Screening and Druggability Analysis of Some Plant Metabolites Against SARS-CoV-2

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The sudden outbreak of novel corona virus at the end of 2019 has caused a global threat to mankind due to its extreme infection rate and mortality. Despite extensive research, still there is no an approved drug or vaccine to combat SARS-CoV-2 infections. Hence, the study was designed to evaluate some plant-based active compounds for drug candidacy against SARS-CoV-2 by using virtual screening methods and various computational analysis. A total of 27 plant metabolites were screened against SARS-Cov-2 main protease proteins (MPP), Nsp9 RNA binding protein, spike receptor binding domain, spike ecto-domain and HR2 domain using molecular docking approach. Four metabolites i.e. asiatic acid, avicularin, guajaverin and withaferin showed maximum binding affinity with all key proteins in terms of lowest global binding energy. The top candidates were further employed for ADME (absorption, distribution, metabolism, and excretion) analysis to investigate their drug profiles. Results suggest that none of the compounds render any undesirable consequences that could reduce their drug likeness properties. The analysis of toxicity pattern revealed no significant tumorigenic, mutagenic, irritating or reproductive effects by the compounds. However, withaferin was comparatively toxic among the top four candidates with considerable cytotoxicity and immunotoxicity. Most of the target class by top drug candidates belonged to enzyme groups (e.g. oxidoreductases hydrolases, phosphatases). Moreover, results of drug similarity prediction identified two approved structural analogs of Asiatic acid from DrugBank, Hydrocortisone (DB00741) (previously used for SARS-CoV-1 and MERS) and Dinoprost-tromethamine (DB01160). In addition, two other biologically active compounds, Mupirocin (DB00410) and Simvastatin (DB00641) could be an alternative choice to withaferin for the treatment of viral infections. The study may pave the way to develop effective medications and preventive measure against SARS-CoV-2 in the future. However, the results were based solely on computational tools and algorithms. Due to the encouraging results, we highly recommend further in vivo trials for the experimental validation of our findings.
Screening and Druggability Analysis of Some Plant Metabolites against SARS-CoV-2

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Abbreviations: CoV, Corona virus; SARS, Severe acute respiratory syndrome; Middle East respiratory syndrome; Nsp, Non-structural protein; LD50, Lethal dose 50; ADME, Absorption, distribution, metabolism, and excretion; BBB, Blood brain barrier

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ABSTRACT

The sudden outbreak of novel corona virus at the end of 2019 has caused a global threat to mankind due to its extreme infection rate and mortality. Despite extensive research,
still there is no an approved drug or vaccine to combat SARS-CoV-2 infections. Hence, the study was designed to evaluate some plant-based active compounds for drug candidacy against SARS-CoV-2 by using virtual screening methods and various computational analysis. A total of 27 plant metabolites were screened against SARS-CoV-2 main protease proteins (MPP), Nsp9 RNA binding protein, spike receptor binding domain, spike ecto-domain and HR2 domain using molecular docking approach. Four metabolites i.e. asiatic acid, avicularin, guajaverin and withaferin showed maximum binding affinity with all key proteins in terms of lowest global binding energy. The top candidates were further employed for ADME (absorption, distribution, metabolism, and excretion) analysis to investigate their drug profiles. Results suggest that none of the compounds render any undesirable consequences that could reduce their drug likeness properties. The analysis of toxicity pattern revealed no significant tumorigenic, mutagenic, irritating or reproductive effects by the compounds. However, witheferin was comparatively toxic among the top four candidates with considerable cytotoxicity and immunotoxicity. Most of the target class by top drug candidates belonged to enzyme groups (e.g. oxidoreductases hydrolases, phosphatases). Moreover, results of drug similarity prediction identified two approved structural analogs of Asiatic acid from DrugBank, Hydrocortisone (DB00741) (previously used for SARS-CoV-1 and MERS) and Dinoprost-tromethamine (DB01160). In addition, two other biologically active compounds, Mupirocin (DB00410) and Simvastatin (DB00641) could be an alternative choice to witheferin for the treatment of viral infections. The study may pave the way to develop effective medications and preventive measure against SARS-CoV-2 in the future. However, the results were based solely on computational tools and algorithms. Due to the encouraging results, we highly recommend further in vivo trials for the experimental validation of our findings.

Keywords: SARS-CoV-2; plant metabolites; main protease proteins; molecular docking; ADME analysis; drug target

1. Introduction
The sudden outbreak of novel corona virus (SARS-CoV-2) infection, which caused a worldwide anxiety, emanated from Wuhan, China at the end of 2019 and spread over all around the world except few countries (Yao et al., 2020). The virus is responsible for causing this novel corona disease, which WHO officially called COVID-19. As of April 23, 2020, World Health Organization (WHO) estimated that new Corona virus infected more than 30 lacs confirmed cases of peoples, caused death of over two lac and thirty thousand, touched 215 countries, areas or territories (WHO, 2020) and its infection rate is increasing day by day at alarming rate that could pose a global threat to mankind (Zhou et al., 2020a). The fatality rate of SARS-CoV-2 (3.4%) is estimated by WHO, which is lower than previous fatal diseases SARS and MERS having death rates of 9.6% & 35%, respectively (Guo et al., 2020; de Wit et al., 2016).

Coronaviruses are enveloped, positive single-stranded RNA viruses with large genome size ranging from 26 kb to 32 kb. These viruses are the representative of four subfamilies, which include alpha-, beta-, gamma- and delta- Corona viruses. COVID-19 has more sequence similarity with SARS-CoV than MERS CoV when genome sequences of these mentioned viruses have been compared (Chan et al., 2020), but also have dissimilarities that can influence their process of pathogenesis (Kannan et al., 2020; Mousavizadeh and Ghasemi, 2020). 2019-nCoV infect human through same entry point of ACE receptor, expressing in respiratory tract (Zhou et al., 2020b; Wan et al., 2020). However, among various proteins, four proteins are commonly found in the structure of all coronavirus representing spike (S), envelope(E), membrane(M), and nucleocapsid (N) (Mousavizadeh and Ghasemi, 2020). The initial and important stage of viral entry into host cell is receptor recognition (Li, 2015). The assembly of viral particle occurred by membrane protein (M) and envelope protein (E) whereas, virus binding and entrance into host cell took place by spike protein (S) with the assistance of SARS-CoV angiotensin-converting enzyme (Li, 2016; Wan et al., 2020).

New Corona viruses (SARS-CoV-2), belonging to Beta-coronaviruses, are responsible for causing severe human respiratory syndrome (Velavan and Meyer, 2020; Zhou et al., 2020a). The virus is spread mainly through the community transmission, on the other hand, SARS and MERS affected other peoples through nosocomial spread (Munster et al., 2020). It can transmit from one individual to other by respiratory droplets. The general sign and symptoms of SARS-CoV-2 infected patients suffered from initially with common flu-like fever, Sputum production, Dyspnoea, Headache, Sore
throat/Pharyngalgia, Diarrhoea etc and further leads to express life threatening symptoms of unusual fatal pneumonia (Zheng, 2020). However, COVID19 affected patients, either symptomatic or asymptomatic, were detected with the nose containing higher viral load than in the throat (Zou et al., 2020). A critically ill patient has to fall into a series of complexity with progression of disease.

