

# Molecular Docking Analyses of Phytochemicals Obtained from African Antiviral Herbal Plants Exhibit Inhibitory Activity against Therapeutic Targets of SARS-CoV-2

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## Research Article

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# Abstract

Presently, the global public health threat of international concern is the coronavirus disease-2019 (COVID-19), a viral disease of worldwide prevalence caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), at present the disease has no known cure or vaccine. Plants worldwide including plants of African ethnopharmacological relevance are a natural source of abundant and diverse phytochemicals with bioactivity against microorganisms including viruses. We selected 13 plants used in African traditional medicine for the treatment of viral diseases to screen for phytochemicals capable of interfering with SARS-CoV-2 therapeutic targets using AutoDock Vina *in silico* tool. 25 phytochemicals from these plants that passed the Lipinski rule of drug-likeness were assessed for antiviral activity against three SARS-CoV-2 therapeutic targets, namely: spike glycoprotein, Papain-like protease and 3C-like proteinase. The crystal structure of the viral protein targets was obtained from the protein databank website (<https://www.rcsb.org/>). The active sites of the target proteins were predicted using SCFBio Server (<http://www.scfbio-iitd.res.in/dock/ActiveSite.jsp>) from the PDB file as input. The antiviral herbal phytochemical compounds were then docked with prepared targets: Papain-like protease, 3C-like proteinase and spike glycoprotein. The Autodocking hit results generated six lead phytochemicals out of a library of twenty-five (25) phytochemicals from the African traditional herbs with potential anti-SARS-CoV-2 activity. The lead molecules with their binding affinities against Papain-like protease and 3C-Like Proteinase are as follows: Ginsenosides (-9.9 kcal/mol), ursolic acid (-9.4 kcal/mol), oleanolic acid (-9.4 kcal/mol), cynarine (-8.9 kcal/mol), glabridin (-8.5 kcal/mol) and cinnamoyl-echinadiol (-8.2 kcal/mol). ADMET profile shows glabridin, cinnamoyl-echinadiol and neral obtained from Licorice, *Echinacea purpurea* and lemongrass respectively, exhibited best-fit values as drugs candidate. We advocate for further *in vitro* and *in vivo* studies to evaluate the activity of these lead compounds with a view to optimized drug intervention against COVID-19 pandemic.

## 1.0 Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19), a viral disease recently declared a global public health emergency by the World Health Organization (Lai et al., 2020). The Coronaviruses are enveloped, positive-sense single-stranded RNA viruses with a nucleocapsid of helical symmetry. Coronaviruses have widely been known to cause respiratory and intestinal infections in humans after the outbreak of “severe acute respiratory syndrome (SARS)” in Guangdong, China. SARS was caused by SARS-CoV during 2002 and 2003, and it emerged in a market where civets were sold out. Only a decade later, the world witnessed another outbreak of “Middle East respiratory syndrome (MERS)” caused by MERS-CoV in the Middle East (Khan et al., 2020). Coronavirus disease-2019 (COVID-19) outbreak was first reported in December 2019 in Wuhan China (Yuen et al., 2020) and the disease has spread worldwide with over 3 million cases and 200,000 mortality. The country’s worst-hit (reporting over 10,000 cases) are USA, Italy, Spain, China, Germany, France, Iran, UK, Switzerland, Belgium, Netherlands, Turkey, Austria (Lai et al., 2020). As of April 30th, 2020, the Nigerian Centre for Disease Control (NCDC) reported over 1550 confirmed cases with 44 fatalities in

