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/prorein 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 inhibitorby 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 bythese 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. Theserver 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 ofSARS-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 andwithaferin 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 guajaverinbound 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 effectswith 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 witheferin, while lower for guajaverin and avicularin. Moreover, blood-brain barrier (BBB) permeation was calculated by BOILED-Egg model which revealed no BBB permeantamong 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 witheferin 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. Witheferin, however, found to be relatively toxic among the four candidates with considearble 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), phosphatasesand lyases (i.e. carbonic anhydrase) (Figure 6 and Table 5).Ligand-based virtual screening was performedto 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 witheferin with high prediction score (Table 6). The findingssuggest 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 treatSARS-CoV-2infected 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-2as probable drug targets. In this study, we screenedsome naturalmetabolites 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 (S_1) 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 metabolitesi.e. asiatic acid, avicularin, guajaverin and withaferin scored best for eachsix 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). Ithas 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).

Guaijaverin 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 microbicidial activity of is attributable to guajaverine. Anti-plaque activity is attributed to microbicidial 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 asevere 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 witheferin, was found to be comparatively toxic among the top four candidates.

However drug similarity prediction identified two approved structural analogsof witheferin,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*trialsfor theexperimental 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), Guenjaverin (B), Avicularin (C) and Witheferin (D)

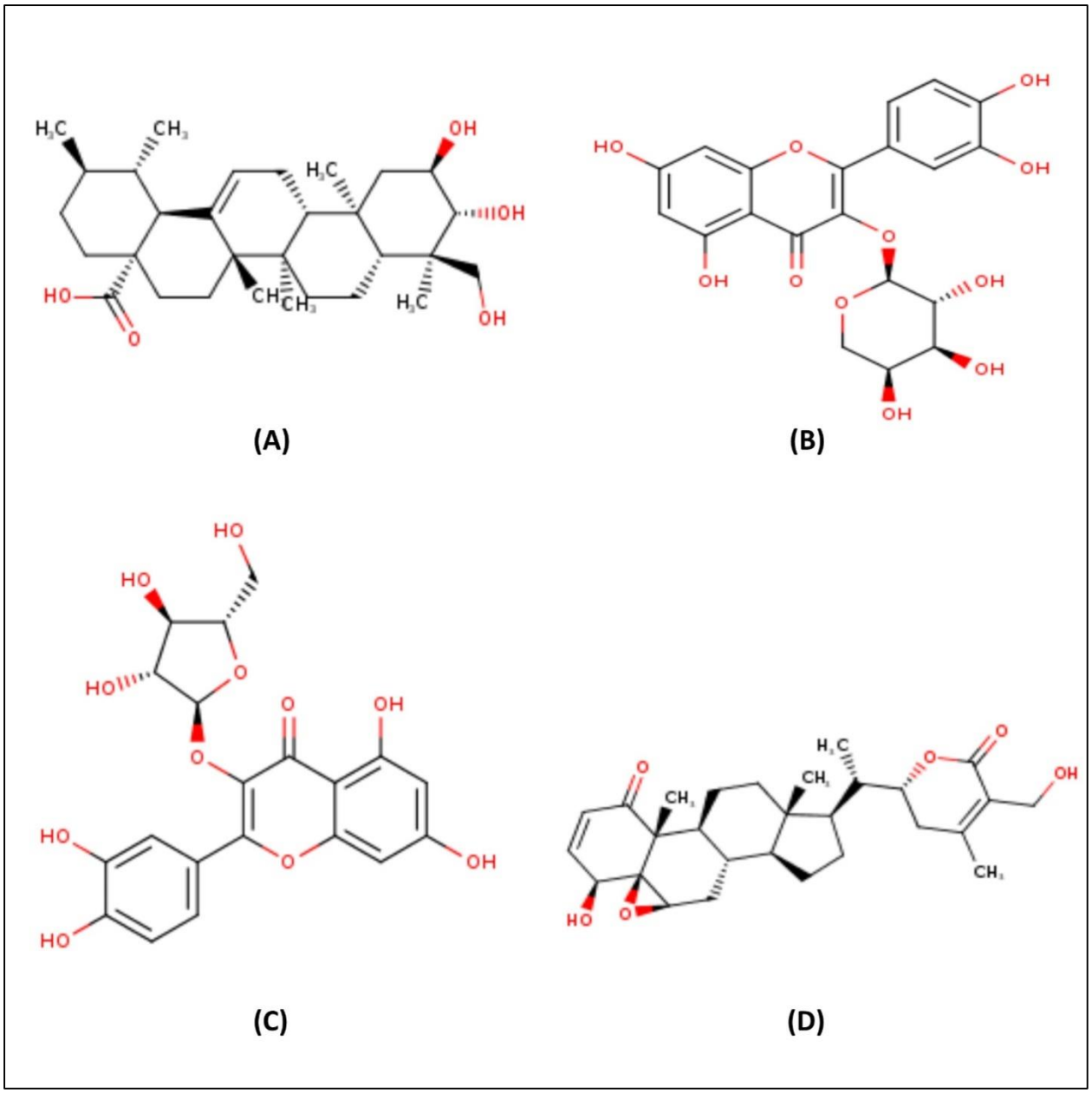
Figure 2: Molecular interaction of Asiatic acid with SARS-CoV-2 main protease (A), Nsp9 RNA binding protein (B) and spike ectodomain (C)