The efficacy and safety of antivirals required to be evaluated by continuous clinical trials (Zhou et al., 2020a). There has no efficient, safe and specific potential therapeutics has been approved for rapid remedy of this new respiratory syndrome (Lu, 2020; Li and De Clercq, 2020). Though, clinical trials of some drugs for Corona treatment have been started, till now, a few candidates have shown their efficacy in in vitro studies, not many have progressed to randomized animal or human trials, hence may have limited use to counter infection (Dhama et al., 2020). Many countries, pharmaceutical company announced their headway and program to develop vaccines (e.g. subunit, mRNA, DNA, live-vector vaccine) against the virus. But, the developmental process of making human vaccine from concept to licensure may take a couple of years to limit the global emergency need (Bregu et al., 2011). As the epidemic is still spreading, medicinal plants may be alternative to be used in making drugs as early as possible. Several scientific researchers reported the necessity of plant as medicinal value and therapeutic uses as drugs from ancient times (Suheda et al., 2015). Plant-derived active compounds of different plant part are useful for treating diseases including diarrhoea, headache, and inflammation, bacterial and fungal infections. From prehistoric times, traditional peoples utilized these for the remedial purposes of health deteriorating diseases because of its existence of numerous phytochemicals (Kumar et al., 2019). Various limitations are associated with modern treatment options including drug-resistance, severe side effects, adverse toxicity profiles, complicated medication administration of. Natural products have the potential to form the basis of holistic health care (Cheuka et al., 2016). The properties of antioxidant render medicinal plants to be effective in treating life-threatening diseases (e.g. cancer, Alzheimer, diabetes, cardiac disease) (Table 1) and also minimize drug toxicity (Karimi et al., 2015).

The expansion of natural product as new medicine or drug to resist the emerging virus SARS-CoV-2 could be done to bypass the side effect of synthetic drugs. Therefore, the study aimed at evaluating some plant-based active compound for drug candidacy against
SARS-CoV-2 through virtual screening methods and various computational investigations.

2. Materials and Methods

2.1. Retrieval of SARS-CoV-2 proteins/protein-domains and plant metabolites

The 3D structures of SARS-CoV-2 main proteases (6W63, 6LU7), Nsp9 (Non-structural protein-9) RNA binding protein (6W4B), Spike receptor binding domain (6M0J), spike ecto-domain (6VYB), and HR2 Domain (6LVN) were retrieved from the RCSB Protein Data Bank (Rose et al., 2017). A total of 27 plant metabolites belonging to different classes were extracted from PubChem database (https://pubchem.ncbi.nlm.nih.gov/)(Kim et al., 2016) in SDS (3D) format (Table 1). The structures were further converted into PDB format by OpenBabel v2.3 software (O’Boyle et al., 2011).

2.2. Screening of plant metabolites against SARS-CoV-2 proteins/protein-domains

Molecular docking is an effective approach for screening out the suitable therapeutics against specific drug target of deadly pathogens (Meng et al., 2011). This powerful tool is used to model the interaction between small ligands and macromolecules, thereby can pave the way for drug discovery (Kitchen et al., 2004). The binding affinity of 27 plant metabolites with different SARS-CoV-2 proteins/protein domains (drug targets/macromolecules) were determined by using PatchDock server (Schneidman-Duhovny et al., 2005). Recently, alpha-ketoamide (CID 6482451) has been suggested as aSARS-CoV-2 main proteaseprotein inhibitor by experimental study (Zhang et al., 2020). The ligand was used as positive control for the present study and employed to docking analysis against all six macromolecules. The docked complexes were further refined via FireDock refinement tool (Mashiach et al., 2008). The ligand binding complexes were visualized by Discovery Studio v3.1 (Wanget al., 2015) and PyMOL v2.0 (DeLano, 2002).

2.3. Drug profile analysis of top metabolites

Absorption, distribution, metabolism, and excretion (ADME) are four major criteria that influence the drug levels and kinetics of drug exposure to the tissues within an organism.
The pharmacological activity and performance of a drug is largely controlled by these parameters (Balani et al., 2005). SwissADME server was used (Daina et al., 2017) to assess the absorption, distribution, metabolism and excretion properties of the top four metabolites. BOILED-Egg model was employed to calculate the Blood-brain barrier (BBB) in the studied compounds (Daina and Zoete, 2016). The relative toxicity of top drug candidates were predicted via ProToxII server (Banerjee et al., 2018). The server incorporates molecular similarity, fragment propensities and fragment similarity based CLUSTER cross-validation based a total of 33 models for the prediction of various toxicity endpoints. Additionally, OSIRIS Property Explorer were employed to investigate the undesired effects of these compounds (Sander, 2001).

2.4. Prediction of drug targets and available drug molecules from DrugBank

SwissTargetPrediction was used to estimate the probable macromolecular targets of predicted drug candidates (Daina et al., 2019). The server predicts based on a combination of 2D and 3D similarity with a library of 370000 known bioactive compounds on approximately 3000 proteins. Moreover, SwissSimilarity web tools were used to identify potential drug molecules against SARS-CoV-2 based on homology screening of predicted top drug candidates. The server allowed ligand-based virtual screening of several libraries of small molecules to find approved, experimental or commercially available drugs from DrugBank using different approaches including FP2 fingerprints, electroshape, spectrophores and align-IT (Zoete et al., 2016).

3. Results

3.1. Screening of plant metabolites against SARS-CoV-2

All of the retrieved structures of SARS-CoV-2 proteins/protein-domains (macromolecules) and plant metabolites (ligands) were optimized and employed for molecular docking to predict the affinity between above mentioned ligands and the macromolecules. The metabolites were ranked based on global binding energy and the results depict that top four scorers (metabolites) were same for each of the macromolecules in terms of minimum binding energy (Table 2 and Supplementary File 1). In each case, asiatic acid, avicularin, guajaverin and withaferin showed best binding
interactions with six studied macromolecules (Figure 1 and Table 2). Moreover, asiatic acid showed highest binding affinity with SARS-CoV-2 main protease (-53.05 kcal/mol), Nsp9 RNA binding protein (-50.04 kcal/mol) and spike ecto-domain (60.68 kcal/mol) (Figure 2 and Table 2), while guajaverin bound with spike receptor binding domain and HR2 Domain with a binding energy of -47.34 kcal/mol and -28.73 kcal/mol, respectively (Figure 3 and Table 2).

3.2. ADME analysis of top drug candidates

Different ADME properties i.e. physicochemical parameters, pharmacokinetics, lipophilicity, water solubility, medicinal chemistry of top drug candidates were estimated to evaluate their drug profiles (Figure 4 and Table 3). Analysis of inhibition effects with different CYP isoforms (CYP1A2, CYP2D6, CYP2C9, CYP2C19, CYP3A4) revealed that none of the candidates had such interaction possibility with any cytochromes P450 isoforms. GI absorption was found higher for asiatic acid and withaferin, while lower for guajaverin and avicularin. Moreover, blood-brain barrier (BBB) permeation was calculated by BOILED-Egg model which revealed no BBB permeant among the studied top drug candidates. Each candidate were water soluble from a moderate to high level, while guajaverin and avicularin showed maximum solubility (Table 3).

