese Medicine herb licorice root (*Glycyrrhiza radix*). Glycyrrhizin was shown to be a good treatment for SARS by influencing the viral adsorption and penetration before (Cinatl et al., 2003). In other study docking results demonstrated that glycyrrhizin has the potential to bind to ACE2 with binding energy of -9 kcal/mol, and the binding sites were ARG-559, GLN-388, ARG-393, ASP-30. It was shown that this phytochemical might be a potential candidate to have anti-2019-nCoV activity (Chen and Du, 2020). In a study 15 derivatives of glycyrrhizin were studied for their anti-SARS effect and was found that presence of 2-acetamido-β-D-glucopyranosylamine in the glycoside chain of glycyrrhizin cause a 10-fold increase in anti-SARS-CoV activity in compare to glycyrrhizin with EC50 of 40 ± 13 µM. Glycyrrhizin amides and conjugates of it with two of

the amino acid residues and a free 30-COOH had caused up to 70-fold increase in its anti-SARS-CoV activity with EC50 of 5 to 50 µM but also increased its cytotoxicity (Hoever et al., 2005).

Saikosaponins A, B2, C and D which are saponin glycosides were also studied for their anti-SARS-CoV effect. Results displayed that all of the examined compounds showed antiviral activity at concentrations of 0.25–25 µmol/L, and saikosaponin B2 had the highest inhibitory activity with IC50 of 1.7 ± 0.1 mmol/L. Moreover, it had inhibitory effect on viral penetration and attachment (Cheng et al., 2006).

7. Organosulfur Compounds

Garlic essential oil is very good source of organosulfur compounds which are known for their therapeutic properties. Also these compounds are expected to interact with ACE2 protein's amino acids. In a study, researchers investigated organosulfur compounds' effect against SARS-CoV-2. Results of MolDock study showed that allyl disulfide and allyl trisulfide which are the most abundant compounds in garlic essential oil, have the best binding affinity to the 6LU7 protein of SARS-Cov-2, followed by diallyl tetrasulfide. Trisulfide, 2-propenyl propyl and diallyl tetrasulfide was found to have the best interaction with ACE2 receptor. Moreover, organosulfur compounds in garlic showed stronger interaction with 6LU7. Generally, Results exhibited that the essential oil extracted from garlic is a precious natural antivirus source (Thuy et al., 2020).

8. Lectin

Lectins are proteins which can bind to carbohydrates to form glycoproteins. They can agglutinate cells and in this way lead to precipitation of glycoconjugates (Vasconcelos and Oliveira, 2004).

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In addition to this, they can make binds with carbohydrates, reversibly. Lectin proteins have been showed to make hydrophobic and hydrogen bonding and van der Waals interactions (Singh, et al., 1999). Lectines are not immunoglobulins and they do not change the functional properties of carbohydrates binded (Lagarda-Diaz et al., 2017).

Generally, lectins can be divided into seven different protein groups (Damme et al., 1998). It has been revealed that these compounds have strong effect on commonly known HIV replication in lymphocyte cell cultures (Hann, 1989). As a result of numerous research, it was revealed that, lectin proteins attack directly to the virus cell and prevent HIV fusion (Dudley et al., 2016). In addition HIV, it was reported that plant lectins have inhibitory effects on various virus species such as respiratory syncytial and influenza A virus infections which threat human health (Balzarini, 2007). Moreover, plant lectins were proved to have strong impact on SARS-CoV (Ritchie et al., 2010). Glycan binded lectin proteins have inhibitory effect on coronavirus infectivity. In the scope of wide reserach, 33 different plant lectins having diverse specificities were studied for their antiviral acitivity on SARS-CoV. According to the outcomes, two third of species had strong antiviral effect on SARS CoV (Keyaerts et al., 2007). Results also revealed that mannose specific lectin proteins have stronger antiviral effect on SARS-CoV (Mazalovska and Kouokam, 2018). In order to see the effect of mannospecific lectin, mannosespecific lectin of amaryllis (HHA) was used for further experiments. According to the results, it was observed that HHA added infections had one log reduced viral load in compare to the positive control. Furthermore, lectin led to 5 hours delay on SARS-CoV infected cell growth (Keyaerts et al., 2007).

Generally, replication of coronaviruses are prevented by plant based lectins within the cell culture (van der Meer et al., 2007). Specifically, mannose-based HHA, the GlcNAc-specific

agglutinin NICTABA, (GlcNAc)n-specific agglutinin, and Urtica dioica agglutinin (UDA) are found as potential coronavirus inhibitors as a result of *in-vitro* studies (Barnard and Kumaki, 2011).

Griffithsin (GRFT), a specific type of lectin obtained from *Griffithsia sp*., has the ability to decrease viral infections in humans. It can act as strong inhibitor of SARS-CoV infection (O'Keefe et al., 2010). GRFT prevent the entrance of genetic information to the host cell and spike protein function. Therefore, it blocks coronavirus infection at the initial stage (Carr et al., 2016). It was reported that GRFT have also significant functional effect on MERS-CoV. However, GRFT inhibited viral function during entry to the cell (Zaki et al., 2012). Another patient study was performed to see the antiviral effect of mannose binding lectin (MBL) on SARS-CoV. Their investigations showed that MBL is able to bind to SARS-CoV, *in vitro*, in a dose- and calcium-dependent and also mannan-inhibitable manner, showing that carbohydrate identification domains of MBL are responsible for its binding. These findings signifies the potential role of MBL in defense against SARS-CoV infection by binding to the S protein of SARS-CoV before releasing of a particular antibody (Ip et al., 2005).

9. Herb extracts and essential Oils

Essential oils (EOs) have widely used for thrapeutic purposes due to their antiviral, antimicrobial and antifungal activities. Majorly, these secondary metabolites of aromatic herbs and plants show effective inhibition acitivities against viral infections. They are used to heal non-infectious and infectious diseases caused by bacteria and viruses (Mickymaray, 2019). Extraction of active secondary metabolites are achieved by using diverse techniques such as steam distillation, ultrasound or microwave methods, cold pressing or maceration (Chouhan, 2017). The main