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

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

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

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



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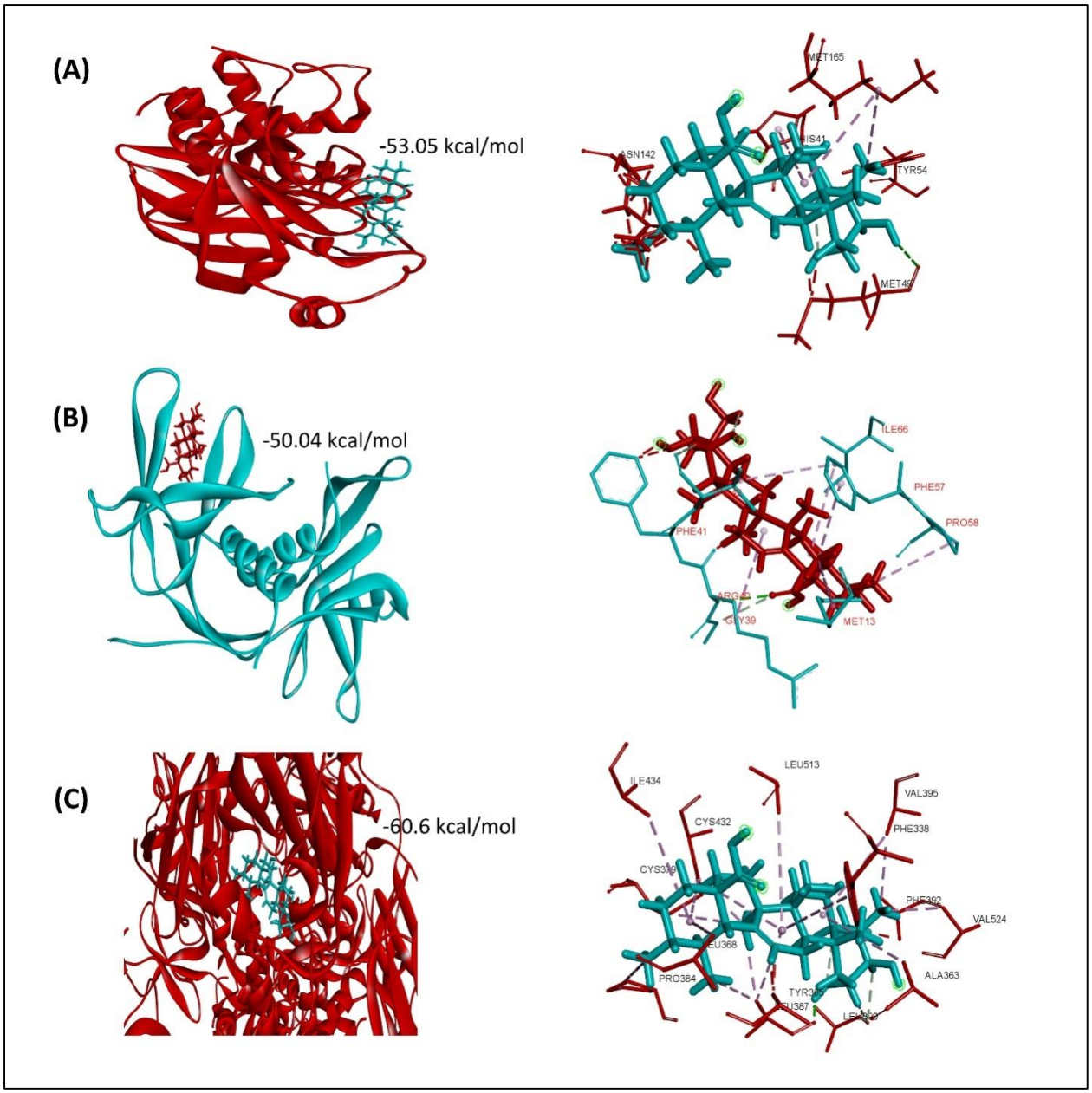
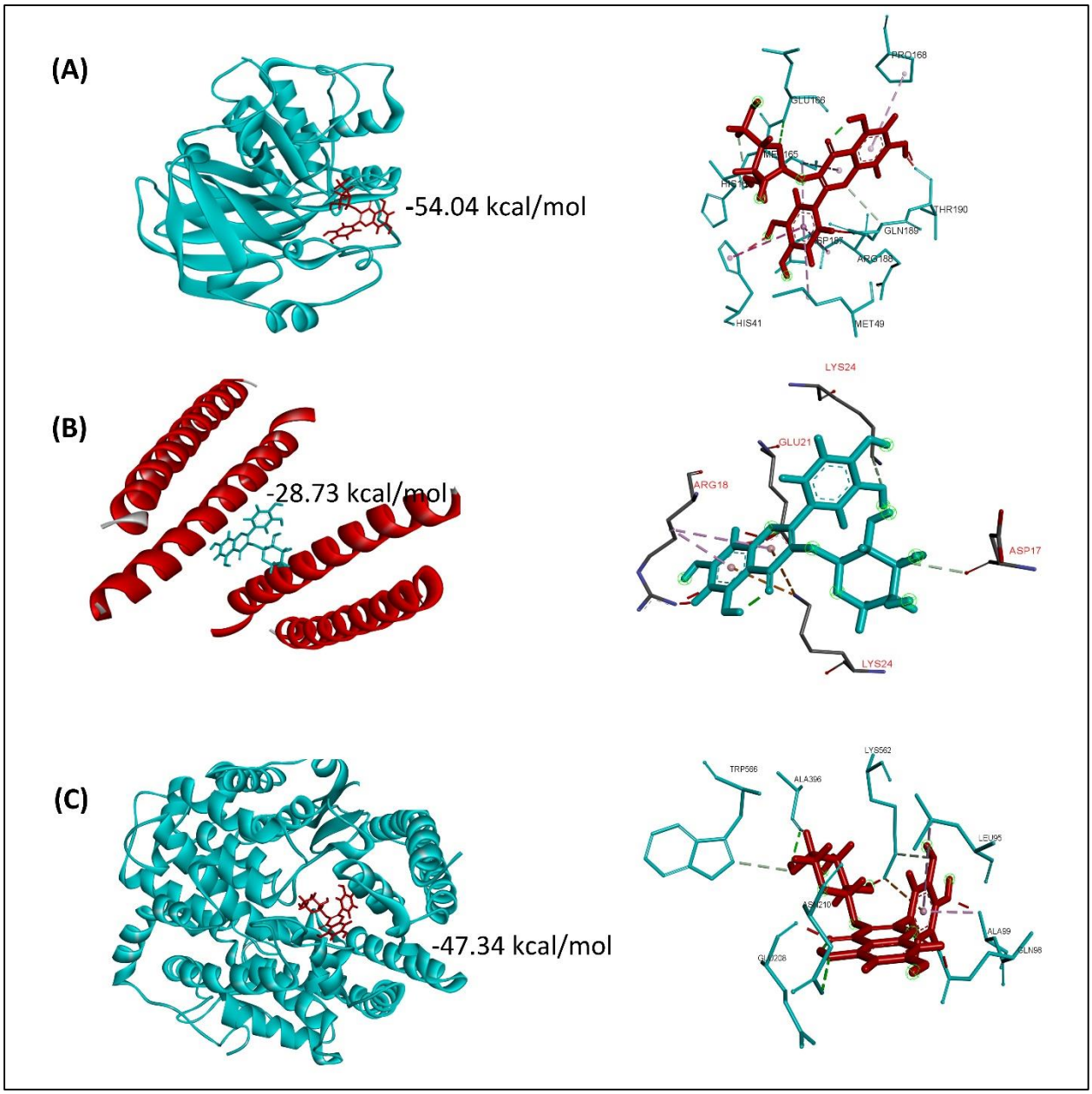


Figure 2: Molecular interaction of Asiatic acid with SARS-CoV-2 main protease (A), Nsp9 RNA binding protein (B) and spike ectodomain (C)



