# Bioinformatic Analysis of Antiviral Medicinal Compounds Against Sars Cov-2 Proteases

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## Abstract

The world is under siege from a global pandemic caused by a novel class of coronaviruses called severe acute respiratory syndrome coronavirus-2 (SARS CoV-2). These viruses cause severe respiratory illness leading to death. Molecular studies reveal that SARS CoV-2 proteases are involved in the processing of viral polyproteins**.** This study was conducted to obtain antiviral agents for SARS CoV-2 proteases. An extensive library of antiviral medicinal compounds was scrutinized to determine the probable interaction with both main and 3-chymotrypsin like proteases. Six antiviral compounds (Abietic Acid, Gallic Acid, Piceatannol, Piperine, Sinomenine, and Triptolide) were capable of establishing hydrogen bonds with the active pocket residues of the viral proteases, with appreciable binding energy. These compounds were subjected to root mean square analysis and tested not only for acute toxicity, but also for absorption, distribution, metabolism, excretion, and toxicity properties. Results were favourable for use in the treatment of SARS COV-2 infection.

**Keywords:** Severe acute respiratory syndrome coronavirus-2; virtual Screening; antiviral Medicinal Compounds; viral Proteases; ADMET Properties

## 1. Introduction

An unprecedented surge of severe acute respiratory syndrome coronavirus-2 is currently being observed worldwide. There are millions of infected individuals and several thousand impending deaths. It was first reported in Wuhan, China during the Chinese New Year, and it turned into a global pandemic due to its unfamiliar nature and subclinical manifestation. Symptoms include a high fever, dry cough, convulsions, headaches, sore throat, loss of taste or smell, muscle pain, and lymphopenia. Severe respiratory distress can be observed due to lung consolidation inflicting physiological failure. An individual infected with this virus remains asymptomatic for a long time, hence acting as a vector for disease transmission (Bai *et al*., 2020; Lai *et al*., 2020). The mortality rate ranges from 4 – 6% but this number dramatically increases in the elderly as well as in the people with underlying secondary illnesses or immune conditions. Preliminary studies assumed that these viruses derive from bats and are transmitted to humans through critical mutational events and possibly through palm civets as intermediate hosts (Zhou et al., 2020). However, the ancestor of this virus is still unknown, and many studies are underway in order to establish the possible leads.

Severe acute respiratory syndrome coronavirus 2 is a member of genus Betacoronavirus, family Coronaviridae, suborder Cornidovirineae, order Nidovirales, and realm Riboviria (Nand *et al.*, 2020). The members of this group are notorious for causing severe respiratory distress in humans and animals. These viruses are composed of positive-sense, single-stranded RNA, enclosed within a lipid envelope. Upon infection, the spikes protruding from the virion

impersonate typical eukaryotic mRNA, with their 5'cap and poly-A tails (Kang *et al*., 2020). The virion is about 60–160 nm in size, and the genomic sequence has about 19 –32 kilobase pairs. The SARS-COV-2 genome possesses 14 annotated open reading frames, which are readily translated by the host ribosome in order to produce viral polyproteins (Kaul, 2020). These polyproteins are further processed by two cysteine proteases 3C-like protease and main-like protease encoded by ORF1a of SARS COV-2 RNA (Báez-Santos *et al*., 2015; Jo *et al*., 2020). These proteases together facilitate the proteolytic processing of polyproteins into respective protein monomers, and are considered essential molecular drug targets in order to avert viral propagation.

Medicinal compounds are well known for a multitude of pharmacological activity against various types of diseases. However, recent reports highlighted their antiviral activity, including substantial viral load reduction and immunological stimulation toward viral antigens (Ben-Shabat *et al*., 2019). Such compounds could be promising medications for the treatment of this debilitating disease. In this study, we opted for a virtual screening method by employing different antiviral medicinal compounds. We were able to determine the probable interaction of the antiviral compounds with these viral proteases and assess the ADMET profile and possible adverse effects of these compounds, in order to expedite the discovery of drugs.