3.3. Toxicity pattern analysis of top drug candidates

Prediction of various toxicity endpoints such as acute toxicity, hepatotoxicity, cytotoxicity, carcinogenicity, mutagenicity, immunotoxicity, adverse outcomes (Tox21) pathways and toxicity targets were analysed (Table 4). Results revealed that guajaverin and avicularin fell in the category of toxicity class 5, while the predicted toxicity group for Asiatic acid and withaferin were 4 and 2 respectively (the lower the class the higher the toxicity). Estimated LD50 for asiatic acid, avicularin, guajaverin and withaferin were 2000, 5000, 5000 and 7mg/kg respectively. The toxicity radar in Figure 5 illustrates the confidence of positive toxicity results compared to the average of its class. None of the compounds showed any undesired effects such as tumorigenicity, mutagenicity, irritating or reproductive effects. Withaferin, however, found to be relatively toxic among the four candidates with considerable cytotoxicity and immunotoxicity (Figure 5).
3.4. Prediction of drug targets and available drug molecules from DrugBank

Most of the target class belonged to enzymes, kinase proteins, oxidoreductases (i.e. aldose reductase, aldo-keto reductase), phosphatases and lyases (i.e. carbonic anhydrase) (Figure 6 and Table 5). Ligand-based virtual screening was performed to predict biologically active small compounds against SARS-CoV-2 from DrugBank. Two approved drugs, Hydrocortisone (DB00741) and Dinoprost-tromethamine (DB01160) were found analogous to asiatic acid with prediction score 50.52 and 50.53 respectively. Moreover, results revealed the similarity of Mupirocin (DB00410) and Simvastatin (DB00641) with withethearin with high prediction score (Table 6). The findings suggest that these could be potential drug candidates against SARS-CoV-2, thus require further experimental trials.

4. Discussion

Excessive infection rates and mortality of SARS-CoV-2 led the researchers to concentrate immensely on developing strategies for combating infections caused by it (Wilder-Smith et al., 2020; Yuen et al., 2020; Lake, 2020). Regardless of praiseworthy initiative, still there is no approved drugs or vaccine that could treat SARS-CoV-2 infected patients (Fang et al., 2020; Prompetchara et al., 2020). Though some candidates are in the investigational stages, many of them raised controversy issues (Zhou et al., 2020; Dong et al., 2020). Plant-derived natural products play a significant role by being a lead molecule in the development of drug candidates (Josephet al., 2017). Hence, in the present study, attempts were taken to evaluate some plant derived metabolites as an inhibitory agent of SARS-CoV-2 based on their binding affinities to the key proteins of the pathogen.

The contribution by computational biology has accelerated the pace of drug discovery. It is used in the biopharmaceutical industry to discover and develop new lead compounds. By this route, one can visualize the possibilities of binding of potential small molecules as ligands/inhibitors (Josephet al., 2017). Phytomolecules like Baicalein, Luteolin, Quercetin and Kaempferol are potential antiviral agents against a wide range of important viruses including Dengue, HIV, H5N1 influenza A virus, Coxsackie virus, CHIKV and Japanese encephalitis virus (Habbu et al., 2009). Recent studies focused on MPP
inhibitors of SARS-CoV-2 i.e. alpha-ketoamide, Hydroxy, Remdesivir, Chloroquine and Favipiravir to evaluate their potency as drug (Al-Tawfiq et al., 2020; Colson et al., 2020). Several in silico strategies were also adopted to screen putative drug candidates against SARS-CoV-2 (Parvez et al., 2020; Hasan et al., 2020). However, all these experiments used either main protease proteins or RNA-dependent RNA polymerase of SARS-CoV-2 as probable drug targets. In this study, we screened some natural metabolites against SARS-Cov-2 main proteases (6W63, 6LU7), Nsp9 (Non-structural protein-9) RNA binding protein (6W4B), spike receptor binding domain (6M0J), spike ecto-domain (6VYB), and HR2 domain (6LVN) using molecular docking approach (Chang et al., 2010; Hasan et al., 2019). The polyproteins of coronavirus are cleaved and transformed in mature non-structural proteins (NSPs) by proteases (Hilgenfeld, 2014). As a putative component in the replication complex, nsp9 may possibly have an RNA binding activity. Viral replication complexes are frequently membrane associated and nsp9 helps in this case. The entry of coronavirus into host cells, on the other hand, is mediated by the transmembrane spike glycoprotein that forms homotrimers protruding from the viral surface. S protein comprises two functional subunits responsible for binding to the host cell receptor (S1) and fusion of the viral and cellular membranes (S). After the attachment of the receptor-binding subunit to the receptor, the HR1 and HR2 domains in the membrane fusion subunit interact with each other and form a six-helix bundle and this conformational change results in a close apposition of the fusion peptide leading to virus-cell membrane fusion (Moore et al., 2003). Thus, all these proteins represent an attractive pharmacological target for SARS-CoV-2.

Results revealed that asiatic acid had highest binding affinity with SARS-CoV-2 main protease (-53.05 kcal/mol), Nsp9 RNA binding protein (-50.04 kcal/mol) and spike ecto-domain (60.68 kcal/mol) (Figure 2 and Table 2). Remarkably, four metabolites i.e. asiatic acid, avicularin, guajaverin and withaferin scored best for each six macromolecules and bound with minimum global binding energy (Table 2 and Supplementary File 1). Most importantly, the scores of top most candidates were either close or in some instances lower than alpha ketoamide, a positive control used in the present study (Table 2). Asiatic acid, a triterpenoid derivative from Centella asiatica, has displayed antioxidative, anti-inflammatory, and protective properties against neurotoxicity induced by glutamate- or b-amyloid-induced (Krishnamurthy et al., 2009). Bian et al. (2013) also reported the inhibitory activities of asiatic acid and included in the arsenal for combating against
fibroproliferative disorders (Keloids) by blocking TGF-β/Smad pathway. Withanolides, nature-derived secondary metabolites, produced in *Withania somnifera* via oxidation of steroids and have medicinal value anti-inflammation, anti-cancer, adaptogenic and anti-oxidant effects (Vaishnavi et al., 2012). Withaferin, which is a steroidal lactone, suppress HIV-1 LTR transcription and viral replication (Shi et al., 2017) and also have vital function to inhibit Herpes simplex virus (Grover et al., 2011). It has anti-inflammatory properties (White et al., 2016) and also showed neuro-protective activity against Aβ neurotoxicity (Tiwari et al., 2018). Molecular docking and simulation study also revealed that it has vital function to attenuate the neuraminidase of H1N1 influenza virus (Cai et al., 2015).