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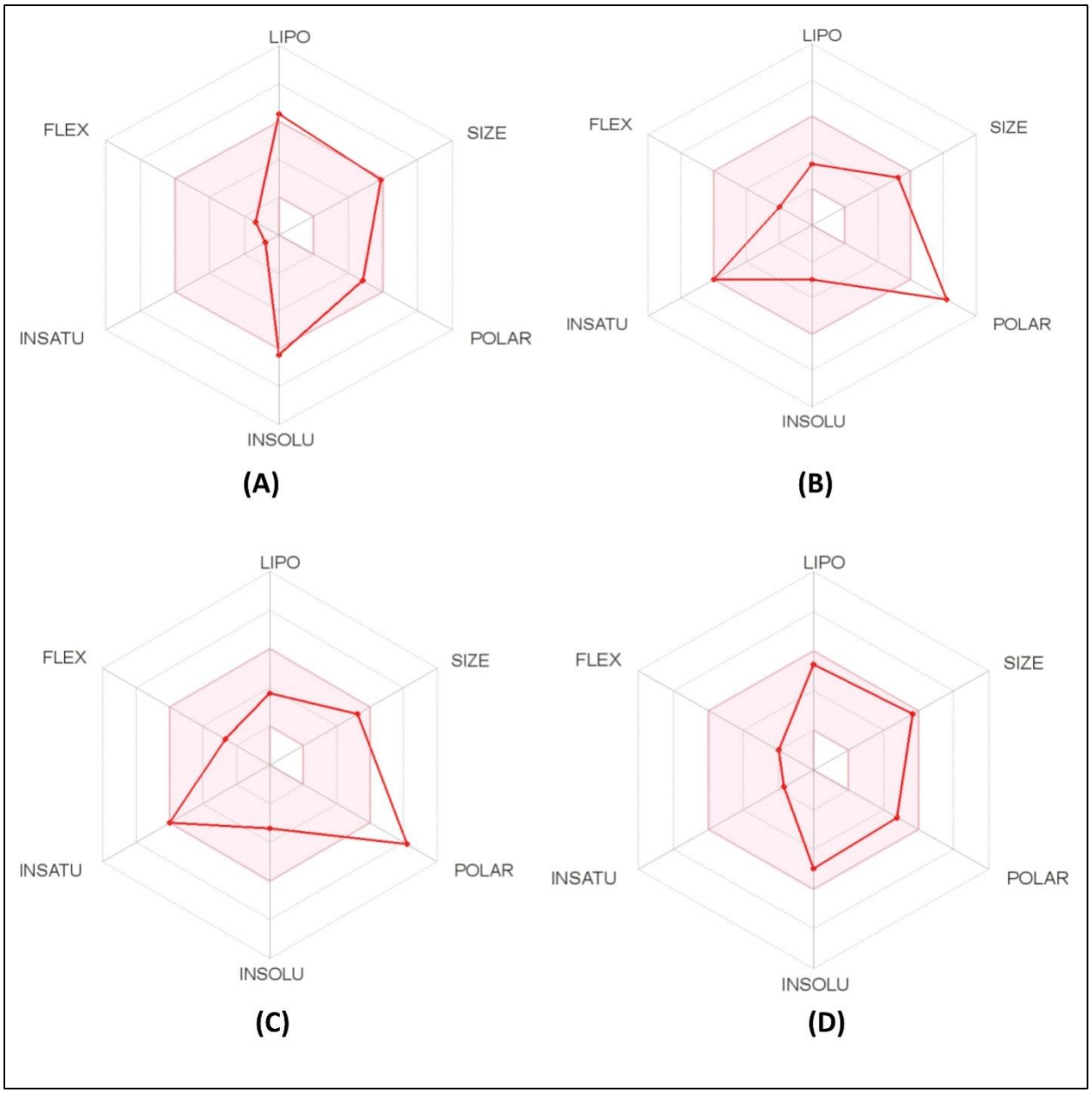

Figure 4: ADME analysis of top four metabolites; A: Asiatic acid, B: Guenjaverin, C: Avicularin, and D: Witheferin