## 2. Methodology

### 2.1.Prediction of Active Site Residues

Two structural proteases of SARS COV-2, the COVID main-protease (6LU7) (Jo *et al.*, 2020)and 3-chymotrypsin-like protease (4WY3) (Jin et al., 2020), known for their proteolytic processing of viral polyproteins, were chosen as target receptors and procured from the Protein data bank. Active site pocket residues were identified through Metapocket 2.0, to highlight the potential ligand-binding sites (Zhang *et al*., 2011).

### 2.2.Preparation of Ligands and Receptors

A library of ligands was prepared by selecting antiviral medicinal compounds as discussed in the study (Ben-Shabat *et al*., 2019). Receptors and ligands were appropriately prepared with the Modrefiner(Xu et al., 2011)and PRODRG servers (Schüttelkopf *et al*., 2004) and then subjected to virtual screening using Autodock Vina equipped with Raccoon2 plugin.

### 2.3.Docking Validation

The validation of our screening method was confirmed by re-docking N-[(5-Methylisoxazol-3-Yl)Carbonyl]Alanyl-L-Valyl-N~1~-((1R,2Z)-4-(Benzyloxy)-4-Oxo-1-{[(3R)-2-Oxopyrrolidin-3-Yl]Methyl}But-2-Enyl)-L-Leucinamide and (2S)-2-({[(3R,4aS,8aR)-2-(biphenyl-4-ylcarbonyl)decahydroisoquinolin-3-yl]methyl}amino)-3-(1H-imidazol-5-yl)propanal into their original active sites in these receptors.

### 2.4.Docking Stability and ADMET Analysis

Efficiently interacted ligands were further analyzed for the root mean square deviation, using LigRMSD, acute toxicity and adverse effects through the GUSAR and Adver-Pred databases.

ADMET properties were predicted with Swiss ADME, ADMET SAR 2.0 and pKCSM (Lagunin *et al*., 2011; Pires *et al*., 2015; Daina *et al.*, 2017; Ivanov *et al*., 2018; Yang *et al.*, 2019; Velázquez-Libera *et al*., 2020).

## 3. Results

### 3.1.Screening, Validation and Stability Analysis

Molecular docking is a bioinformatic modeling algorithm that is employed for drug discovery purposes. This technique determines the possible interaction and binding mode of a ligand with the target receptor. Docking validation of our virtual screening parameters successfully docked the original ligands of main protease and 3CL protease into their aboriginal position, which further paved the way to commence our screening study.

In this study, we selected two SARS COV-2 proteases as receptors, and the ligands were antiviral medicinal compounds. Both ligands and receptors were refined and minimized through PRODRG (Schüttelkopf *et al.*, 2004) and Modrefiner (Xu *et al.*, 2011). The active site of these receptors was scrutinized with Metapocket 2.0 (Zhang *et al*., 2011) to identify the possible active amino acid residues within these viral proteins. Docking interaction was performed through Raccoon2, a virtual screening platform of Autodock vina to analyze an extensive library of antiviral medicinal compounds against SARS COV-2 proteases. These ligands were converged at the active site to determine their interaction with the active residues of these viral receptors (Supplementary Table 1). The results obtained from the docking study were analyzed based on the hydrogen bonding of the ligands with active residues of receptors and low binding energy. Interaction with anything other than the predicted active site was omitted. Six promising drug candidates (Abietic Acid, Gallic Acid, Piceatannol, Piperine, Sinomenine, and Triptolide) formed hydrogen bonds with the active residues of these viral receptors (Figure 1 and Supplementary Figure 1). Furthermore, these compounds exploited their hydroxy along with oxygen groups (=O, -O) to form hydrogen bonds with the active site of these receptors (Figure 2 and Supplementary Figure 2). Some ligands shared a chemical affinity for the active site residues of viral receptors, which is a strong indicator of similar activity. Active site residues of 4WY3, such as ASP153, were used by Abietic Acid, Gallic Acid, and Piceatannol whereas GLN110 was used by Gallic Acid, Piceatannol and Sinomenine. ASN151 was the binding residue for Gallic Acid and Triptolide, whereas Sinomenine, and Gallic Acid both used THR292 for interaction. Among all these ligands, Gallic Acid, Sinomenine, and Piceatannol were found to be more active in establishing hydrogen bonds with the active pocket of 4WY3 protease. A similar type of binding interaction was also observed for 6LU7 protease. TYR54, GLY143, CYS145, and ASN145 were the common active residues exploited by these compounds for interaction. Among them, Triptolide was the only candidate active against 6LU7 protease in terms of hydrogen bonds. Further stability studies revealed that all of these successful ligands had a low binding energy and minimal RMSD values (1.01–2.79 Å), suggesting a stable adduct, in line with the reported studies (Ding *et al*., 2016; Xiao *et al.*, 2018). The complete docking results are summarized in Table 1.