phytochemical compounds of EOs can be given as monoterpenes, phenylpropanoids and oxygenated sesquiterpenes. They are widely used in pharmacological and medical fields (D'agostino, et al., 2019). Essential oils are known as volatile compounds which constitute secondary metabolites such as terpenes, aromatic compounds and oxygenated derivatives (Goodger et al., 2016). Essential oils have been accepted as plant-based antiviral molecules and used in prevention of some human infected viruses such as immunodeficiency virus, herpes simplex, hepatitis B (Cos et al., 2006; Schnitzler et al., 2008). According to study by Schuhmache et al., essential oils can distrupt the membrane of SARS-CoV due to their lipophilic nature or treat viral envelope proteins in the host cell (Schuhmache et al., 2003). Resylts of a study on the Peels of *Citrus sinensis* (Cs), *Anthemis hyalina* (Ah), and *Nigella sativa* (Ns) effect on coronavirus showed that TRP genes' expression is down-regulated, in the cells infected with CoV and also the cells which were treated with herb extracts. Moreover, the virus loads were decreased after extract treatments (Ulasli et al., 2013). Another study about the antiviral activity of essential oil from eucaliptus against coronavirus has been conducted by using eucalyptol (1,8 cineole) which is known as major component of eucalyptus oil. It has found that eucalyptol could be potential antiviral compound for COVID-19. Chemical structure of eucalyptol which is mainly composed of Hydroxy (-OH), ketone (=O) and ether groups (-O) are the responsible groups for inhibition of COVID-19 (Sharma, 2020). In an in vitro and in vivo study about the effect of a natural product including a synergistic blend of plant based oleoresins and essential oils in a liquid emulsion labeled as QR448(a) against IBV, it was shown that it was effective against IBV irrespective of serotype. The QR448(a)'s effect was more considerable on cell free based study. These results were important because they can be used for other enveloped respiratory viruses such as other coronaviruses (Jackwood et al., 2010). Also there are studies on

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the plant extracts from *Astragalus mongholicus, Houttuynia cordata*, *Alium sativum,* and *Sambucus nigra* which demonstrated that they are effective against both IBV coronavirus replication and amount of viruses before inhibition (Mohajer Shojai et al., 2016; Chen et al., 2014; Zhang et al., 2018; Yin et al., 2011). *Houttuynia cordata* had demonstrated to have anti-murine coronavirus effect with IC50 of 0.98 µg/mL (Chiow et al., 2016). Moreover, it was shown that it has inhibitory activity on 3CL$_{pro}$ of SARS-CoV (Lau et al., 2008). In addition, extracts of *Satureja (S.) montana, Origanum (O.) vulgare, Mentha (M.) piperita, Melissa (M.) officinalis, Thymus (T.) vulgaris, Hyssopus (H.) officinalis, Salvia (S.) officinalis* and *Desmodium (D.) canadense* have been discovered as natural antiviral against several IBV coronavirus. However, *M. piperita, T. vulgaris and D. canadense* extracts had strogenst antiviral effect. EC50 of the extracts were reported between 0.003 and 0.0076 µg (Lelešius et al., 2019). In another *in silico* study The present *in silico* study molecular docking studies was conducted to determine the effect of Jensenone which is compound in essential oil from eucalyptus oil, on COVID-19 M$_{pro}$. Results showed that, Jensenone can make complexes with M$_{pro}$ through hydrophobic, hydrogen bond, and strong ionic interactions. Based on the dock score results, these complexes have 4 different poses with docking scores ranging from -4.8 to -5.5, and the one with highest negative values indicated maximum binding affinity (Table.1). Thus, this compound may be a possible treatment to COVID-19 (Sharma and Kaur, 2020). In a study by Kim et al., medicinal extracts of*, Meliae cortex, Coptidis rhizoma, Sophora subprostrata radix, Phellodendron cortex, Cimicifuga rhizoma* herbs, were investigated for their anti- MHV effect and *Torilis fructus, Sophorae radix, Acanthopanacis cortex* and, *Sanguisorbae radix* were selected as potential candidate to cure coronaviruses. EC50 values of these extracts were from 2.0 to 27.5 µ/ml (Kim et al., 2010). *Lycoris radiata, Artemisia annua, Pyrrosia lingua,* and *Lindera aggregate* were

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other herbal extracts studied for their anti-SARS-CoV effect with EC50 of 2.4 (± 0.2), 34.5 (± 2.6), 43.2 (± 14.1), and 88.2 (± 7.7) µ/ml, respectively. Also alkaloid isolated from *Lycoris radiata* (lycorine) had EC50 of 15.7 (± 1.2) nM, whereas commercial lycorine has EC50 of 48.8 (± 3.6) nM (Li et al., 2005).

10. Vitamins

Micronutrients and phytonutrients found in fruits and vegetables mainly vitamins (vitamin A,C and E) are responsible for immune functions (Calder et al., 2020). Recently, it has been revealed that vitamins are also effective options for COVID-19 infections (Conti et al., 2020). There are numerous micronutrients, mainly vitamin A, C, D and E which show antiviral properties against coronavirus. It might be sufficient to use these nutrients without any treatment or medical aid. However, these nutrients are needed to be focused, in order to prevent viral infections such as SARS-CoV-2 (Gasmi et al., 2020). A couple of studies and systematic reviews have showed that vitamin D can provide protection against SARS (Calder et al., 2020). Vitamin D has been accepted as an important tool to provide antiviral immunity and immunoregulatory defense (Gasmi et al., 2020). It has inhibitory mechanisms by reducing infection risk and death (Grant et al., 2020). It can help to protect important tight junctions such as gap junction and adherens junctions like E-cadherin (Schwalfenberg, 2011). Vitamin D increases cellular immunity by decreasing cytokine storm (Grant et al., 2020). Innate immune system induced cytokine storm, creates inflammatory and anti-inflammatory cytokines in COVID-19 cases. Therefore, there is a relation between vitamin D mechanism and immunity of patients (Huang et al., 2020). It has been also added that for people who are at risk of COVID-19, high concentrations of 25(OH)D such as 40-60 ng/ml (100-150 nmol/l) should be applied in order to get effective treatment

results (Grant et al., 2020). Furthermore, vitamin D might decrease production of anti-inflammatory Th1 cytokines like interferon and tumor necrosis (Sharifi et al., 2019). By introduction of vitamin D, expression of pro-inflammatory cytokines can be diminished and anti-inflammatory cytokines by macrophages can be enhanced (Gombart et al., 2020). Vitamin D is also effective on adaptive immunity (Cantorna, 2010). 1,25(OH)2D3 can inhibit the responses coming from T helper cell type 1 (Th1). Moreover, 1,25(OH)2D3 can slow down the activities of T regulatory cells, so inflammatory activities can be prevented (Jeffery et al., 2009).