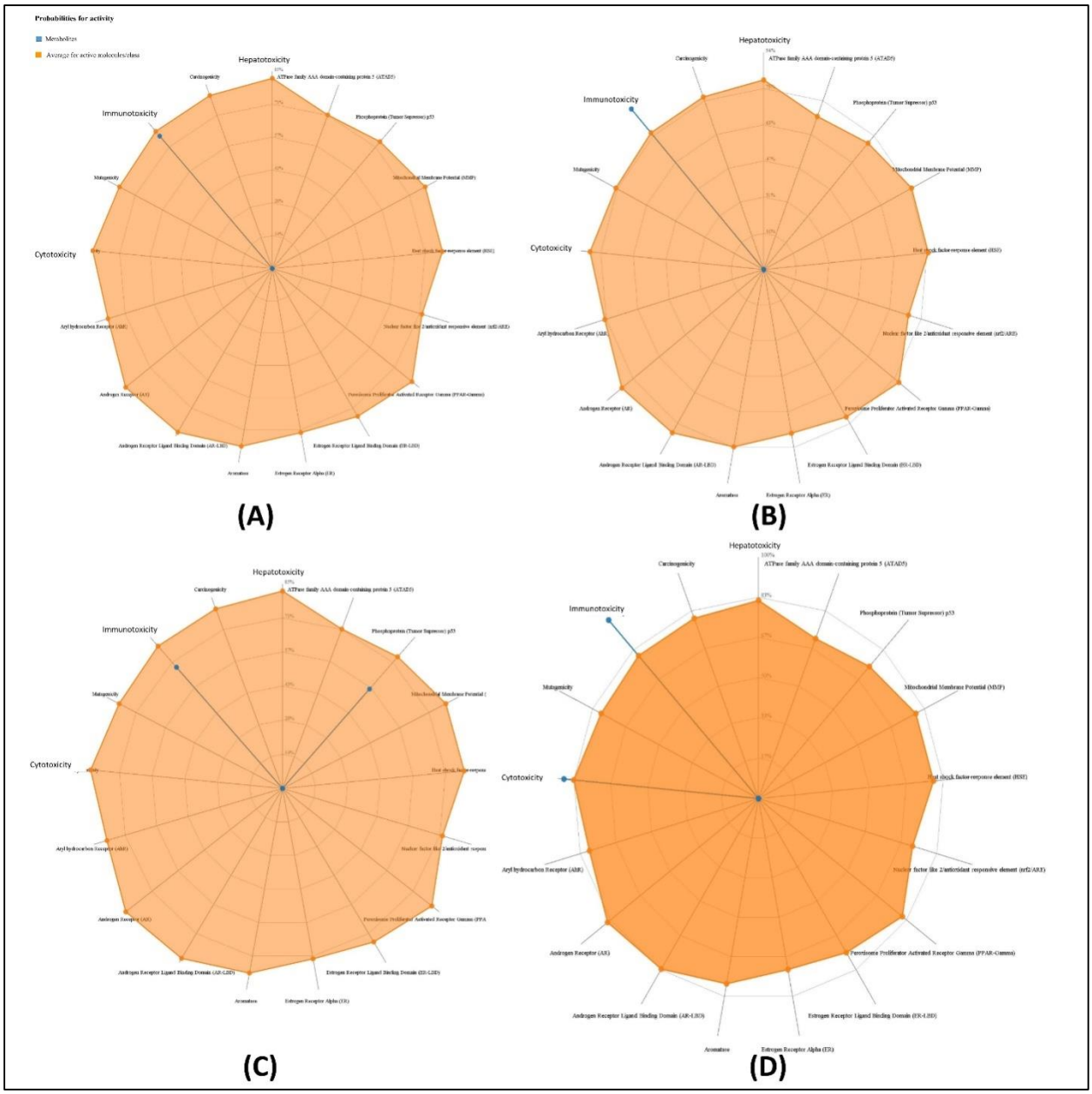

Figure 5: Toxicity patterns of top four drug candidates; A: Asiatic acid, B: Guenjaverin, C: Avicularin, and D: Witheferin