Nigeria. The widely accepted theory on the source of COVID-19 infection relates to animal-human transmission as the virus jumps the species-barrier at a local fish and wild animal market in Wuhan of Hubei province in China (Yuen et al., 2020). Studies have now established the disease ongoing spread is via humans by way of aerosolized droplets or through direct contact, with an average incubation day of 6.4 (range 2-14 days) and a basic reproduction number of 2.24-3.58 (Sun et al., 2020). The infection is majorly characterized by pneumonia, fever, muscle soreness, abnormal respiratory distress syndrome (ARDS) and other rare symptoms such as diarrhoea, haemoptysis, headache, sore throat and shock (Yuen et al., 2020). Isolation of confirmed and suspected cases and their contacts is the central plank in the control of transmission, adopted by countries worldwide; the success of this approach is yet to be verified. In the meantime, no drug or vaccine is available for the treatment of confirmed cases and prevention of COVID-19 in the uninfected, presently clinicians are repurposing (repositioning) drugs developed for existing medical conditions such as that for malaria (chloroquine (CQ) / hydroxychloroquine (HCQ)), Human Immunodeficiency Virus (HIV) and EBOLA (remdesivir), anti-staphylococcal drug (teicoplanin) in the management of COVID-19 (Colson et al., 2020). Earlier studies had shown CQ as a potent inhibitor of most coronaviruses, including SARS-CoV-1 (Devaux et al., 2020). Without a known cure, the supposed antiviral properties of CQ and HCQ and their potential benefits in inhibiting the replication of SARS-CoV-2 have given the medical world a ray of hope in the fight against COVID-19. Preliminary trials of chloroquine repurposing in the treatment of COVID-19 in China have been encouraging, leading to several new trials. Hitherto, no clinical trial has indicated CQ treatment of any acute virus infection, however, a modest treatment effect of CQ was observed with chronic hepatitis C virus (HCV) infection (Touret and de Lamballerie, 2020). The pandemic is still ongoing, hence the need to urgently find new preventive and therapeutic agents as soon as possible. Development of these treatments may require years, meaning that a more immediate remedy should be found in earnest. The virus; SARS-CoV-2 encodes several proteins some of which are essential to viral entry and replication. Among these proteins are 3C-Like proteinase (3CL-pro) alternatively also called Main protease (M-pro) and spike protein (S) (Gao et al., 2020). The SARS 3CL-pro is a cysteine proteinase indispensable to the viral life cycle while the spike protein uses angiotensin-converting enzyme 2 as a receptor to mediate virus cell entry. These proteins are considered attractive targets for drug development and several chemical modelling for inhibitors of these targets are actively being pursued in the search for COVID-19 cure (Cunningham et al., 2020). Plants are a natural resource for abundant and diverse bioactive compounds evident by its deployment in the traditional pharmacopoeia of almost all cultures and society. Innovative therapeutic approaches in modern science involve the screening of plants phytochemicals/ secondary metabolites for bioactive molecules able to interfere with microbial disease processes. Investigation of African folk/traditional medicines used in the treatment of viral diseases necessitated our study of phytochemicals from 13 different African plants species, namely; oregano, sage, basil, fennel, garlic, lemongrass, peppermint, *Echinacea purpurea*, rosemary, *Sambucus nigra*, liquorice, ginger, ginseng.

We hypothesize that the antiviral effects of these plants represent a potentially valuable resource for therapeutic intervention against SARS-CoV-2. Hence, the application of bioinformatics molecular docking

tool AutoDock Vina to quickly screen African herbal plants for molecules with the potential to directly inhibit targets in SARS-CoV-2 the causative agent of COVID-19.

## 2.0 Materials And Methods

### 2.1 Literature Search

Literature search and compound selection in google search engine concerning natural compounds against SARS or MERS coronavirus activity were selected using the query “coronavirus AND inhibitor AND (SARS OR MERS OR SARS-CoV OR MERS-CoV).” After careful reading of the studies returned by this search, the natural compounds that had biologically confirmed antiviral activities were compared with existing medicinal plants in Pubchem (<https://pubchem.ncbi.nlm.nih.gov/>) and NCBI (<https://www.ncbi.nlm.nih.gov>) for Natural compounds in herbs associated with antiviral activity were examined in a stepwise manner viz:- Discovery Studio Visualized; Protein Data Bank (PDB) (<https://www.rcsb.org/>); Open babel GUI software; Supercomputing Facility for Bioinformatics & Computational Biology (<http://www.scfbio-iitd.res.in/dock/ActiveSite.jsp>) and Auto dock Vina as shown in Fig. 1.