Evidences of coronavirus inhibited effects of vitamin D can be emphasized by analyzing case-fatality rates based on age or disease comorbidity and lower concentrations of 25(OH)D (Gasmi et al., 2020). Moreover, studies have revealed that elderly people having vitamin D deficiency have required hospitalized treatment for diseases (Elliott et al., 2003). Vitamin A has been predicted to show effective antiviral properties. It has been approved that vitamin A deficient patients are more prone to viral infections including respiratory syncytial viruses (Mcgill et al., 2019). There is no exact proof that shows antiviral impact of vitamin A on coronavirus. However, it has been verified that vitamin A has immune supporting roles such as cytokine expression, antibody production, cell killing like macrophages or monocytes (Jee et al., n.d.). Vitamin A is the first plant based vitamin which has three different forms within the body like, retinol, retinal and retinoic acid. Intake of vitamin A can provide protections against lung diseases, malaria, diarrheal disease and measles (Mantay, 2020). It has been accepted as anti-infective against various viral infections such as human immunodeficiency virus (HIV) (Zhang and Liu, 2020; Villamor et al., 2002). In addition, it has been reported that fat soluble vitamin A deficiency may result in higher susceptibility to coronaviruses such as bovine coronavirus or bronchitis coronavirus (IBV). It has been detected that vitamin A deficient chicken fed diet

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results in coronavirus infection in chickens (Mcgill et al., 2019). Vitamin A inhibited measles replication of innate immune system. Additionally, uninfected bystander cells were made immune against coronavirus infection. Therefore, it has been approved that vitamin A can be used as treatment method for novel coronavirus (COVID-19) (Zhang and Liu, 2020). Water soluble vitamin B which is known as part of coenzymes are also effective on coronaviruses. Specifically, vitamin B2 (riboflavin) is essential for energy metabolism of cells (Powers, 2003). It had been reported that vitamin B2 may decrease the titer of MERS-CoV within human plasma (Keil et al., 2016). Moreover, vitamin B3 (nicotinamide) might be used as a treatment for ventilator induced lung injuries by inhibiting the neutrophil infiltration of the lungs, but conversely it can cause hypoxemia (Jones et al., 2015). Generally, it has been approved that vitamin B groups can be selected as a supporting treatment for COVID-19 and deficiencies in this vitamin can cause weakness in human's immune system (Zhang and Liu, 2020).

Moreover, it has been found that vitamin C may also be used as treatment for respiratory diseases (Hemilä, 2017). Ascorbic acid (water soluble vitamin C) plays a vital role in collagen synthesis and it is accepted as natural antioxidant. It is also known as protector against respiratory infections such as coronavirus (Hemilä, 2003). It has been reported that vitamin C had the effect to enhance resistance of chick embryo tracheal organ cultures against coronavirus infection (Atherton et al., 1978). Furthermore, trials on humans have been revealed that vitamin C usage has declined respiratory tract infections. Therefore, it can be deduced that vitamin C may decrease respiratory tract symptoms in recent COVID-19 infection (Zhang and Liu, 2020). Fat soluble vitamin E containing tocopherols and tocotrienols also has significant effect to decrease oxidative stress by binding to free radicals due to its antioxidant property (Galmés et al., 2018). It has been reported that vitamin E deficiency might lead to myocardial injuries

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caused by RNA viruses (Beck and Suppl, 1997). It can be deduced that vitamins can be additional supplements alternatives due to their immune supporting roles and can be used to decrease risk of coronavirus infections (Grant et al., 2020).

11. Nicotianamine

Nicotianamine (a Fe chelator in plants) which is rich in soybean was investigated for its inhibitory effect on ACE2 and was shown to inhibit the ACE2 activity, with IC50 value of 84 nM (Takahashi et al., 2015). Molecular docking of nicotianamine was conducted to determine its affinity to ACE2 enzyme, it was shown that binding energy of nicotianamine to ACE2 is -5.1 kcal/mol (Chen and Du. 2020).

Table 1. Docking score, binding energy and IC50 of plant metabolite against coronaviruses

Compounds	Activity	IC50 (µM)	Docking Score and binding energy (Kcal mol⁻¹)	Ref
AMPLS	Binding to the SARS-CoV 3CL^{pro}	364 ± 8.7	-9.9	Nguyen et al., 2012
EGCG	Binding to the SARS-CoV 3CL^{pro}	73 ± 2	-11.7	Nguyen et al., 2012
GCG	Binding to the SARS-CoV 3CL^{pro}	47 ± 0.9	-14.1	Nguyen et al., 2012
Diadzein	Binding to the SARS-CoV 3CL^{pro}	351 ± 2.9	-8.6	Nguyen et al., 2012
Puerarin	Binding to the SARS-CoV 3CL^{pro}	381 ± 12.5	-11.3	Nguyen et al., 2012
Quercetin	Binding to the SARS-CoV 3CL^{pro}	73 ± 4	-10.2	Nguyen et al., 2012
EGC	Binding to the SARS-CoV 3CL^{pro}	-	-9.3	Nguyen et al., 2012
Hesperidin	Binding to the PDB ID: 6LU7 of COVID 19	-	-178.5910	Adem et al., 2020
Diosmin	Binding to the PDB ID: 6LU7 of COVID 19	-	-174.1260	Adem et al., 2020
Apiin	Binding to the PDB ID: 6LU7 of COVID 19	-	-171.0080	Adem et al., 2020
Diacetylcurcumin	Binding to the PDB ID: 6LU7 of COVID 19	-	-169.2550	Adem et al., 2020
Rutin	Binding to the PDB ID: 6LU7 of COVID 19	-	-176.2740	Adem et al., 2020
Hesperidin	Binding to ACE2 receptor of COVID 19	-	-4.21	Cheng et al., 2020
Naringenin	Binding to ACE2 receptor of COVID 19	-	-6.05	Cheng et al., 2020
Naringin	Binding to ACE2 receptor of COVID 19	-	-6.85	Cheng et al., 2020
Hesperetin	Binding to ACE2 receptor of COVID 19	-	-6.09	Cheng et al., 2020
Neohesperidin	Binding to ACE2 receptor of COVID 19	-	-3.78	Cheng et al., 2020
Nobiletin	Binding to ACE2 receptor of COVID 19	-	-5.42	Cheng et al., 2020
Baicalein	Binding to ACE2 receptor of COVID 19	-	-4.70	Cheng et al., 2020
Chloroquine	Binding to ACE2 receptor of COVID 19	-	-5.70	Cheng et al., 2020
Emodin	Binding to ACE2 receptor of SARS-CoV	200	-	Ho et al., 2006
Promazine	Binding to ACE2 receptor of SARS-CoV	-	-	Ho et al., 2006
Rhein	Binding to ACE2 receptor of SARS-CoV	-	-	Ho et al., 2006
Chrysin	Binding to ACE2 receptor of SARS-CoV	-	-	Ho et al., 2006
Aloeemodin	Binding to the 3CL^{pro} of SARS-CoV	132	-	Lin et al., 2005
Hesperetin	Binding to the 3CL^{pro} of SARS-CoV	60	-	Lin et al., 2005