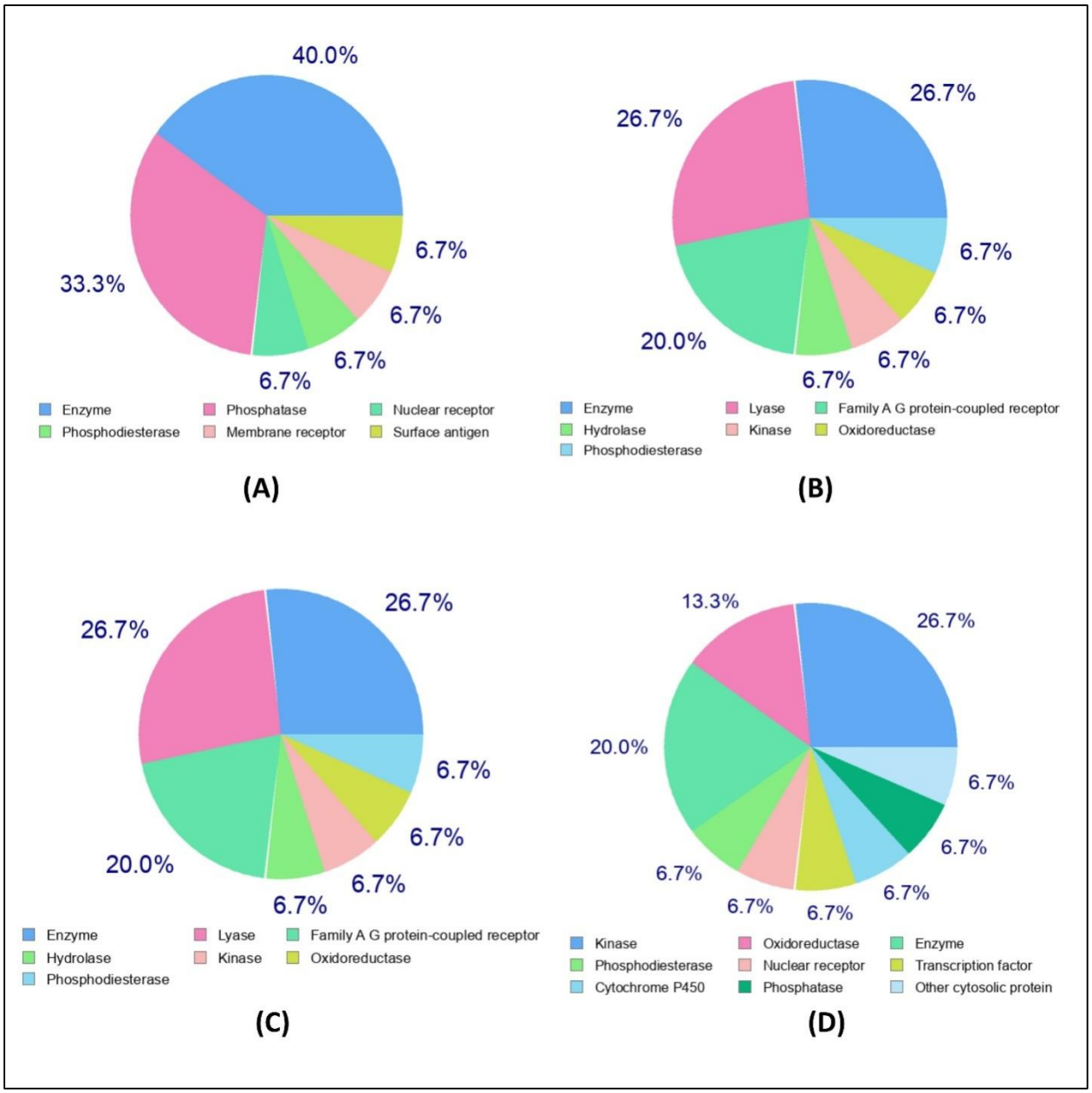

Figure 6: Prediction of drug targets for Asiatic acid (A), Guenjaverin (B), Avicularin (C) and Witheferin (D)

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*	Antimicrorial, 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 guyava, Lespedeza cuneata*	anti-inflammatory, anti-oxidant, 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
Gentisic acid	3469	Phenolic acid	*Gentiana*, *Citrus, H. rosa*-sinensis, *O. europaea,S. indicum*	Antioxidant, neuroprotective, antiinflammatory, hepatoprotective, antimicrobial activities	Abedi et al., 2019
Guajaverin	5481224	Flavonoid	*Psidium guyava*	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-arthritic, 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	Monoterpene	*Nigella sativa*	Anti-oxidant and anti-inflammatory properties, Anti-microbial, Anti-arthritic, anti-cancer efficacy	Ahmad et al., 2019;
Vincamine	15376	Alkaloid	*Catharanthus roseus, Vinca minor*	Cerebral disorders, antiulcer 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 Officinale	Anti-ulcer, antibacterial, cytoxic effect	Johji et al., 1988