### 3.2.Acute Toxicity and Adverse Effects

Acute toxicity and adverse effect prediction were carried out to determine the lethality and adverse effect profile of these compounds. These compounds incite toxicity at >11,000 mg/kg

through the intravenous route, and >100,000 mg/kg for the oral route. Most of these compounds were classified as class 3 chemicals in terms of toxicity except for Gallic acid and Piceatannol, which were class 5, according to the OECD report. The probable side effects of these compounds were relatively low, as evident in their Pa value (<0.7) (Khanal *et al*., 2019). Rare side effects include hepatotoxicity, arrhythmia, and myocardial infarction. The results of acute toxicity and adverse effects of these compounds are depicted in Table 2 and Table 3.

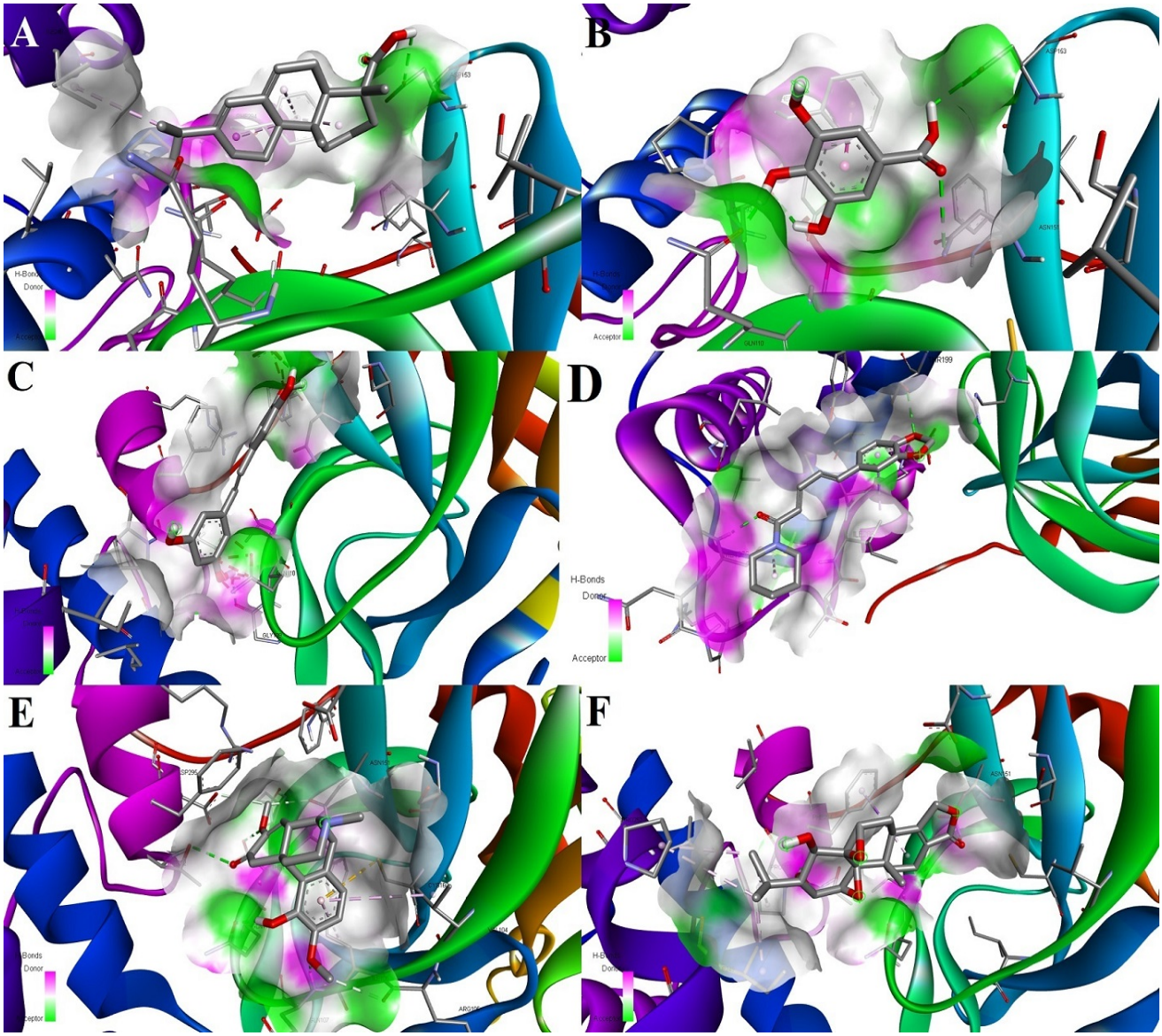


**Fig.1.** 3D Docked Structures of 3CL like Proteases of SARS COV-2 with Antiviral Medicinal Compounds. A) Abietic Acid, B) Gallic Acid, C) Piceatannol. D) Piperine, E) Sinomenine, F) Triptolide