Diadzein	Binding to the 3CL^{pro} of SARS-CoV	105		-	Lin et al., 2005
Baicalein	Binding to ATPase domain of nsP13 of SARS-CoV	0.47 ± 0.09		-	Keum et al., 2013
Scutellarein	Binding to ATPase domain of nsP13 of SARS-CoV	2.71 ± 0.19		-	Keum et al., 2013
Myricetin	Binding to ATPase domain of nsP13 of SARS-CoV	0.86 ± 0.48		-	Keum et al., 2013
Broussochalcone B	Binding to PL$_{pro}$ and 3CL$_{pro}$ of SARS-CoV	**3CL$_{pro}$** 57.8 ± 0.5	**PL$_{pro}$** 11.6 ± 0.7	-	Park et al., 2017
Broussochalcone A	Binding to PL$_{pro}$ and 3CL$_{pro}$ of SARS-CoV	88.1 ± 13.0	9.2 ± 1.5	-	Park et al., 2017
4-hydroxyisolonchocarpin	Binding to PL$_{pro}$ and 3CL$_{pro}$ of SARS-CoV	202.7 ± 3.9	35.4 ± 11.3	-	Park et al., 2017
Papyriflavonol A	Binding to PL$_{pro}$ and 3CL$_{pro}$ of SARS-CoV	103.6 ± 17.4	3.7 ± 1.6	-	Park et al., 2017
30-(3-methylbut-2-enyl)-30,4,7-trihydroxyflavane	Binding to PL$_{pro}$ and 3CL$_{pro}$ of SARS-CoV	30.2 ± 6.8	35.8 ± 6.7	-	Park et al., 2017
Kazinol A	Binding to PL$_{pro}$ and 3CL$_{pro}$ of SARS-CoV	84.8 ± 10.4	66.2 ± 6.8	-	Park et al., 2017
Kazinol B	Binding to PL$_{pro}$ and 3CL$_{pro}$ of SARS-CoV	233.3 ± 6.7	31.4 ± 2.9	-	Park et al., 2017
Broussoflavan A	Binding to PL$_{pro}$ and 3CL$_{pro}$ of SARS-CoV	92.4 ± 2.1	30.4 ± 5.5	-	Park et al., 2017
Kazinol F	Binding to PL$_{pro}$ and 3CL$_{pro}$ of SARS-CoV	43.3 ± 10.4	27.8 ± 2.5	-	Park et al., 2017
Kazinol J	Binding to PL$_{pro}$ and 3CL$_{pro}$ of SARS-CoV	64.2 ± 1.7	15.2 ± 1.6	-	Park et al., 2017
Isoliquiritigenin	Binding to PL$_{pro}$ and 3CL$_{pro}$ of SARS-CoV	61.9 ± 11.0	24.6 ± 1.0	-	Park et al., 2017
Kaempferol	Binding to PL$_{pro}$ and 3CL$_{pro}$ of SARS-CoV	116.3 ± 7.1	16.3 ± 2.1	-	Park et al., 2017
Quercetin	Binding to PL$_{pro}$ and 3CL$_{pro}$ of SARS-CoV	52.7 ± 4.1	8.6 ± 3.2	-	Park et al., 2016
Quercetin-β-galactoside	Binding to PL$_{pro}$ and 3CL$_{pro}$ of SARS-CoV	128.8 ± 4.5	51.9 ± 5.5	-	Park et al., 2017
Quercetin-3-β-galactoside	Binding to the SARS-CoV 3CL$_{pro}$	42.79 ± 4.97		-	Chen et al., 2006
Quercetin-3-β-galactoside	Binding to the SARS-CoV 3CLpro Q189A	127.89 ± 10.06		-	Chen et al., 2006
Amentoflavone	Binding to the 3CL$_{pro}$ of SARS-CoV	8.3 ± 1.2		-	Ryu et al., 2010
Bilobetin	Binding to the 3CL$_{pro}$ of SARS-CoV	72.3 ± 4.5		-	Ryu et al., 2010
Ginkgetin	Binding to the 3CL$_{pro}$ of SARS-CoV	32.0 ± 1.7		-	Ryu et al., 2010
Sciadopitysin	Binding to the 3CL$_{pro}$ of SARS-CoV	38.4 ± 0.2		-	Ryu et al., 2010
18-hydroxyferruginol	Binding to the 3CL$_{pro}$ of SARS-CoV	220.8 ± 10.4		-	Ryu et al., 2010
Hinokiol	Binding to the 3CL$_{pro}$ of SARS-CoV	233.4 ± 22.2		-	Ryu et al., 2010
Ferruginol	Binding to the 3CL$_{pro}$ of SARS-CoV	49.6 ± 1.5		-	Ryu et al., 2010
18-oxofer-ruginol	Binding to the 3CL$_{pro}$ of SARS-CoV	163.2 ± 13.8		-	Ryu et al., 2010

O-acetyl-18-hydroxyferruginol	Binding to the 3CL$_{pro}$ of SARS-CoV	128.9 ± 25.2	-	Ryu et al., 2010
Methyl dehydroabi- etate	Binding to the 3CL$_{pro}$ of SARS-CoV	207.0 ± 14.3	-	Ryu et al., 2010
Isopimaric acid	Binding to the 3CL$_{pro}$ of SARS-CoV	283.5 ± 18.4	-	Ryu et al., 2010
Kayadiol	Binding to the 3CL$_{pro}$ of SARS-CoV	137.7 ± 12.5	-	Ryu et al., 2010
Diallyl Disulfide	Inhibiting COVID_19 protease	-	-52	Mohammadi et al., 2020
Curcumin	Inhibiting COVID_19 protease	-	-127	Mohammadi et al., 2020
Capsaicin	Inhibiting COVID_19 protease	-	-107	Mohammadi et al., 2020
Limonene	Inhibiting COVID_19 protease	-	-54	Mohammadi et al., 2020
Thymol	Inhibiting COVID_19 protease	-	-55	Mohammadi et al., 2020
Coumarin	Inhibiting COVID_19 protease	-	-57	Mohammadi et al., 2020
Verbascoside	Inhibiting COVID_19 protease	-	-95	Mohammadi et al., 2020
glucuronic acid	Inhibiting COVID_19 protease	-	-64	Mohammadi et al., 2020
Diosmin	Binding to the active sites of SARS-CoV-2 3CLpro model	-	-10	Chen et al 2020
Hesperidin	Binding to the active sites of SARS-CoV-2 3CLpro model	-	-10	Chen et al 2020
3-Isotheaflavin-3-gallate (TF2B)	Binding to the 3CL$_{pro}$ of SARS-CoV	7	-	Chen et al., 2005
Tannic acid	Binding to the 3CL$_{pro}$ of SARS-CoV	3	-	Chen et al., 2005
Oolong tea extract	Binding to the 3CL$_{pro}$ of SARS-CoV	125	-	Chen et al., 2005
Green tea extract	Binding to the 3CL$_{pro}$ of SARS-CoV	70	-	Chen et al., 2005
Black tea extract	Binding to the 3CL$_{pro}$ of SARS-CoV	25	-	Chen et al., 2005
Puer tea extract	Binding to the 3CL$_{pro}$ of SARS-CoV	100	-	Chen et al., 2005
Caffeine	Binding to the 3CL$_{pro}$ of SARS-CoV	100	-	Chen et al., 2005
Theophylline	Binding to the 3CL$_{pro}$ of SARS-CoV	100	-	Chen et al., 2005
Catechin (C)	Binding to the 3CL$_{pro}$ of SARS-CoV	100	-	Chen et al., 2005