Table 2: Analysis ofglobal 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	-235.80	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 $P_{o/w}$ (iLOGP)	2.95	1.77	1.86	3.24
	Log $P_{o/w}$ (XLOGP3)	5.70	0.43	0.98	3.83
	Log $P_{o/w}$ (WLOGP)	5.03	0.10	0.10	3.35
	Log $P_{o/w}$ (MLOGP)	4.14	-2.06	-2.06	2.75
	Log $P_{o/w}$ (SILICOS-IT)	3.96	-0.10	0.06	3.93
	Consensus Log $P_{o/w}$	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_p (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
Medicinal Chemistry	Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5	No; 1 violation: MW>350	No; 1 violation: MW>350	No; 2 violations: MW>350, XLOGP3>3.5
	Bioavailability Score	0.56	0.17	0.17	0.55
	PAINS	0 alert	1 alert: catechol_A	1 alert: catechol_A	0 alert
	Synthetic accessibility	6.56	5.05	5.04	6.83

Table 4: Toxicity model reports of top four drug candidates

Classification	Target	Prediction and Probability			
		Asiatic Acid	***Aviculerin***	***Guanjaverin***	***Witheferin***
Organ toxicity	Hepatotoxicity	Inactive (0.91)	Inactive (0.80)	Inactive (0.80)	Inactive (0.93)
Toxicity end points	Carcinogenicity	Inactive (0.70)	Inactive (0.79)	Inactive (0.79)	Inactive (0.55)
Toxicity end points	Immunotoxicity	Active(0.77)	Active (0.68)	Active (0.93)	Active (0.99)
Toxicity end points	Mutagenicity	Inactive (0.81)	Inactive (0.73)	Inactive (0.79)	Inactive (0.79)
Toxicity end points	Cytotoxicity	Inactive (0.73)	Inactive (0.72)	Inactive (0.69)	Active (0.87)
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	Inactive (0.99)	Inactive (0.85)	Inactive (0.90)	Inactive (0.98)
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	Inactive (0.59)	Inactive (0.92)	Inactive (0.96)	Inactive (0.63)
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	Inactive (0.51)	Inactive (0.98)	Inactive (0.97)	Inactive (0.54)
Tox21-Nuclear receptor signalling pathways	Aromatase	Inactive (0.91)	Inactive (0.98)	Inactive (0.97)	Inactive (0.80)
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 Supressor) 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

Metab-olites	Drug Targets	Common Name	Uniprot ID	ChEMBL ID	Target Class	Probability
Asiatic Acid	Aldo-keto reductase family 1 member B10	AKR1B10	O60218	CHEMBL5983	Enzyme	
	Protein-tyrosine phosphatase 1B	PTPN1	P18031	CHEMBL335	Phosphatase	
	11-β-hydroxysteroid dehydrogenase 1	HSD11B1	P28845	CHEMBL4235	Enzyme	
	DNA polymerase beta	POLB	P06746	CHEMBL2392	Enzyme	
	T-cell protein-tyrosine phosphatase	PTPN2	P17706	CHEMBL3807	Phosphatase	
	Phospholipase A2 group 1B	PLA2G1B	P04054	CHEMBL4426	Enzyme	
Guanjaverin & Aviculerin	Aldose reductase	AKR1B1	P15121	CHEMBL1900	Enzyme	
	Carbonic anhydrase II	CA2	P00918	CHEMBL205	Lyase	
	Carbonic anhydrase VII	CA7	P43166	CHEMBL2326	Lyase	
	Carbonic anhydrase XII	CA12	O43570	CHEMBL3242	Lyase	
	Carbonic anhydrase IV	CA4	P22748	CHEMBL3729	Lyase	
	NADPH oxidase 4	NOX4	Q9NPH5	CHEMBL1250375	Enzyme	
	Adrenergic receptor alpha-2	ADRA2C	P18825	CHEMBL1916	Family A G protein-coupled-receptor	
	Acetylcholinesterase	ACHE	P22303	CHEMBL220	Hydrolase	
	Quinone reductase 2	NQO2	P16083	CHEMBL3959	Enzyme	
	Ribosomal protein S6 kinase alpha 3	RPS6KA3	P51812	CHEMBL2345	Kinase	
	Neuromedin-U receptor 2	NMUR2	Q9GZQ4	CHEMBL1075144	Family A G protein-coupled receptor	
Witheferin	Protein kinase C alpha	PRKCA	P17252	CHEMBL299	Kinase	
	Cyclooxygenase-2	PTGS2	P35354	CHEMBL230	Oxidoreductase	
	Isoleucyl-tRNA synthetase	IARS	P41252	CHEMBL3235	Enzyme	
	Protein kinase C delta	PRKCD	Q05655	CHEMBL2996	Kinase	
	HMG-CoA reductase	HMGCR	P04035	CHEMBL402	Oxidoreductase	
	Phosphodiesterase 4D	PDE4D	Q08499	CHEMBL288	Phosphodiesterase	
	Telomerase reverse transcriptase	TERT	O14746	CHEMBL2916	Enzyme	
	Androgen Receptor	AR	P10275	CHEMBL1871	Nuclear receptor	
	Protein kinase C epsilon	PRKCE	Q02156	CHEMBL3582	Kinase	
	Proto-oncogene c-JUN	JUN	P05412	CHEMBL4977	Transcription factor	
	Protein-tyrosine phosphatase 1B	PTPN1	P18031	CHEMBL335	Phosphatase	