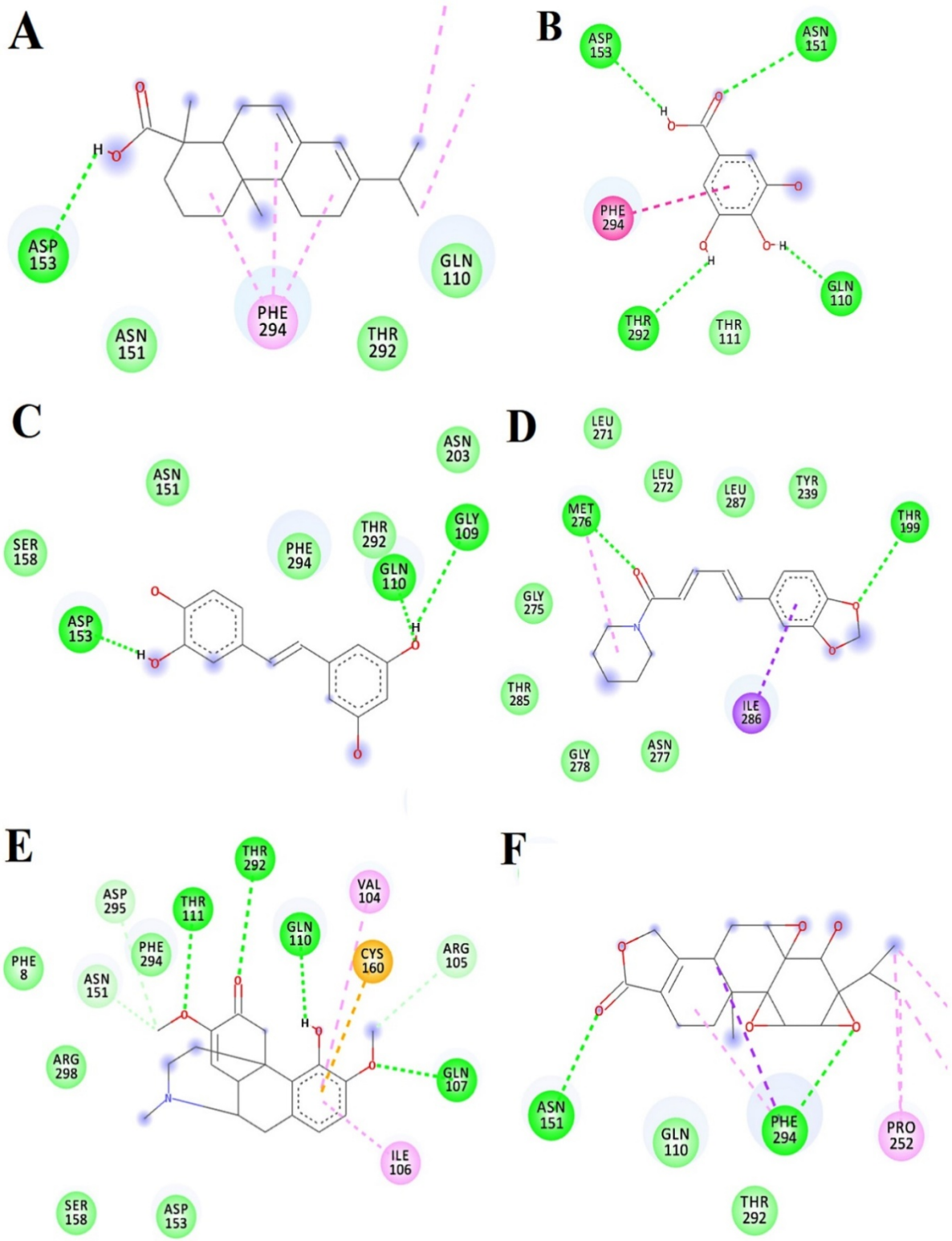


**Fig. 2.** Structural Visualization of Antiviral Medicinal Compounds interaction with 3CL like Proteases of SARS COV-2 A) Abietic Acid, B) Gallic Acid, C) Piceatannol. D) Piperine, E) Sinomenine, F) Triptolide

**Table 1.** Docking Analysis of Ligands Establishing Hydrogen Bonds with the Active site of Target Viral Receptors

| Ligands | Receptor (PDB ID) | Active Site Subunits (Predicted) | Ligands Hydrogen Interaction with Receptor Active Residues | LigRMSD(A) | Binding Energy (Kcal/mol) |
|---|---|---|---|---|---|
| Abietic Acid | SARS-CoV Peptidase (2GTB) | LEU202, LEU242, ASP245, ILE249, ASP248, PRO241, THR243, **GLN110**, PRO108, GLU240, **GLY109,** ILE200, ASN203, PRO132, **GLN107**, **THR111**, **ASN151**, **THR292**, **PHE294**, ASP295, ARG298, ILE106, CYS160, VAL104, ARG105, SER158, **ASP153**, ILE152, CYS156, PHE08, GLN127, PRO293, LYS102, VAL297, PRO252, **THR199**, ASP155, LEU253 | ASP153 | 1.53 | -7.2 |