### 2.2 Phytochemicals Hits Screening, Preparation and Optimization

A literature review of African Traditional Medicines with antiviral activities was conducted and a list of herbs with antiviral activities was produced. Further research was done on the list to produce the phytochemical bioactive compounds responsible for the antiviral activity using the websites Pubchem (<https://pubchem.ncbi.nlm.nih.gov/>) and NCBI (<https://www.ncbi.nlm.nih.gov>). The 3D chemical structures and the physiochemical properties of these antiviral phytochemical compounds were downloaded from the PubChem database ([www.ncbi.nlm.nih.gov/pubchem](http://www.ncbi.nlm.nih.gov/pubchem)) in .sdf format. The energy of the compounds was minimized and converted to .pdbq format using Open Babel software. Summary of all the antiviral phytochemical compounds used in these studies is represented in **Table 1**. Lipinski's rule of five parameters such as molecular weight, Log P, and the number of hydrogen bond donors and the number of hydrogen bond acceptors were taken from the PubChem database for the herbs-derived phytochemical compounds.

### 2.3 Protein Retrieval and Preparation

The crystal structures of the three main protein targets of SARS-CoV-2 were searched and downloaded in .pdb format via protein data bank website (<https://www.rcsb.org/>) namely: 3C-Like- proteinase SARS CoV-2(2BX4); papain-like proteinase SARS CoV-2 (6W9C); Spike glycoprotein SARS CoV-2 (6VSB). The unwanted molecules such as water, a ligand in a complex with the protein structures retrieved were removed using discovery studio visualizer software (Version 17.2.0) and Open babel software was used to convert the proteins from .pdb to .pdbq format.

### 2.4 Active Site Prediction

A search tool that determines the total number of active sites along with information on their amino acid sequence, cavity points and the average volume of the cavity was employed. The active sites of the target proteins were predicted using SCFBio Server (<http://www.scfbio-iitd.res.in/dock/ActiveSite.jsp>) using a .pdb file as input.

## 2.5 Docking Studies with AutoDock Vina

Molecular docking studies were performed for the selected antiviral phytochemical compounds with the selected target proteins of SARS CoV-2 by an automated docking tool, AutoDock Vina 4.2. Autodock Vina 4.2 employed empirical free energy and a Lamarckian Genetic Algorithm. Docking simulation was repeated. During virtual screening with AutoDock Vina 4.2 complex formation was achieved by allowing all rotatable bonds of the chemical ligands free choice of torsional degrees of freedom and Rapid Grid-Based (RGB) energy evaluation (Rasool et al., 2020).

## 2.6 ADMET Analyses of Lead Phytochemicals

Adsorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) Discovery Studio 4.0 was used to study the adsorption and distribution of lead compounds. In the ADMET studies the following parameters were assessed: Molecular weight; Bioavailability score; Drug-like values; Blood-brain barrier permeability (BBB permeant) and gastrointestinal tract absorption (GI absorption). The threshold values indicating effectiveness for the bioavailability score, drug-like values blood-brain permeability and gastrointestinal absorption indices were > 30%, > 0.4, > 0.18 and Yes, respectively, as recommended by (Fatima et al., 2019).