Epigallocatechin (EGC)	Binding to the 3CL$_{pro}$ of SARS-CoV	100	-	Chen et al., 2005
Epigallocatechin gallte (EGCg)	Binding to the 3CL$_{pro}$ of SARS-CoV	100	-	Chen et al., 2005
Epicatechin (EC)	Binding to the 3CL$_{pro}$ of SARS-CoV	100	-	Chen et al., 2005
Epicatechin gallate (ECg)	Binding to the 3CL$_{pro}$ of SARS-CoV	100	-	Chen et al., 2005
Theaflavin (TF1)	Binding to the 3CL$_{pro}$ of SARS-CoV	56	-	Chen et al., 2005
Theaflavin-3-gallate, TF-2a and Theaflavin-3´-gallate, TF-2b mixture (TF2)	Binding to the 3CL$_{pro}$ of SARS-CoV	43	-	Chen et al., 2005
Theaflavin-3,3´-digallate (TF3)	Binding to the 3CL$_{pro}$ of SARS-CoV	9.5	-	Chen et al., 2005
Isobavachalcone	Binding to the 3CL$_{pro}$ and PL$_{pro}$ of SARS-CoV	**3CL$_{pro}$** 39.4 ± 5.2	**PL$_{pro}$** 13.0 ± 0.9	-	Park et al., 2015
4-hydroxyderricin	Binding to the 3CL$_{pro}$ and PL$_{pro}$ of SARS-CoV	81.4 ± 8.5	26.0 ± 1.5	-	Park et al., 2015
Xanthoangelol	Binding to the 3CL$_{pro}$ and PL$_{pro}$ of SARS-CoV	38.4 ± 3.9	11.7 ± 3.2	-	Park et al., 2015
Xanthoangelol F	Binding to the 3CL$_{pro}$ and PL$_{pro}$ of SARS-CoV	34.1 ± 4.8	5.6 ± 0.5	-	Park et al., 2015
Xanthoangelol D	Binding to the 3CL$_{pro}$ and PL$_{pro}$ of SARS-CoV	26.6 ± 5.2	19.3 ± 1.8	-	Park et al., 2015
Xanthoangelol E	Binding to the 3CL$_{pro}$ and PL$_{pro}$ of SARS-CoV	11.4 ± 1.4	1.2 ± 0.4	-	Park et al., 2015
Xanthoangelol B	Binding to the 3CL$_{pro}$ and PL$_{pro}$ of SARS-CoV	22.2 ± 6.5	11.7 ± 0.3	-	Park et al., 2015
Xanthoangelol G	Binding to the 3CL$_{pro}$ and PL$_{pro}$ of SARS-CoV	129.8 ± 1.3	46.4 ± 7.8	-	Park et al., 2015
Xanthokeistal A	Binding to the 3CL$_{pro}$ and PL$_{pro}$ of SARS-CoV	44.1 ± 1.3	21.1 ± 5.6	-	Park et al., 2015
Betulonic acid	Binding to the 3CLpro of SARS-CoV	10	-	Wen et al., 2007
Betulinic acid	Binding to the 3CLpro of SARS-CoV	>100	-	Wen et al., 2007
Hinokinin	Binding to the 3CLpro of SARS-CoV	>100	-	Wen et al., 2007
Savinin	Binding to the 3CLpro of SARS-CoV	25	-	Wen et al., 2007
Curcumin	Binding to the 3CLpro of SARS-CoV	40	-	Wen et al., 2007

Tetrandrine	Supressing HCoV-OC43 replication and viral S and N protein expression	0.33 ± 0.03	-	Kim et al., 2019
Fangchinoline	Supressing HCoV-OC43 replication and viral S and N protein expression	1.01± 0.07	-	Kim et al., 2019
Ceparanthine	Supressing HCoV-OC43 replication and viral S and N protein expression	1.01± 0.07	-	Kim et al., 2019
Emetine	MERS-CoV replication inhibitor	0.01	-	Bleasel and Peterson, 2020
Hupehemonside	Binding to ACE2 receptor of 2019- nCoV	-	-7.1	Cheng J. et al., 2020
Imperialine-3-β-D-glucoside	Binding to ACE2 receptor of 2019- nCoV	-	-7.1	Cheng J. et al., 2020
Pseudojervine	Binding to ACE2 receptor of 2019- nCoV	-	-6.8	Cheng J. et al., 2020
Zhebeininoside	Binding to ACE2 receptor of 2019- nCoV	-	-6.8	Cheng J. et al., 2020
Veratroylzygadenine	Binding to ACE2 receptor of 2019- nCoV	-	-6.8	Cheng J. et al., 2020
Zhebeinone-3-β-D-glucoside	Binding to ACE2 receptor of 2019- nCoV	-	-6.7	Cheng J. et al., 2020
Mulberroside E	Binding to ACE2 receptor of 2019- nCoV	-	-6.7	Cheng J. et al., 2020
Hupehenisine	Binding to ACE2 receptor of 2019- nCoV	-	-6.6	Cheng J. et al., 2020
Verdine	Binding to ACE2 receptor of 2019- nCoV	-	-6.6	Cheng J. et al., 2020
Verticinone-3-β-D-glucoside	Binding to ACE2 receptor of 2019- nCoV	-	-6.6	Cheng J. et al., 2020
(E)-Resveratrol 3,5-O-β-diglucoside	Binding to ACE2 receptor of 2019- nCoV	-	-6.6	Cheng J. et al., 2020
Peimisine	Binding to ACE2 receptor of 2019- nCoV	-	-6.4	Cheng J. et al., 2020
15-O-(2-Methylbutanoyl)-3- O-veratroylprotoverine	Binding to ACE2 receptor of 2019- nCoV	-	-6.4	Cheng J. et al., 2020
3-Acetylzygadenine	Binding to ACE2 receptor of 2019- nCoV	-	-6.4	Cheng J. et al.,

				2020
Polydatin IV	Binding to ACE2 receptor of 2019- nCoV	-	-6.4	Cheng J. et al., 2020
Piceatannol 3,4'-di-β-D-glucopyranoside	Binding to ACE2 receptor of 2019- nCoV	-	-6.4	Cheng J. et al., 2020
Puqietinone	Binding to ACE2 receptor of 2019- nCoV	-	-6.3	Cheng J. et al., 2020
Indigodole B	Blocking the PLP 2 activity of HCoV NL63	2.09 ± 0.89	-	Tsai et al., 2020
Tryptantrin	Blocking the PLP 2 activity of HCoV NL63	0.06 ± 0.04	-	Tsai et al., 2020
Glycyrrhizin	Binding to ACE2 receptor of 2019-nCoV	-	-9	Chen and Hudson , 2020
Hesperetin	Binding to ACE2 receptor of 2019-nCoV	-	-8.3	Chen and Hudson , 2020
Scutellarin	Binding to ACE2 receptor 2019-nCoV	-	-14.9	Chen and Hudson , 2020