| Gallic Acid | | | GLN110, ASN151, ASP153, THR292 | 1.96 | -5.5 |
| Piceatannol | | | GLY109, GLN110, ASP153 | 1.72 | -6.6 |
| Piperine | | | THR199, MET276 | 1.65 | -6.7 |
| Sinomenine | | | GLN107, GLN110, THR111, THR292 | 1.46 | -7.0 |
| Triptolide | | | ASN151, PHE294 | 1.15 | -7.6 |
| Abietic Acid | COVID-19 Main protease (6LU7) | **LEU141**, **ASN142**, **CYS145**, HIS163, MET165, **GLU166**, HIS41, **THR25**, HIS164, ASP187, ARG188, **GLN189**, **TYR54**, MET49, CYS44, PRO52, GLN192, **GLY143**, THR25, LEU27, THR26, SER144, LEU167, PRO168, THR190, PHE140, HIS172, ALA191, TYR118, THR24, ASN119, THR45, THR24, SER46, ASP48, ALA193, LEU50, ASN51, VAL42, GLU47, THR26 | ASN142 | 1.06 | -5.9 |
| Gallic Acid | | | LEU141, CYS145, GLU166 | 2.79 | -4.9 |
| Piceatannol | | | ASN53, TYR54, GLU55 | 1.67 | -5.7 |
| Piperine | | | TYR54 | 1.68 | -6.1 |
| Sinomenine | | | GLY143, CYS145, GLN189 | 1.13 | -6.0 |
| Triptolide | | | THR25, ASN142, GLY143, CYS145 | 1.01 | -7.5 |