# 3.0 Results

## 3.1 Drug-Likeness Result

*In silico* study of the selected antiviral herbal compounds on the three main protein targets of SARS Cov-2 (3CLP, PLO, Spike Glycoprotein) using AutoDock Vina showed the following results and compounds which follow Lipinski's rule of five were all subjected to docking experiment. Twenty-five (25) antiviral herbal compounds satisfied Lipinski's rule of five for drug-likeness (**Table 1**). Lipinski rule of 5 is used to distinguish between drug-like and non-drug-like molecules and to predicts a high probability of success or failure due to drug-likeness for molecules complying with 2 or more of rules which are; Molecular mass less than 500 Dalton; High lipophilicity (expressed as LogP less than 5); Less than 5 hydrogen bond donors; Less than 10 hydrogen bond acceptors and Molar refractivity should be between 40-130. These filters serve as checks in early preclinical development which could reduce cost late-stage preclinical and prevents clinical trial failures.

## 3.2 AutoDock Vina Virtual Screening Results

The whole docking procedure was done sequentially (**Figure 1**). The antiviral herbal phytochemical compounds that passed the Lipinski rule of 5 drug-likeness were docked with Papain-like protease, 3C-like proteinase and spike glycoprotein separately. The docking results are summarized in **Table 1**. The ligands with binding affinity >8 were subjected to further interaction analysis. The findings of the results were solely based on the docking energy value and the interaction at the binding sites. The more negative the value, the more stable the complex is and more binding affinity. According to the energy funnel theory less energy depicts highly stable conformation. Hence more energy would be needed to break the complex that means high dissociation energy.

### 3.3 Inhibition of Papain-like protease

All the selected ligands were docked with Papain-like protease **Table 2**. The docking of ligands was carefully observed and their interaction and orientations were also monitored. Ginsenosides had the highest binding energy (-9.9 kcal/mol), Ursolic (-9.4 kcal/mol), Oleanolic acid (-9.4 kcal/mol), cynarine (-8.9 kcal/mol), glabridin (-8.5 kcal/mol) and cinnamoyl-echinadiol (-8.2 kcal/mol). Ginsenosides inhibit the most because the strength and the catalytic activity of a binding complex are predicted by the hydrogen bonds between them. Ginsenosides interacted with key papain-like protease amino acid residues His89, Trp106, Leu162, Ala107, Tyr273 Tyr264 and Pro248 (**Fig. 2**). Ursolic acid docked with papain-like protease at Leu162, Gly160 and Asn109 sites. Ursolic acid binds in the catalytic site with a greater number of hydrogen bonds when compared to other compounds as having better inhibitory property and possible activity against SARS-CoV-2 target. Oleanolic acid interacted with papain-like protease at Leu162 and Gly269. These findings are strongly supported by RMSD/UB, RMSD/LB, TPSA and molar refractivity values as shown in **Table 1**.

### 3.4 Inhibition of 3C-Like Protease

All the selected ligands were docked with 3C-Like Protease and the results are shown in **Table 2**. The docking of ligands was carefully observed and their interaction and orientations were also monitored. **Table 2**, showed that ursolic having the highest binding energy (-8.4 kcal/mol) and neral (-9.3 kcal/mol). Ursolic acid interacted with 3C-Like protease at the Arg298, Phe294, Thr292 and Asp295 amino acid residues. These residues are in the active site region of 3C-Like Proteinase. The amino acid residues with which hydrogen bonds formed are shown in **Figures 5**. While neral a phytochemical from lemongrass interacted with Phe294, Arg298, Thr292 and Thr111 amino acid residues (**Figure 6**),

### 3.5 Inhibition of Spike Glycoprotein

All the selected ligands were docked with spike glycoprotein where the docking of ligands was carefully observed and their interaction and orientations were also monitored. The output showed that cynarine having the highest binding energy (-9.1 kcal/mol) followed by oleanolic acid (-8.5 kcal/mol), ursolic (-8.3 kcal/mol) as shown in **Table 2**. Hence cynarine display a greater inhibitory activity against SAR-CoV-2 spike glycoprotein. The strength and the catalytic activity of a binding complex are predicted by their hydrogen bonds between them.