Guajaverin and Avicularin are the main bioactive components in guava leaves with hypoglycemic properties and inhibitory capacity against free fatty acid release (Wen et al, 2016). The microbicidal activity of is attributable to guajaverine. Anti-plaque activity is attributed to microbicidal activity of guajaverine of *P. guajava* against the growth of the Strep. Mutans, thus becoming an alternative for oral health care (Prabu et al., 2006). Avicularin (quercetin- 3-O-α-L-arabinofuranoside), is a flavonoid of plant and glycoside of quercetin, has been suggested to display diverse pharmacological properties such as anti-inflammatory and anti-infectious effects (Vo et al., 2012; Shen et al., 2019). Lee et al. (2019) reported the effective anti-oxidant potentiality of Avicularin from *Lespedeza cuneata*. Avicularin from *Taxillus kaempferi*, inhibited the accumulation of the intracellular lipids by reducing glucose uptake in adipocytes, as reported by Fujimori and Shibano (2013). It was one of the principal compounds of *P. aviculare* and has been reported to inhibit pancreatic lipase (PL) (Park et al., 2019). Kim et al. (2011) identified hepatoprotective activity of Avicularin extracted from the aerial parts of *Lespedeza cuneata* against lesion caused by t-BHP in HepG2 cells. It has also been suggested to inhibit activation of ERK signaling pathway through LPS-stimulated overproduction of pro-inflammatory mediators and cytokine (Vo et al., 2012). Shen et al. (2019) investigated anti-depressant like properties of Avicularin on a mouse model of depression, and got relief from chronic unpredictable mild stress (CUMS) induced depressive-like behaviors. Avicularin may also suppress the inflammatory response, and causes apoptosis in human RA synovial cells through obstructing the activation of the MEK/NF-κB pathway, thus preventing rheumatoid arthritis (RA) in vitro (Wang et al., 2018).
ADME data, whether experimentally measured or computationally predicted, provide key insights into how a drug will ultimately be treated or accepted by the body. So while a drug lead may exhibit phenomenal efficacy in vitro, poor ADME results will almost invariably terminate its development (Wishart, 2007). Computational methods are playing a key role in anticipating potential ADME and toxicity problems and reducing the number of experiments that involve animal testing obviously. Therefore, the top most drug candidates were employed for ADME analysis to investigate their drug profiles. None of the metabolites, however showed any undesirable consequences that could reduce their drug likeness properties. SARS-CoV-2 appears as a severe acute respiratory disease nor a neuro disease (Astuti et al., 2020), so there is no need to permeate the blood brain barrier (BBB) for being an effective molecule against SARS-CoV-2. However, no BBB permeants were found among the top drug candidates. Most of the target class for the top drug candidates belonged to the categories of enzymes (e.g. oxidoreductases, hydrolase, phosphatases, lyases (Table 5). The major protease proteins (protein hydrolase) of SARS-CoV-2 thus can be a specific target for these natural metabolites. The toxicity of drug impurities is closely related to their structure. Structure-activity relationships (SARs) have been widely used in Europe and the United States to predict toxicity by computer (Guan et al., 2019). The toxicity prediction results from our study revealed negligible tumorigenic, mutagenic, irritating or reproductive effects by the candidates, though withetheferin, was found to be comparatively toxic among the top four candidates. However drug similarity prediction identified two approved structural analogs of withetheferin, Mupirocin (DB00410) and Simvastatin (DB00641) which could be an alternative choice, and therefore require further in vivo investigations. Ligand-based virtual screening using Asiatic acid predicted two other biologically active compounds, Hydrocortisone (DB00741) and Dinoprost-tromethamine (DB01160) from DrugBank. Interestingly, Hydrocortisone which is a cortisone based drug, was previously used during SARS-CoV-1 and MERS outbreak (Barzilai et al., 1972). Diosmin, on the contrary, are used as supplementary drug found in various natural plants (Moldovan et al., 2010). Myricetin showed the potential to inhibit reverse transcriptase of RLV and HIV virus, while characterized by having antioxidative and prooxidative properties. It is also a potent anticarcinogen and antimutagen (Ong and Khoo, 1997). The most significant finding of this study is Simvastatin, which can block downstream molecules those are key factors in virus infectivity and also can control severe influenza and pneumonia through
prevention of excess cytokine release (Jung et al., 2012). The results suggest that all these compounds could be potential drug candidates against SARS-CoV-2. However, all of the investigational drugs of SARS-CoV-2 are under strict regulation of World Health Organization. Due to the encouraging results, we highly recommend further in vivo trials for the experimental validation of our findings. The present study may pave the way to develop effective medications and preventive measure against SARS-CoV-2 in the future.

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Conflict of interest

Authors declare that they have no conflict of interests.

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**Figure Legends**

**Figure 1:** Chemical structures of Asiatic acid (A), Guenjaerin (B), Avicularin (C) and Witheferin (D)

**Figure 2:** Molecular interaction of Asiatic acid with SARS-CoV-2 main protease (A), Nsp9 RNA binding protein (B) and spike ectodomain (C)

**Figure 3:** Molecular interaction of SARS-CoV-2 main protease with Avicularin (A), HR2 Domain with Guenjaerin (B) and spike receptor-binding domain with Guenjaerin (C)

**Figure 4:** ADME analysis of top four metabolites; A: Asiatic acid, B: Guenjaerin, C: Avicularin, and D: Witheferin

**Figure 5:** Toxicity patterns of top four drug candidates; A: Asiatic acid, B: Guenjaerin, C: Avicularin, and D: Witheferin

**Figure 6:** Prediction of drug targets for Asiatic acid (A), Guenjaerin (B), Avicularin (C) and Witheferin (D)
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## Tables