**Table 2**. Toxicity and Chemical Profile of Successful Antiviral Medicinal compounds

| No. | Compounds | IV LD50 (mg/kg) | Oral LD50 (mg/kg) | Toxicity Classification by OECD Project |
|---|---|---|---|---|
| 1 | Abietic Acid | 29,250 | 2,287,000 | Class 3 Chemicals |
| 2 | Gallic Acid | 465,900 | 1,606,000 | Class 5 Chemicals |
| 3 | Piceatannol | 150,700 | 2,571,000 | Class 5 Chemicals |
| 4 | Piperine | 33,950 | 861,000 | Class 3 Chemicals |
| 5 | Sinomenine | 32,450 | 203,000 | Class 3 Chemicals |
| 6 | Triptolide | 11,100 | 140,700 | Class 3 Chemicals |

**Table 3**. Rare Adverse effects of Successful Antiviral Medicinal Compounds; *Pa: Probability of activity, Pi: Probability of inactivity

| No | Compounds | Pa Value | Pi Value | Side Effects |
|---|---|---|---|---|
| 1 | Abietic Acid | 0.941 | 0.004 | Myocardial infarction |
| 2 | Gallic Acid | 0.699 | 0.101 | Hepatotoxicity |
| 3 | Piceatannol | 0.314 | 0.282 | Arrhythmia |
| 4 | Piperine | 0.556 | 0.167 | Hepatotoxicity |
| 5 | Sinomenine | 0.453 | 0.146 | Arrhythmia |
| 6 | Triptolide | 0.302 | 0.193 | Myocardial infarction |

3.3. ADMET Properties

To determine the nature and behavior of these compounds inside an organism, it is necessary to ascertain their adsorption, distribution, metabolism, excretion, and toxicity (ADMET), prior to animal and clinical studies (Table 4). These selected medicinal compounds possess a high GI absorption with active oral bioavailability, apart from Piceatannol and Sinomenine whereas Gallic Acid lacks Caco-2 permeability. High BBB penetration was reported for Abietic acid, Sinomenine, Triptolide, and Piperine, while Piperine, Piceatannol, and Sinomenine were potential substrates for P-Glycoprotein. Only Piperine had the capability to inhibit P- Glycoprotein-I. Abietic acid, Sinomenine, and Triptolide were CYP3A4 substrates, and Piperine and Piceatannol were CYP2C9 substrates. CYP2C19 was efficiently inhibited by Abietic acid, Piperine, and Piceatannol, but CYP2D6 and CYP1A2 were only inhibited by Piceatannol. Sinomenine only inhibited CYP2D6. Gallic Acid was the only compound that showed no interaction with any CYP variant. The highest total clearance was noted for Sinomenine and Abietic acid, and the lowest was observed for Piperine. Possible substrates for Renal OCT2 were Abietic acid, Piperine, and Sinomenine.

**Table 4.** ADMET and Druglikeness Properties of Successful Antiviral Medicinal Plants. *CYP: Cytochromes P450, hERG: human Ether-à-go-go-Related Gene, BBB: Blood-Brain Barrier, OCT2: Organic Cation Transporter-2,Caco-2 cells: human colon epithelial cancer cell line,.**X means no activity and ✓ means activity.**