			6LU7	Spike	ACE2	
Curcumin	Binding to Protease Domain (6LU7) ,Spike Glycoprotein, and RBD-ACE2 (6LXT) (6VW1) of SARS-CoV-2	-	-11.82	-8.39	-9.04	Utomo et al., 2020
Desmethylcurcumin (DMC)	Binding to Protease Domain (6LU7) ,Spike Glycoprotein, and RBD-ACE2 (6LXT) (6VW1) of SARS-CoV-2	-	-11.21	-6.41	-8.04	Utomo et al., 2020
BDMC (Bisdesmethylcurcumin)	Binding to Protease Domain (6LU7) ,Spike Glycoprotein, and RBD-ACE2 (6LXT) (6VW1) of SARS-CoV-2	-	-11.51	-8.64	-7.48	Utomo et al., 2020
Tangeretin	Binding to Protease Domain (6LU7) ,Spike Glycoprotein, and RBD-ACE2 (6LXT) (6VW1) of SARS-CoV-2	-	-10.55	-8.18	-6.51	Utomo et al., 2020
Hesperetin	Binding to Protease Domain (6LU7) ,Spike Glycoprotein, and RBD-ACE2 (6LXT) (6VW1) of SARS-CoV-2	-	-12.36	-9.08	-6.71	Utomo et al., 2020
Hesperidin	Binding to Protease Domain (6LU7) ,Spike Glycoprotein, and RBD-ACE2 (6LXT) (6VW1) of SARS-CoV-2	-	-13.51	-9.61	-9.50	Utomo et al., 2020
Nobiletin	Binding to Protease Domain (6LU7) ,Spike Glycoprotein, and RBD-ACE2 (6LXT)	-	-10.38	-7.76	-7.88	Utomo et al., 2020

Compound	Target					Reference
	(6VW1) of SARS-CoV-2					
Naringenin	Binding to Protease Domain (6LU7) ,Spike Glycoprotein, and RBD-ACE2 (6LXT) (6VW1) of SARS-CoV-2	-	-12.44	-7.40	-7.69	Utomo et al., 2020
Brazilein	Binding to Protease Domain (6LU7) ,Spike Glycoprotein, and RBD-ACE2 (6LXT) (6VW1) of SARS-CoV-2	-	-10.52	-7.56	-7.43	Utomo et al., 2020
Brazilin	Binding to Protease Domain (6LU7) ,Spike Glycoprotein, and RBD-ACE2 (6LXT) (6VW1) of SARS-CoV-2	-	-12.36	-7.50	-7.49	Utomo et al., 2020
Galangin	Binding to Protease Domain (6LU7) ,Spike Glycoprotein, and RBD-ACE2 (6LXT) (6VW1) of SARS-CoV-2	-	-12.96	-7.89	-7.60	Utomo et al., 2020
Aceto Cavicol Acetate (ACA)	Binding to Protease Domain (6LU7) ,Spike Glycoprotein, and RBD-ACE2 (6LXT) (6VW1) of SARS-CoV-2	-	-9.94	-6.05	-6.16	Utomo et al., 2020
Kaempferol	Binding to the 3CL$_{pro}$-6LU7 SARS-CoV-2	-		-8.58		Khaerunnisa et al., 2020
Quercetin	Binding to the 3CL$_{pro}$-6LU7 SARS-CoV-2	-		-8.47		Khaerunnisa et al., 2020
Luteolin-7- glucoside	Binding to the 3CL$_{pro}$-6LU7 SARS-CoV-2	-		-8.17		Khaerunnisa et al., 2020
Demetoxycurcumine	Binding to the 3CL$_{pro}$-6LU7 SARS-CoV-2	-		-7.99		Khaerunnisa et al., 2020
Naringenin	Binding to the 3CL$_{pro}$-6LU7 SARS-CoV-2	-		-7.89		Khaerunnisa et al., 2020
Apigenine-7- glucoside	Binding to the 3CL$_{pro}$-6LU7 SARS-CoV-2	-		-7.83		Khaerunnisa et al., 2020
Oleuropein	Binding to the 3CL$_{pro}$-6LU7 SARS-CoV-2	-		-7.31		Khaerunnisa et al., 2020
Catechin	Binding to the 3CL$_{pro}$-6LU7 SARS-CoV-2	-		-7.24		Khaerunnisa et al., 2020
Curcumin	Binding to the 3CL$_{pro}$-6LU7 SARS-CoV-2	-		-7.05		Khaerunnisa et al., 2020
Epicatechin-gallate	Binding to the 3CL$_{pro}$-6LU7 SARS-CoV-2	-		-6.67		Khaerunnisa et al.,

				2020
Zingerol	Binding to the 3CL$_{pro}$-6LU7 SARS-CoV-2	-	-5.40	Khaerunnisa et al., 2020
Gingerol	Binding to the 3CL$_{pro}$-6LU7 SARS-CoV-2	-	-5.38	Khaerunnisa et al., 2020
Allicin	Binding to the 3CL$_{pro}$-6LU7 SARS-CoV-2	-	-4.03	Khaerunnisa et al., 2020
Scutellarein	Inhibiting ATPase activity of nsP13 of SARS-CoV	0.86 ± 0.48	-	Yu et al., 2012
Myricetin	Inhibiting ATPase activity of nsP13 of SARS-CoV	2.71 ± 0.19	-	Yu et al., 2012
Myricetin	Binding to the receptor-binding site of SARS-CoV-2 3CL$_{pro}$	-	-15.64	ul Qamar et al., 2020
Methyl rosmarinate,	Binding to the receptor-binding site of SARS-CoV-2 3CL$_{pro}$	-	-15.44	ul Qamar et al., 2020
Calceolarioside B	Binding to the receptor-binding site of SARS-CoV-2 3CL$_{pro}$	-	-19.87	ul Qamar et al., 2020
Licoleafol	Binding to the receptor-binding site of SARS-CoV-2 3CL$_{pro}$	-	-13.63	ul Qamar et al., 2020
Amaranthin	Binding to the receptor-binding site of SARS-CoV-2 3CL$_{pro}$	-	-12.67	ul Qamar et al., 2020
Myricetin 3-O-beta-D-glucopyranoside	Binding to the receptor-binding site of SARS-CoV-2 3CL$_{pro}$	-	-13.70	ul Qamar et al., 2020
(2S)-Eriodictyol 7-O-(6"-O-galloyl)-beta-D-glucopyranoside	Binding to the receptor-binding site of SARS-CoV-2 3CL$_{pro}$	-	-14.41	ul Qamar et al., 2020
3,5,7,3',4',5'-hexahydroxy flavanone-3-O-beta-D-glucopyranoside	Binding to the receptor-binding site of SARS-CoV-2 3CL$_{pro}$	-	-14.42	ul Qamar et al., 2020
Nelfinavir- blank	Binding to the receptor-binding site of SARS-CoV-2 3CL$_{pro}$	-	-12.20	ul Qamar et al., 2020
Prulifloxacin- blank	Binding to the receptor-binding site of SARS-CoV-2 3CL$_{pro}$	-	-11.32	ul Qamar et al., 2020
Colistin- blank	Binding to the receptor-binding site of SARS-CoV-2 3CL$_{pro}$	-	-13.73	ul Qamar et al., 2020