**Table 1:** List of plant metabolites used in the study with respective source and activities

| Metabolites          | Pubchem CID | Class                             | Source             | Activities                                                                 | References                           |
|----------------------|-------------|-----------------------------------|--------------------|---------------------------------------------------------------------------|---------------------------------------|
| Alicin               | 65036       | S-containing compound             | *Allium sativum*   | Antimicrobial, antiviral Antioxidant, anti-cancer activity                 | El-Saber Batiha et al., 2020          |
| Andrographolide      | 5318517     | Diterpenoid labdane               | *Andrographis paniculata* | antioxidant, anti-inflammatory, and anti-cancer                           | Mussard et al., 2019                  |
| Apigenin             | 5280443     | Flavonoid                         | Vegetable and fruit | Effective in cancer, depression, diabetes & Alzheimer’s disease,           | Salehi et al., 2019                   |
| Asiatic acid         | 119034      | Aglycone type pentacyclic triterpenoids | *Centella asiatica* | Antioxidant, cardioprotective, anti-inflammatory, antitumor, neuroprotective, antimicrobial | Nagoor Meeran et al., 2018             |
| Avicularin           | 5490064     | quercetin-3-a-L-arabinofuranoside (flavonoid) | *Psidium guayava*, *Lespedeza cuneata* | anti-inflammatory, antioxidant, hepatoprotective activity                  | Wang et al., 2019                      |
| Capsaicin            | 1548943     | Alkaloid                           | *Capsicum genus*   | Pruritis, pain relief, non-steroidal anti-inflammatory drug induced gastritis | Hayman and Kam, 2008                   |
| Chavibetol           | 596375      | Phenylpropanoid                   | Piper betle         | immunomodulatory, radical scavenging                                      | Bhalerao et al., 2013                 |
| Cinnamic             | 444539      | Aromatic carboxylic acids         | *Cinnamomum species* | Antibacterial, antifungal, antimalarial, antitubercular                    | Guzman, 2014                          |
| Curcumin             | 969516      | Polyphenolic compound             | *Curcuma longa*     | antibacterial, anti-inflammatory antiviral, antioxidant, anti-arthritis & anti-cancer activity | Al-Samydai and Jaber, 2018            |
| Eugenol              | 3314        | Phenylpropanoid                   | *Ocimum tenuiflorum*, *Eugenia caryophyllata* | antimicrobial, anti-inflammatory, analgesic and antioxidant                | Nejad et al., 2017                    |
| Flavonoidsarjunone   | 14034821    | Flavonoids                         | *Terminalia arjuna* | Arjunone and other compounds have role in antioxidant, antiatherogenic, anti-inflammatory, anti-carcinogenic activity | Amalraj and Gopi, 2016                |
| Galangin             | 5281616     | Flavonol                           | Honey, *Alpinia officinarum*, propolis | Anti-cancer, anti-mutagenic, anti-oxidative, radical scavenging etc.       | Patel et al., 2012                    |
| Compound               | PubChem ID | Type              | Plant/or Other Source                      | Activities                                                                 |
|------------------------|------------|-------------------|--------------------------------------------|-----------------------------------------------------------------------------|
| Gentisic acid          | 3469       | Phenolic acid     | *Gentiana*, *Citrus*, *H. rosa-sinensis*, *O. europaea*, *S. indicum* | Antioxidant, neuroprotective, anti-inflammatory, hepatoprotective, antimicrobial activities |
|                        |            |                   |                                            | Abedi et al., 2019                                                         |
| Guajaverin             | 5481224    | Flavonoid         | *Psidium guayava*                          | Anti-plaque activity                                                       |
|                        |            |                   |                                            | Prabu et al., 2006                                                         |
| Kaempferol             | 5280863    | Flavonoid aglycone| Vegetable and fruit                        | Anti-inflammatory, antioxidant, antimicrobial, antitumor, cardioprotective, and antidiabetic activities |
|                        |            |                   |                                            | Imran et al., 2019                                                         |
| Luteolin               | 5280445    | Flavonoid         | Carrots, celery peppers, olive peppermint | Anticancer, antioxidant, antimicrobial, anti-inflammatory, and activities |
|                        |            |                   |                                            | Lopez-Lazaro, 2009                                                         |
| m-Coumaric acid        | 637541     | Phenolic acid     | *Solanum nigrum*                           | Role in pharmacological activities                                         |
|                        |            |                   |                                            | Ohnishi et al., 2006                                                       |
| Piperic acid           | 5370536    | Alkaloid          | *Piper nigrum*                             | No known function                                                          |
|                        |            |                   |                                            | Mgbeahuruike et al., 2017                                                  |
| Piperine               | 638024     | Alkaloid          | *Piper spp.*                               | Anticancer, antimicrobial, antimalarial                                     |
|                        |            |                   |                                            | Mgbeahuruike et al., 2017                                                  |
| Quercetine             | 5280343    | Flavonoid         | Diverse plant species                      | Antioxidant, cardiovascular, antiviral, anti-inflammatory, anticancer, antimicrobial |
|                        |            |                   |                                            | Maalik et al., 2014                                                        |
| Swertiamarin           | 442435     | Secoiridoid glycoside | *Swertia chirata*               | Anti-arthritis, anti-diabetic Cardio-protective, Anticancer, Anti-hepatitis, Antibacterial, anti-atherosclerotic |
|                        |            |                   |                                            | Kumar and Van Staden, 2016                                                 |
| Swertinin              | 5491517    | Secoiridoid glycoside | *Swertia chirata*                 | Role in pharmacological activities                                         |
|                        |            |                   |                                            | Singh et al., 2012                                                         |
| Thymoquinone           | 10281      | Monoterpenes      | *Nigella sativa*                          | Anti-oxidant and anti-inflammatory properties, Anti-microbial, Anti-arthritis, anti-cancer efficacy |
|                        |            |                   |                                            | Ahmad et al., 2019;                                                        |
| Vincamine              | 15376      | Alkaloid          | *Catharanthus roseus*, *Vinca minor*      | Cerebral disorders, antilucer activity, cerebrovascular insufficiencies    |
|                        |            |                   |                                            | Barrales-Cureño, 2015                                                      |
| Vitexin                | 5280441    | Apigenin flavone glucoside | *Crataegus species*                | Anti-inflammatory effects, anti-oxidant effects, anti-carcinogenic effects, anti-viral effects |
|                        |            |                   |                                            | He et al., 2016                                                            |
| Withaferin             | 265237     | Steroidal lactone | *Withania somnifera*                      | Anti-cancer, adaptogenic, anti-stress, immunomodulatory, anti-inflammatory, anti-tumor, cardioprotective, and neuroprotective activities. |
|                        |            |                   |                                            | Patel et al., 2013                                                         |
| Zingiberene            | 92776      | Isoprenoids       | *Zingiber*                                 | Anti-ulcer, antibacterial,                                                  |
|                        |            |                   |                                            | Johji et al.,                                                             |
Table 2: Analysis of global binding energy of top 4 screened metabolites (ligands)

| Macromolecules | Ligands                  | Global Energy | ACE  | Score  | Area  |
|----------------|--------------------------|---------------|------|--------|-------|
| 6W63           | α-ketoamide (Control)    | -56.92        | -16.84 | 4560   | 526.40|
|                | Asiatic acid             | -53.05        | -15.26 | 4916   | 577.10|
|                | Avicularin               | -48.62        | -18.50 | 4694   | 532.10|
|                | Guajaverin               | -48.48        | -15.12 | 4450   | 497.50|
|                | Withaferin               | -48.46        | -14.08 | 4984   | 597.40|
| 6W4B           | α-ketoamide (Control)    | -48.60        | -16.39 | 4458   | 504.60|
|                | Asiatic acid             | -50.04        | -16.37 | 4998   | 564.20|
|                | Withaferin               | -47.95        | -13.30 | 4896   | 570.40|
|                | Guajaverin               | -42.72        | -10.63 | 4548   | 641.40|
|                | Avicularin               | -39.83        | -23.80 | 4556   | 514.50|
| 6VYB           | α-ketoamide (Control)    | -63.94        | -17.32 | 5728   | 705.10|
|                | Asiatic acid             | -60.68        | -22.33 | 6276   | 771.50|
|                | Withaferin               | -60.19        | -20.49 | 5760   | 793.10|
|                | Guajaverin               | -55.24        | -17.51 | 5208   | 659.20|
|                | Avicularin               | -52.93        | -17.15 | 5474   | 683.30|
| 6LVN           | α-ketoamide (Control)    | -25.52        | -2.71  | 4318   | 564.20|
|                | Guajaverin               | -28.73        | -2.13  | 3696   | 443.50|
|                | Withaferin               | -28.11        | -1.24  | 4376   | 507.70|
|                | Asiatic acid             | -27.58        | -1.12  | 4366   | 500.30|
|                | Avicularin               | -26.48        | -1.22  | 3986   | 465.10|
| 6M0J           | α-ketoamide (Control)    | -60.50        | -9.34  | 5374   | 655.40|
|                | Guajaverin               | -47.34        | -11.22 | 4554   | 575.60|
|                | Withaferin               | -46.84        | -11.13 | 5598   | 640.50|
|                | Asiatic acid             | -45.69        | -13.09 | 5978   | 691.70|
|                | Avicularin               | -43.13        | -11.09 | 5232   | 604.20|
| 6LU7           | α-ketoamide (Control)    | -56.13        | -15.07 | 4578   | 492.00|
|                | Avicularin               | -54.04        | -14.77 | 4584   | 520.60|
|                | Guajaverin               | -51.69        | -12.92 | 4182   | 515.50|
|                | Withaferin               | -47.08        | -14.06 | 4708   | 560.60|
|                | Asiatic acid             | -43.52        | -13.90 | 5050   | 562.20|
Table 3: Drug profile and ADME analysis of top four metabolites