| ADMET Parameters | Compounds<br>Abietic Acid | Gallic Acid | Piceatannol | Piperine | Sinomenine | Triptolide |
|---|---|---|---|---|---|---|
| **ABSORPTION** | | | | | | |
| Human Intestinal Absorption | High | High | High | High | High | High |
| Human oral bioavailability | High | High | High | High | High | High |
| Caco-2 Permeability | High | Low | High | High | High | High |
| Water solubility | Soluble | Soluble | Soluble | Soluble | Soluble | Soluble |
| Subcellular Localization | Mitochondria | Mitochondria | Mitochondria | Mitochondria | Mitochondria | Mitochondria |
| Skin Permeability (Log Kp) | -4.75 cm/s | -6.84 cm/s | -5.76 cm/s | -5.58 cm/s | -6.78 cm/s | -8.34 cm/s |
| **DISTRIBUTION** | | | | | | |
| P-glycoprotein substrate | X | X | ✓ | ✓ | ✓ | X |
| P-glycoprotein I inhibitor | X | X | X | ✓ | X | X |
| P-glycoprotein II inhibitor | X | X | X | X | X | X |
| BBB permeability | ✓ | X | X | ✓ | ✓ | ✓ |
| **METABOLISM** | | | | | | |
| CYP2D6 substrate | X | X | X | X | ✓ | ✓ |
| CYP3A4 substrate | ✓ | X | ✓ | ✓ | X | X |
| CYP1A2 inhibitor | X | X | ✓ | X | X | X |
| CYP2C19 inhibitor | ✓ | X | ✓ | ✓ | X | X |
| CYP2C9 inhibitor | ✓ | X | X | X | X | X |
| CYP2D6 inhibitor | X | X | ✓ | X | ✓ | X |
| CYP3A4 inhibitor | X | X | X | X | X | X |
| **EXCRETION** | | | | | | |
| Total Clearance (log ml/min/kg) | 0.915 | 0.518 | 0.484 | 0.232 | 0.955 | 0.484 |
| Renal OCT2 substrate | ✓ | X | X | ✓ | ✓ | X |
| **TOXICITY** | | | | | | |
| AMES toxicity | X | X | X | X | X | X |
| Hepatotoxicity | X | X | X | X | X | X |
| hERG Inhibition | X | X | X | X | X | X |
| Eye irritation | X | X | X | X | X | X |
| Carcinogenicity | X | X | X | X | X | X |
| **BIOAVAILABILITY AND DRUGLIKNESS** | | | | | | |
| Bioavailability Score | 0.56 | 0.56 | 0.55 | 0.55 | 0.55 | 0.55 |
| Lipinski | Yes; 1 Violation | Yes; 0 violation | Yes; 0 violation | Yes; 0 violation | Yes; 0 violation | Yes; 0 violation |

## 4. Discussion

SARS COV-2 is spreading rapidly all over the world in a similar way to the 1918 influenza pandemic with its enigmatic disease nature, elevated risk of transmission, and high morbidity and mortality rates (Yang *et al.*, 2020).There are currently no universally approved medications available to treat this infection. However, the World Health Organization approved Chloroquine and Hydroxychloroquine for SARS COV-2 treatment (Abd El-Aziz *et al.*, 2020), while Gilead Sciences proposed the potential benefits of Remdesivir to expedite patient recovery (Kaul, 2020).These drugs employed for the treatment of SARS COV-2 showed promising results in *in vitro* studies, but cause a life-threatening array of adverse effects, including hepatotoxicity (Amirian *et al*., 2020), neurological, and cardiovascular impairment (Devaux *et al.*, 2020). In addition, these novel viruses possess 3'−5' exonuclease protein (ExoN) which weakens the effects of different nucleoside analogue drugs, by a proofreading mechanism (Sevajol *et al*., 2014).Therefore, there is no option but to search for promising drug candidates, which suppress rapid disease proliferation. Our study attempted to scrutinize various antiviral medicinal compounds for their probable interaction with SARS COV-2 proteases.

Screening analysis filtered six promising ligands as potential drug candidates. These drug candidates employed their oxygen and hydroxyl groups to form hydrogen bonds with the active residues of the viral proteases, whereas carbon rings and other oxy groups established hydrophobic connections to stabilize the docked complex. The formation of hydrogen bonds with the active pocket by the ligand caused functional alterations in the target viral receptor, hence disrupting their enzymatic activity, as evident from the following study (Pandey *et al*., 2019). Moreover, hydrogen bonding amplifies the binding strength of ligand attachment to the receptor, compared to other types of bonds (Raschka *et al*., 2018). Further molecular studies revealed that most of these compounds had RMSD values within 1.01–2.79 Å, reflecting coherence between experimentally solved structures and the predicted ligand conformation at the microscopic level as obtained from docking interaction (Ding *et al*., 2016). In addition, these compounds have low acute toxicity, which means high doses are required to incite toxicity and adverse reactions.

## 5. Conclusion

Screening results revealed six promising compounds with an efficient chemical affinity for SARS COV-2 viral proteases. These compounds have good ADMET properties and low acute toxicities and could be subjected to further *in vitro* studies in order to confirm their therapeutic efficacy against this disease. The current study provided a small number of lead compounds which showed encouraging interactions with the target viral proteins of SARS COV-2. Moreover, we also elucidated the mechanism of action and pharmacokinetic profile of these compounds that might be useful for other researchers searching for potential therapies for this disease.

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