Table 6: Predicted bioactive molecules from drug bank

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-oxooctadeca-9,12-dienoic acid	0.510	Experimental
Guanjaverin	DB08995	Diosmin	0.280	Approved
	DB02375	Myricetin	0.236	Experimental
Witheferin	DB00410	Mupirocin	0.481	Approved
	DB00641	Simvastatin	0.447	Approved
	DB08224	hexahydro-7-methyl-8-[2-[(2r,4r)-tetrahydro-4-hydroxy-6-oxo-2h-pyran-2-yl]ethyl]-1-naphthalenol	0.501	Experimental
	DB04775	Reidispongiolide C	0.479	Experimental
Avicularin	DB08995	Diosmin	0.249	Approved
	DB02375	Myricetin	0.210	Experimental

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
	Asiatic acid	-53.05	-15.26	4916	577.10
	Avicularin	-48.62	-18.50	4694	532.10
	Capsaicin	-41.50	-12.59	4204	477.70
	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
	Zingiberne	-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
	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	-43.64	-13.93	3992	481.50

	Asiatic acid	-60.68	-22.33	6276	771.50
	Avicularin	-52.93	-17.15	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
	Kaempferol	-40.28	-12.75	4336	517.10
	Luteolin	-43.23	-13.67	4408	523.80
	Mcoumaric acid	-30.38	-9.56	3086	363.50
	Piperic acid	-35.99	-8.74	3824	447.40
	Piperine	-46.36	-15.55	4770	597.80
	Quercetine	-43.18	-13.59	4256	507.90
	Swertiamarin	-42.10	-15.05	4822	565.40
	Swertinin	-38.75	-12.81	4262	532.30
	Thymoquinine	-30.45	-10.06	3418	398.70
	Vincamine	-51.86	-17.31	5160	650.10
	Vitexin	-46.25	-16.25	5028	669.00
	Withaferin	-60.19	-20.49	5760	793.10
	Zingiberene	-32.99	-8.48	4436	489.20
HR2 Domain (6LVN)	Allicin	-20.47	-8.64	2164	259.40
	Andrographolide	-20.77	-0.89	3640	395.00
	Apigenin	-23.85	-8.57	3028	384.40
	Asiatic acid	-27.58	-1.12	4366	500.30
	Avicularin	-26.48	-1.22	3986	465.10
	Capsaicin	-21.84	-1.23	3362	361.50
	Chavibetol	-15.00	-2.47	2104	254.70
	Cinnamic	-17.36	-6.08	2080	232.60
	Curcumin	-21.32	1.33	4458	540.00
	Eugenol	-19.49	-7.02	2392	275.80

	Flavonoids (arjunone)	-17.71	1.90	4122	467.10
	Galangin	-21.97	0.21	3242	338.00
	Gentisic acid	-16.43	-4.95	1924	200.40
	Guajaverin	-28.73	-2.13	3696	443.50
	Kaempferol	-18.68	-7.45	3114	387.40
	Luteolin	-22.77	-1.23	2966	309.40
	M-coumaric acid	-19.79	-6.26	2070	244.60
	Piperic acid	-22.49	-7.06	2664	309.50
	Piperine	-23.52	0.42	3390	381.50
	Quercetine	-21.16	-4.54	2892	377.50
	Swertiamarin	-21.47	1.84	3538	426.30
	Swertinin	-18.60	0.71	3304	367.70
	Thymoquinone	-19.94	-6.76	2310	239.10
	Vincamine	-20.94	-1.78	3728	410.40
	Vitexin	-24.76	-1.95	3502	424.90
	Withaferin	-28.11	-1.24	4376	507.70
	Zingiberene	-19.52	-2.19	3054	315.20
Spike receptor binding domain (6M0J)	Allicin	-29.23	-10.78	2906	331.60
	Andrographolide	-40.95	-10.29	4296	574.70
	Apigenin	-38.49	-10.17	3702	449.80
	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)	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	-26.59	-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
	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