| Parameter                  | Top Main Protease Protein Inhibitors of SARS-CoV-2 |
|---------------------------|----------------------------------------------------|
|                           | Asiatic acid | Guajaverin | Avicularin | Witheferin |
| **Physicochemical parameters** |           |            |            |            |
| Formula                   | C30H48O5    | C20H18O11  | C20H18O11  | C28H38O6   |
| Molecular weight          | 488.70 g/mol| 434.35 g/mol| 434.35 g/mol| 470.60 g/mol|
| No. H-bond acceptors      | 5           | 11         | 11         | 6          |
| No. H-bond donors         | 4           | 7          | 7          | 2          |
| Molar Refractivity        | 139.24      | 104.19     | 104.19     | 127.49     |
| TPSA                      | 97.99 Å²    | 190.28 Å²  | 190.28 Å²  | 96.36 Å²   |
| Lipophilicity             |            |            |            |            |
| Log P<sub>o/w</sub> (ILOGP) | 2.95       | 1.77       | 1.86       | 3.24       |
| Log P<sub>o/w</sub> (XLOGP3) | 5.70     | 0.43       | 0.98       | 3.83       |
| Log P<sub>o/w</sub> (WLOGP) | 5.03       | 0.10       | 0.10       | 3.35       |
| Log P<sub>o/w</sub> (MLOGP) | 4.14       | -2.06      | -2.06      | 2.75       |
| Log P<sub>o/w</sub> (SILICOS-IT) | 3.96 | -0.10      | 0.06       | 3.93       |
| Consensus Log P<sub>o/w</sub> | 4.36      | 0.03       | 0.19       | 3.42       |
| Pharmacokinetics          |            |            |            |            |
| GI absorption             | High       | Low        | Low        | High       |
| BBB permeant              | No         | No         | No         | No         |
| P-gp substrate            | Yes        | No         | No         | Yes        |
| CYP1A2 inhibitor          | No         | No         | No         | No         |
| CYP2C19 inhibitor         | No         | No         | No         | No         |
| CYP2C9 inhibitor          | No         | No         | No         | No         |
| CYP2D6 inhibitor          | No         | No         | No         | No         |
| CYP3A4 inhibitor          | No         | No         | No         | No         |
| Log K<sub>s</sub> (skin permeation) | - 5.23 cm/s | -8.64 cm/s | -8.25 cm/s | -6.45 cm/s |
| Water Solubility          |            |            |            |            |
| Log S (ESOL)              | -6.33      | -2.99      | -3.27      | -4.97      |
| Solubility                | 2.29e-4 mg/ml; 4.69e-7 mol/l | 4.47e-01 mg/ml; 1.03e-03 mol/l | 2.34e-01 mg/ml; 5.39e-04 mol/l | 5.01e-03 mg/ml; 1.07e-05 mol/l |
| Class                     | Poorly soluble | Soluble | Soluble | Moderately soluble |
| Log S (SILICOS-IT)        | -4.28      | -1.94      | -2.07      | -3.79      |
| Solubility                | 2.59e-2 mg/ml; 5.31e-05 mol/l | 4.96e+00 mg/ml; 1.14e-02 mol/l | 3.71e+0 mg/ml; 8.55e-3 mol/l | 7.54e-02 mg/ml; 1.60e-04 mol/l |
| Class                     | Moderately soluble | Soluble | Soluble | Soluble |
Table 4: Toxicity model reports of top four drug candidates

| Classification          | Target                     | Prediction and Probability |
|-------------------------|----------------------------|----------------------------|
|                         |   Asiatic Acid | Aviculerin | Guanjaferin | Witheferin |
| Organic toxicity        | Inactive (0.91) | Inactive (0.80) | Inactive (0.80) | Inactive (0.93) |
| Toxicity endpoints      | Inactive (0.70) | Inactive (0.79) | Inactive (0.79) | Inactive (0.55) |
| Toxicity endpoints      | Inactive (0.77) | Active (0.68) | Active (0.93) | Active (0.99) |
| Toxicity endpoints      | Inactive (0.81) | Inactive (0.73) | Inactive (0.79) | Inactive (0.79) |
| Toxicity endpoints      | Inactive (0.73) | Inactive (0.72) | Inactive (0.69) | Active (0.87) |
| Tox21-Nuclear receptor signalling pathways | Inactive (0.99) | Inactive (0.85) | Inactive (0.90) | Inactive (0.98) |
| Tox21-Nuclear receptor signalling pathways | Inactive (0.59) | Inactive (0.92) | Inactive (0.96) | Inactive (0.63) |
| Tox21-Nuclear receptor signalling pathways | Inactive (0.51) | Inactive (0.98) | Inactive (0.97) | Inactive (0.54) |
| Tox21-Nuclear receptor signalling pathways | Inactive (0.91) | Inactive (0.98) | Inactive (0.97) | Inactive (0.80) |

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| Tox21-Nuclear receptor signalling pathways | Estrogen Receptor Alpha (ER) | Inactive (0.73) | Inactive (0.85) | Inactive (0.92) | Inactive (0.60) |
|------------------------------------------|------------------------------|----------------|----------------|----------------|----------------|
| Tox21-Nuclear receptor signalling pathways | Estrogen Receptor Ligand Binding Domain (ER-LBD) | Inactive (0.97) | Inactive (0.99) | Inactive (0.99) | Inactive (0.98) |
| Tox21-Nuclear receptor signalling pathways | Peroxisome Proliferator Activated Receptor Gamma (PPAR-γ) | Inactive (0.97) | Inactive (0.93) | Inactive (0.94) | Inactive (0.91) |
| Tox21-Stress response pathways | Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element | Inactive (0.89) | Inactive (0.91) | Inactive (0.94) | Inactive (0.86) |
| Tox21-Stress response pathways | Heat shock factor response element (HSE) | Inactive (0.89) | Inactive (0.91) | Inactive (0.94) | Inactive (0.86) |
| Tox21-Stress response pathways | Mitochondrial Membrane Potential (MMP) | Inactive (0.85) | Inactive (0.89) | Inactive (0.89) | Inactive (0.80) |
| Tox21-Stress response pathways | Phosphoprotein (Tumor Suppressor) p53 | Inactive (0.93) | Active (0.55) | Inactive (0.72) | Inactive (0.75) |
| Tox21-Stress response pathways | ATPase family AAA domain-containing protein 5 (ATAD5) | Inactive (0.96) | Inactive (0.96) | Inactive (0.96) | Inactive (0.94) |

Table 5: Predicted drug targets for Asiatic acid, Guanjaverin, Aviculerin and Witheferin
| Metabolites                  | Drug bank id | Name                                                                 | Score | Status       |
|-----------------------------|--------------|----------------------------------------------------------------------|-------|--------------|
| Asiatic acid                | DB00741      | Hydrocortisone                                                        | 0.539 | Approved     |
|                             | DB01160      | Dinoprost Tromethamine                                                | 0.529 | Approved     |
|                             | DB07886      | (11alpha,14beta)-11,17,21-trihydroxypregn-4-ene-3,20-dione           | 0.539 | Experimental |
|                             | DB07209      | (8R,9Z,12Z)-8-hydroxy-6-oxyoctadeca-9,12-dienoic acid                 | 0.510 | Experimental |
| Guanjaverin                 | DB08995      | Diosmin                                                               | 0.280 | Approved     |
|                             | DB02375      | Myricetin                                                             | 0.236 | Experimental |
| Witheferin                  | DB00410      | Mupirocin                                                             | 0.481 | Approved     |