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Aloe-emodin	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.4	Chandel et al., 2020
Chitranone	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.0	Chandel et al., 2020
Chrysophanol	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.0	Chandel et al., 2020
Diterpene	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.1	Chandel et al., 2020
Elliptinone	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-6.9	Chandel et al., 2020
Emetine	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.0	Chandel et al., 2020
Enoxacin	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.4	Chandel et al., 2020
+(-)Epicatechin	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.6	Chandel et al., 2020
Imatinib	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.4	Chandel et al., 2020
Nelfinavir	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-8.4	Chandel et al., 2020
Niclosamide	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.4	Chandel et al., 2020
Rhein	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-8.1	Chandel et al., 2020
Scutellarein 7 rutinoside	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.3	Chandel et al., 2020
Withaferin A	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.7	Chandel et al., 2020
Withanolide D	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.8	Chandel et al., 2020
27-Hydroxy withanolide	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.3	Chandel et al., 2020
24-Methyl cholesta-5,23E-dien-3beta-ol	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.3	Chandel et al., 2020
17α-Hydroxy withanolide	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.0	Chandel et al.,

	SARS-CoV-2			2020
Aswagandhanoide	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-8.1	Chandel et al., 2020
Kaempferol glycoside (Juglanin)	Inhibiting the 3a protein of SARS-CoV activity	2.3	-	Schwarz et al., 2014
Nelfinavir- blank	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.92 ± 0.057	Ranjan et al., 2020
Lopinavir-blank	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.52 ± 0.022	Ranjan et al., 2020
Ritonavir-blank	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.42 ± 0.68	Ranjan et al., 2020
Kaempfrol	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.68 ± 0.021	Ranjan et al., 2020
Hinkonin	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.51 ± 0.021	Ranjan et al., 2020
Lutein	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.58 ± 0.112	Ranjan et al., 2020
Bavachinin	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.74 ± 0.152	Ranjan et al., 2020
Scopadulcic acid	Binding to 6svb of S protein of SARS-CoV-2	-	-9.6	Ubani et al., 2020
Baicalein	Binding to 6svb of S protein of SARS-CoV-2	-	-9.4	Ubani et al., 2020
Sylibnin	Binding to 6svb of S protein of SARS-CoV-2	-	-9.2	Ubani et al., 2020
Solanidine	Binding to 6svb of S protein of SARS-CoV-2	-	-9.1	Ubani et al., 2020
Narengenin	Binding to 6svb of S protein of SARS-CoV-2	-	-9.0	Ubani et al., 2020
Oleanane	Binding to 6svb of S protein of SARS-CoV-2	-	-9	Ubani et al., 2020
Dammarenolic	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.2	Ubani et al., 2020
Quercetin	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.1	Ubani et al., 2020

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Solanidine	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-7.0	Ubani et al., 2020
Silybinin	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-6.8	Ubani et al., 2020
Loliolide	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-6.7	Ubani et al., 2020
Shikonin	Binding to Protease Domain (6LU7) of SARS-CoV-2	-	-6.6	Ubani et al., 2020
Herbacetin	Binding to the 3CL$_{pro}$ of SARS-CoV	33.17	-	Jo et al., 2020
Rhoifolin	Binding to the 3CL$_{pro}$ of SARS-CoV	27.45	-	Jo et al., 2020
Pectolinarin	Binding to the 3CL$_{pro}$ of SARS-CoV	37.78	-	Jo et al., 2020
Allyl disulfide	Interaction with the ACE2 receptor of SARS- CoV-2	-	-15.32	Lin et al., 2017
Diallyl tetrasulfide	Interaction with the ACE2 receptor of SARS- CoV-2	-	-15.02	Lin et al., 2017
Allyl (E)-1-propenyl disulfide	Interaction with the ACE2 receptor of SARS- CoV-2	-	-13.25	Lin et al., 2017
Allyl methyl trisulfide	Interaction with the ACE2 receptor of SARS- CoV-2	-	-14.36	Lin et al., 2017
Diallyl tetrasulfide	Interaction with the ACE2 receptor of SARS- CoV-2	-	-14.47	Lin et al., 2017
1,2-dithiole	Interaction with the ACE2 receptor of SARS- CoV-2	-	-13.21	Lin et al., 2017
Allyl (Z)-1-propenyl disulfide	Interaction with the ACE2 receptor of SARS- CoV-2	-	-12.60	Lin et al., 2017
2-vinyl-4H-1,3-dithiine	Interaction with the ACE2 receptor of SARS- CoV-2	-	-14.04	Lin et al., 2017
3-vinyl-1,2-dithiacyclohex-4-ene	Interaction with the ACE2 receptor of SARS- CoV-2	-	-13.83	Lin et al., 2017
Carvone	Interaction with the ACE2 receptor of SARS- CoV-2	-	-12.36	Lin et al., 2017
Trisulfide, 2-propenyl propyl	Interaction with the ACE2 receptor of SARS- CoV-2	-	-14.36	Lin et al., 2017
Methyl allyl disulfide	Interaction with the ACE2 receptor of SARS- CoV-2	-	-13.56	Lin et al., 2017