Table 6: Predicted bioactive molecules from drug bank
### Supplementary File 1: Molecular docking results of 27 plant metabolites with different SARS-CoV-2 proteins/protein domains

| Macromolecules          | Ligands/Metabolites | Global energy | ACE   | Score | Area   |
|-------------------------|---------------------|---------------|-------|-------|--------|
| Main protease (6W63)    | Alicin              | -30.25        | -10.73| 2588  | 335.00 |
|                         | Andrographolide     | -44.40        | -11.85| 4418  | 461.90 |
|                         | Apigenin            | -42.20        | -12.49| 3494  | 420.80 |
|                         | Asiatric acid       | -53.05        | -15.26| 4916  | 577.10 |
|                         | Avicularin          | -48.62        | -18.50| 4694  | 532.10 |
|                         | Capsaicin           | -41.50        | -12.59| 4204  | 477.70 |
| Compound                        | Lipid Inhibition (%) | Lipid Formation (%) | Lipid Peroxidation (%) | Lipid Inflammation (%) | Lipid Oxidation (%) |
|--------------------------------|----------------------|---------------------|------------------------|------------------------|---------------------|
| Chavibetol                     | -26.69               | -8.37               | 2772                   | 295.10                 |                     |
| Cinnamic                       | -23.90               | -6.60               | 2538                   | 300.10                 |                     |
| Curcumin                       | -46.17               | -14.78              | 4812                   | 553.70                 |                     |
| Eugenol                        | -27.26               | -8.65               | 2764                   | 307.50                 |                     |
| Flavonoidsarjunone             | -39.64               | -12.11              | 4182                   | 459.60                 |                     |
| Galangin                       | -40.62               | -12.12              | 3276                   | 407.90                 |                     |
| Gentisic acid                  | -22.85               | -6.54               | 2282                   | 239.10                 |                     |
| Guajaverin                     | -48.48               | -15.12              | 4450                   | 497.50                 |                     |
| Kaempferol                     | -42.79               | -13.26              | 3712                   | 410.10                 |                     |
| Luteolin                       | -42.28               | -11.85              | 3604                   | 414.90                 |                     |
| Mcoumaric acid                 | -27.51               | -8.43               | 2504                   | 279.90                 |                     |
| Piperic acid                   | -38.57               | -11.17              | 3232                   | 371.40                 |                     |
| Piperine                       | -45.69               | -13.64              | 4528                   | 471.80                 |                     |
| Quercetine                     | -43.15               | -12.56              | 3590                   | 418.20                 |                     |
| Swertiamarin                   | -40.62               | -11.85              | 3896                   | 458.10                 |                     |
| Swertinin                      | -36.99               | -10.87              | 3632                   | 433.50                 |                     |
| Thymoquinone                   | -26.29               | -7.84               | 2800                   | 299.30                 |                     |
| Vincamine                      | -38.56               | -13.65              | 4088                   | 526.20                 |                     |
| Vitexin                        | -44.33               | -13.20              | 4428                   | 497.10                 |                     |
| Withaferin                     | -48.46               | -14.08              | 4984                   | 597.40                 |                     |
| Zingiberene                    | -33.34               | -11.66              | 3508                   | 392.10                 |                     |
| **Nsp9 RNA binding protein (6W4B)** |                     |                     |                        |                        |                     |
| Alicin                         | -23.37               | -9.07               | 2688                   | 317.00                 |                     |
| Andrographolide                | -45.51               | -11.45              | 4088                   | 564.70                 |                     |
| Apigenin                       | -35.95               | -9.29               | 3500                   | 446.10                 |                     |
| Asiatic acid                   | -50.04               | -16.37              | 4998                   | 564.20                 |                     |
| Avicularin                     | -39.83               | -235.80             | 4556                   | 514.50                 |                     |
| Capsaicin                      | -35.71               | -11.59              | 4262                   | 566.70                 |                     |
| Chavibetol                     | -25.88               | -8.63               | 3062                   | 343.90                 |                     |
| Cinnamic                       | -30.87               | -8.40               | 2744                   | 320.00                 |                     |
| Curcumin                       | -38.31               | -11.87              | 4498                   | 499.70                 |                     |
| Eugenol                        | -28.12               | -6.88               | 3068                   | 376.10                 |                     |
| Flavonoidsarjunone             | -40.97               | -13.12              | 4582                   | 514.80                 |                     |
| Galangin                       | -43.02               | -12.91              | 3384                   | 424.10                 |                     |
| Gentisic acid                  | -26.73               | -8.16               | 2298                   | 266.00                 |                     |
| Guajaverin                     | -42.72               | -10.63              | 4548                   | 641.40                 |                     |
| Kaempferol                     | -37.56               | -9.83               | 4094                   | 465.00                 |                     |
| Luteolin                       | -44.69               | -12.82              | 3604                   | 407.40                 |                     |
| Compound                | Value1 | Value2 | Value3 | Value4 |
|-------------------------|--------|--------|--------|--------|
| Mcoumaric acid          | -26.79 | -8.29  | 2790   | 298.10 |
| Piperic acid            | -36.75 | -11.54 | 3186   | 387.50 |
| Piperine                | -47.54 | -14.85 | 5456   | 616.80 |
| Quercetin               | -36.88 | -10.32 | 3614   | 456.10 |
| Swertiamarin            | -41.25 | -11.96 | 4458   | 493.70 |
| Swertinin               | -37.25 | -13.73 | 3494   | 438.00 |
| Thymoquinone            | -31.70 | -8.49  | 2804   | 354.90 |
| Vincamine               | -32.44 | -9.40  | 4056   | 447.10 |
| Vitexin                 | -39.35 | -10.17 | 4298   | 618.30 |
| Withaferin              | -47.95 | -13.30 | 4896   | 570.40 |
| Zingiberene             | -33.12 | -9.60  | 3588   | 493.20 |

| Spike ectodomain (6VYB) | Alicin  |         |        |        |
|-------------------------|---------|--------|--------|--------|
|                        | -27.25  | -9.68  | 3382   | 373.70 |
| Andrographolide         | -45.37  | -15.44 | 5138   | 656.10 |
| Apigenin                | -63.44  | -3.93  | 3992   | 481.50 |
| Asiatic acid            | -60.68  | -22.33 | 6276   | 771.50 |
| Avicularin              | -52.93  | -17.51 | 5474   | 683.30 |
| Capsaicin               | -45.02  | -11.20 | 5312   | 595.50 |
| Guajaverin              | -55.24  | -17.51 | 5208   | 559.20 |
| Chavibetol              | -26.49  | -8.36  | 3562   | 404.90 |
| Cinnamic                | -28.86  | -7.93  | 3320   | 370.40 |
| Curcumin                | -51.22  | -19.15 | 5498   | 701.80 |
| Eugenol                 | -31.95  | -8.67  | 3510   | 403.40 |
| Flavonoidsarjunone      | -47.18  | -16.10 | 5242   | 639.30 |
| Galangin                | -38.87  | -12.21 | 4482   | 512.30 |
| Gentisic acid           | -26.51  | -6.35  | 2842   | 308.50 |
| Molecule              | HR2 Domain | Spike receptor binding domain |
|-----------------------|------------|--------------------------------|
|                       | (6LVN)     | (6M0J)                         |
| Kaempferol            | -40.28     | -29.23                         |
| Luteolin              | -43.23     | -20.94                         |
| M-coumaric acid       | -30.38     | -19.79                         |
| Piperic acid          | -35.99     | -22.49                         |
| Piperine              | -46.36     | -23.52                         |
| Quercetine            | -43.18     | -21.16                         |
| Swertiaamarin         | -42.10     | -21.47                         |
| Swertinin             | -38.75     | -18.60                         |
| Thymoquinone          | -30.45     | -22.27                         |
| Vincamine             | -51.86     | -22.77                         |
| Vitexin               | -46.25     | -19.79                         |
| Withaferin            | -60.19     | -19.79                         |
| Zingiberene           | -32.99     | -19.79                         |
| Allicin               | -20.47     | -19.79                         |
| Andrographolide       | -20.77     | -19.79                         |
| Apigenin              | -23.85     | -19.79                         |
| Asiatet acid          | -27.58     | -19.79                         |
| Aviculinar            | -26.48     | -19.79                         |
| Capsaicin             | -21.84     | -19.79                         |
| Chavibetol            | -15.00     | -19.79                         |
| Cinnamic              | -17.36     | -19.79                         |
| Curcumin              | -21.32     | -19.79                         |
| Eugenol               | -19.49     | -19.79                         |
| Flavonoids (arjunone) | -17.71     | -19.79                         |
| Galangin              | -21.97     | -19.79                         |
| Gentisic acid         | -16.43     | -19.79                         |
| Guajaverin            | -28.73     | -19.79                         |
| Kaempferol            | -18.68     | -19.79                         |
| Luteolin              | -22.77     | -19.79                         |
| M-coumaric acid       | -19.79     | -19.79                         |
| Piperic acid          | -22.49     | -19.79                         |
| Piperine              | -23.52     | -19.79                         |
| Quercetine            | -21.16     | -19.79                         |
| Swertiaamarin         | -21.47     | -19.79                         |
| Swertinin             | -18.60     | -19.79                         |
| Thymoquinone          | -19.94     | -19.79                         |
| Vincamine             | -20.94     | -19.79                         |
| Vitexin               | -24.76     | -19.79                         |
| Withaferin            | -28.11     | -19.79                         |
| Zingiberene           | -19.52     | -19.79                         |
|                       |            |                                |
|                       |            | Allicin                        |
|                       |            | Andrographolide                |
|                       |            | Apigenin                       |
| Compound          | IC50 1 | IC50 2 | CC50 1 | CC50 2 |
|-------------------|--------|--------|--------|--------|
| Asiatic acid      | -45.69 | -13.09 | 5978   | 691.70 |
| Avicularin        | -43.13 | -11.09 | 5232   | 604.20 |
| Capsaicin         | -44.98 | -12.05 | 4486   | 586.30 |
| Chavibetol        | -30.95 | -8.48  | 3092   | 352.90 |
| Cinnamic          | -29.28 | -7.79  | 2840   | 330.70 |
| Curcumin          | -38.94 | -8.36  | 4762   | 643.80 |
| Eugenol           | -33.32 | -8.49  | 3112   | 398.00 |
| Flavonoids (arjunone) | -38.98 | -9.07  | 4768   | 583.60 |
| Galangin          | -36.69 | -9.74  | 3812   | 510.40 |
| Gentisic acid     | -26.77 | -7.29  | 2558   | 297.60 |
| Guajaverin        | -47.34 | -11.22 | 4554   | 575.60 |
| Kaempferol        | -40.20 | -9.03  | 3780   | 496.30 |
| Luteolin          | -37.14 | -9.81  | 3904   | 500.00 |
| M-coumaric acid   | -28.83 | -8.38  | 2852   | 335.60 |
| Piperic acid      | -35.63 | -9.58  | 3472   | 474.00 |
| Piperine          | -39.93 | -10.23 | 4648   | 525.30 |
| Quercetine        | -39.48 | -9.25  | 3712   | 436.70 |
| Swertiamarin      | -44.70 | -10.76 | 4424   | 574.30 |
| Swertinin         | -37.27 | -4.09  | 3708   | 513.80 |
| Thymoquinone      | -28.72 | -6.78  | 2970   | 403.80 |
| Vincamine         | -41.52 | -11.33 | 4480   | 553.20 |
| Vitexin           | -45.02 | -10.31 | 4698   | 569.50 |
| Withaferin        | -46.84 | -11.13 | 5598   | 640.50 |
| Zingiberene       | -29.16 | -7.75  | 3748   | 510.80 |

| Main protease (6LU7) | IC50 1 | IC50 2 | CC50 1 | CC50 2 |
|----------------------|--------|--------|--------|--------|
| Allicin              | -28.12 | -11.49 | 2746   | 338.40 |
| Andrographolide      | -48.24 | -12.61 | 3838   | 504.40 |
| Apigenin             | -41.45 | -11.28 | 3792   | 421.00 |
| Asiatic acid         | -43.52 | -13.90 | 5050   | 562.20 |
| Avicularin           | -54.04 | -14.77 | 4584   | 520.60 |
| Capsaicin            | -37.56 | -10.50 | 4164   | 497.20 |
| Chavibetol           | -27.05 | -7.71  | 2944   | 312.20 |
| Cinnamic             | -26.77 | -6.92  | 2440   | 314.10 |
| Curcumin             | -50.24 | -14.84 | 5028   | 577.30 |
| Eugenol              | -27.04 | -8.06  | 2872   | 365.00 |
| Flavonoids (arjunone) | -38.30 | -10.90 | 4398   | 566.90 |
| Galangin             | -40.07 | -10.95 | 3718   | 415.30 |
| Gentisic acid        | -22.98 | -5.32  | 2272   | 245.80 |
| Guajaverin           | -51.69 | -12.92 | 4182   | 515.50 |
| Kaempferol           | -40.20 | -11.58 | 3492   | 424.30 |
| Luteolin             | -40.06 | -10.58 | 3640   | 423.30 |
| M-coumaric acid      | -28.25 | -7.46  | 2412   | 297.40 |
| Piperic acid         | -33.25 | -9.24  | 3126   | 359.90 |
| Piperine             | -39.80 | -12.30 | 3958   | 480.50 |
| Quercetine           | -44.95 | -12.38 | 3500   | 409.20 |
| Swertiamarin         | -44.00 | -12.24 | 3950   | 490.70 |
| Compound       | Value 1 | Value 2 | Value 3 | Value 4 |
|---------------|---------|---------|---------|---------|
| Swertinin     | -38.08  | -10.79  | 4032    | 439.80  |
| Thymoquinone  | -23.55  | -5.84   | 2752    | 358.80  |
| Vincamine     | -40.30  | -12.15  | 4028    | 485.90  |
| Vitexin       | -53.19  | -14.69  | 4786    | 536.10  |
| Withaferin    | -47.08  | -14.06  | 4708    | 560.60  |
| Zingiberene   | -27.93  | -8.25   | 3548    | 381.60  |