Diacetonalcohol	Interaction with the ACE2 receptor of SARS- CoV-2	-	-13.26	Lin et al., 2017
Trisulfide, (1E)-1-propenyl 2- propenyl	Interaction with the ACE2 receptor of SARS- CoV-2	-	-12.00	Lin et al., 2017
Allyl sulfide	Interaction with the ACE2 receptor of SARS- CoV-2	-	-14.24	Lin et al., 2017
1-propenyl methyl disulfide	Interaction with the ACE2 receptor of SARS- CoV-2	-	-13.84	Lin et al., 2017
Trisulfide, (1Z)-1-propenyl 2- propenyl	Interaction with the ACE2 receptor of SARS- CoV-2	-	-11.68	Lin et al., 2017
Jensenone	Making complex with COVID-19 M_{pro}	-	-4.8, -5.0, -5.5, -5.5	Sharma and Kaur, 2020
Ecalyptol	Interaction with COVID-19 M_{pro}	-	-3.9, -4.0, -4.1, -4.2	Sharma, 2020
Nicotianamine	Inhibiting ACE2 receptor of 2019-nCoV	-	-5.1	Chen and Du. 2020
L. nobilis	Interaction with ACE2 receptor of SARS-CoV	120 ± 1.2	-	Loizzo et al., 2008
T. orientalis	Interaction with ACE2 receptor of SARS-CoV	130 ± 0.4	-	Loizzo et al., 2008
J. oxycredrus ssp. oxycedrus	Interaction with ACE2 receptor of SARS-CoV	270 ± 1.5	-	Loizzo et al., 2008
C. sempervirens ssp. pyramidalis	Interaction with ACE2 receptor of SARS-CoV	700 ± 2.3	-	Loizzo et al., 2008
P. palaestina	Interaction with ACE2 receptor of SARS-CoV	>1000	-	Loizzo et al., 2008
S. officinalis	Interaction with ACE2 receptor of SARS-CoV	870 ± 1.5	-	Loizzo et al., 2008
S. thymbra	Interaction with ACE2 receptor of SARS-CoV	-	-	Loizzo et al., 2008
Acyclovir	Interaction with ACE2 receptor of SARS-CoV	-	-	Loizzo et al., 2008
Glycyrrhizin	Interaction with ACE2 receptor of SARS-CoV	641.0	-	Loizzo et al., 2008
Allyl disulfide	Interaction with ACE2 receptor of SARS-CoV-2	-	−12.84	Thuy et al., 2020
Allyl trisulfide	Interaction with ACE2 receptor of SARS-CoV-2	-	−12.76	Thuy et al., 2020
Allyl (E)-1-propenyl disulfide	Interaction with ACE2 receptor of SARS-CoV-2	-	−9.07	Thuy et al., 2020
allyl methyl trisulfide	Interaction with ACE2 receptor of SARS-CoV-2	-	−12.50	Thuy et al., 2020
Diallyl tetrasulfide	Interaction with ACE2 receptor of SARS-CoV-2	-	−14.06	Thuy et al., 2020
1,2-dithiole	Interaction with ACE2 receptor of SARS-CoV-2	-	−7.89	Thuy et al., 2020
Allyl (Z)-1-propenyl disulfide	Interaction with ACE2 receptor of SARS-CoV-2	-	−9.04	Thuy et al., 2020
2-vinyl-4H-1,3-dithiine	Interaction with ACE2 receptor of SARS-CoV-2	-	−11.83	Thuy et al., 2020
3-vinyl-1,2-dithiacyclohex-4-ene	Interaction with ACE2 receptor of SARS-CoV-2	-	−10.57	Thuy et al., 2020
carvone	Interaction with ACE2 receptor of SARS-CoV-2	-	−8.58	Thuy et al., 2020
Trisulfide, 2-propenyl propyl	Interaction with ACE2 receptor of SARS-CoV-2	-	−14.01	Thuy et al., 2020

Methyl allyl disulfide	Interaction with ACE2 receptor of SARS-CoV-2	-	−10.32	Thuy et al., 2020
Diacetonalcohol	Interaction with ACE2 receptor of SARS-CoV-2	-	−9.71	Thuy et al., 2020
Trisulfide, (1E)-1-propenyl 2-propenyl	Interaction with ACE2 receptor of SARS-CoV-2	-	−9.57	Thuy et al., 2020
Allyl sulfide	Interaction with ACE2 receptor of SARS-CoV-2	-	−9.38	Thuy et al., 2020

Table 2. Inhibition percentage of plant metabolites on coronaviruses

Compound	Concentration	Inhibition percentage (%)		Reference
Scutellarein	10 µM	100%		Yu et al., 2012
Myricetin	10 µM	100%		Yu et al., 2012
Psoralen	200 µM	**3CL$_{pro}$**	**PL$_{pro}$**	Park et al., 2015
		45	40	
Bergapten	200µM	40	30	Park et al., 2015
Xanthotoxin	200 µM	10	30	Park et al., 2015
Isopimpinellin	200µM	40	80	Park et al., 2015
18-hydroxyferruginol	200 µM	45.8 ± 5.0		Ryu et al., 2010
Hinokiol	200 µM	39.1 ± 11.6		Ryu et al., 2010
Ferruginol	200µM	92.7 ± 3.7		Ryu et al., 2010
18-oxofer- ruginol	200 µM	70.5 ± 1.3		Ryu et al., 2010
O-acetyl-18-hydroxyferruginol	200µM	78.6 ± 8.8		Ryu et al., 2010
Methyl dehydroabi- etate	200 µM	46.7 ± 7.2		Ryu et al., 2010
Isopimaric acid	200µM	28.9 ± 2.2		Ryu et al., 2010
Kayadiol	200 µM	75.2 ± 5.4		Ryu et al., 2010
Apigenin	200µM	280.8± 21.4		Ryu et al., 2010
Luteolin	200 µM	20.0 ± 2.2		Ryu et al., 2010
Quercetin	200µM	23.8 ± 1.9		Ryu et al., 2010
Emodin	200 µM	50		Ho et al., 2006
Promazine	200µM	55		Ho et al., 2006
Rhein	200 µM	<20		Ho et al., 2006
Chrysin	200µM	<20		Ho et al., 2006
Aloeemodin	100 µM	65		Lin et al., 2005

Hesperetin	100 µM	82 0r 83	Lin et al., 2005
Diadzein	100 µM	72 or 73	Lin et al., 2005
Baicalein	10 µM	100%	Keum et al., 2013
Quercetin-3-β-galactoside	50 µM	41.8	Chen et al., 2006
AMPLS	200 µM	34	Nguyen et al., 2012
EGCG	200µM	85	Nguyen et al., 2012
GCG	200 µM	91	Nguyen et al., 2012
Diadzein	200µM	34	Nguyen et al., 2012
Puerarin	200 µM	33	Nguyen et al., 2012
Quercetin	200µM	82	Nguyen et al., 2012
EGC	200 µM	5.4	Nguyen et al., 2012

Conclusion

Plant metabolites can be potential compounds against the activity of coronaviruses. They possess their antiviral activity through binding to main proteases or amino acid residues in the specific protein receptors of the virus in host cell. Looking through the IC50 values, emetine which is an alkaloid was the most effective compound against the Middle East respiratory synrome (MERS-CoV) and it inhibits the virus replication with IC50 value of 0.01 µM and Xanthoangelol E had the best activity against papain like protease (PL$_{pro}$) of severe acute respiratory syndrome (SARS-CoV) with IC50 value of 1.2 ± 0.4 µM. Moreover, other polyphenolic compound, tannic acid, was the most effective compound to inhibit the 3CL$_{pro}$ of SARS-CoV with IC50 value of 3 µM. In addition, tryptantrin had IC50 value of 0.06 and could bind to the ACE2 receptor of human coronavirus (HCoV NL63). Additionally, baicalein could bind to the ATPase domain of nsP13 (coronavirus helicase) of SARS-CoV with IC50 value of 0.47 ± 0.09. On the other hand molecular docking results showed that curcumin, hesperidin, diosmin, apiin, and rutin are

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promising compounds inhibiting COVID-19 protease. Generally studies showed that plant

metabolites can be considered as potential anti-coronavirus compounds.

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High lights

- • Plants metabolites can be potential drugs to inhibit various types of coronaviruses.
- • IC50 value and molecular docking score and binding energy are parameters to inhibit the coronaviruses
- • This is the first comprehenisve study on all secondary plant metabolites such as polyphenols (flavonoids, coumarins, stilbenes), alkaloids, terpenoids, organosulfur compounds saponins, saikosaponins, lectins, essential oils, nico and primary metabolites such as vitamins.