### 3.6 ADMET Analyses of Lead Phytochemicals

ADMET analyses showed three compounds (glabridin, cinnamoyl-echinadiol and neral) with good blood-brain barrier permeability and high intestinal absorption rate, this represents additional evidence for the development of these compounds as COVID-19 therapeutic intervention (Table 3). These three compounds have the bioavailability score of 0.56 which is equivalent to a TPSA of 75-150 Å<sup>2</sup>. TPSA indicates a compound ability to permeate into cells. A TPSA value of <140 Å<sup>2</sup> is required for good permeation of compound into the cell membrane and value <90 Å<sup>2</sup> is required to permeate through the blood-brain barrier, a property essential to any likely drug candidate for SARS-CoV-2.

## 4.0 Discussion

COVID-19 pandemic has threatened global public health with devastating impact on the world economy in a fast and rapidly expanding manner(Lake, 2020). Researches into drugs able to inhibit the several therapeutic targets in SARS-CoV-2 are present of great scientific interest. A significant advantage in the exploration of SARS-CoV-2 drugs is the use of herbal medicine preparations, as they are a potential source of likely new compounds that may be developed into new antiviral drugs, since they can be selected based on their ethnomedicinal use(Usman et al., 2009), for example, against infectious diseases including viruses such as SARS-CoV-2 the causative agent of the current pandemic. These plants produce a variety of phytochemical constituents with the potential to inhibit viral attachment and replication a requirement for the viral pathogenesis(Calland et al., 2012). The antiviral and antimicrobial activities of liquorice, oregano, fennel, sage, peppermint, *Echinachea*, basil, garlic, *Sambucus nigra*, ginger, ginseng, rosemary and lemongrass that supported their use in folk medicine including that of African traditional herbal medicine has been recognized by previous authors(Koné et al., 2007). Among the 13 plants in our collections analysed for phytochemicals able to inhibit targets (spike glycoprotein, 3C-Like proteinase and papain protease) in SARS-CoV-2, five plants above-mentioned turned out 25 lead phytochemicals that sufficiently passed the Lipinski's rule of 5 for drug-likeness. Subsequent docking studies carried out using AutoDock tool and AutoDock Vina to validate the 25 lead phytochemicals that exhibited binding energy of >8 kcal/mol against the different therapeutic targets in SARS-CoV-2 namely: 3C-Like proteinase, spike glycoprotein, papain-like protease.

The spike glycoprotein which is essential for SARS-CoV-2 virus attachment to its angiotensin-converting enzyme 2 (ACE-2) receptor is inhibited by cynarine (-9.1 kcal/mol) oleanolic acid (-8.5 kcal/mol) and ursolic acid (-8.3 kcal/mol). Two polyprotein enzymes( papain-like protease and 3C-Like protease) essential to SARS-CoV-2 replication: the papain-like protease interacted with the following lead compounds ginsenosides (-9.9 kcal/mol), ursolic acid (-9.4 kcal/mol) oleanolic acid (-9.4 kcal/mol), glabridin (-8.5 kcal/mol) and cinnamoyl-echinadiol (-8.2 kcal/mol) while 3C-Like proteinase complexed with ursolic acid (-8.4 kcal/mol) and neral (-8.3 kcal/mol). Optimization of a candidate compound for drugs in modern drug discovery requires the assessment of the pharmacokinetic properties of lead compounds that can pass standard clinical criteria. The ADMET profiling of eight lead compounds (ginsenosides, ursolic acid, oleanolic acid, cynarine, glabridin, cinnamoyl-echinadiol, neral and apigenin) to

pre-identify their safety and effectiveness as drug candidates were carried out using the SwissADME tool.

A commercialized product of *Echinacea purpurea* extracts Echinaforce™ is as effective as a standard antiviral drug Oseltamivir™ for the treatment of the influenza virus the causative agent of the lower respiratory tract (Rauš et al., 2015) similar to COVID-19 a lower respiratory tract disease. Equally antiviral activity of Echinaforce™ from *Echinacea* is shown in cell culture works recognizing its inhibitory activity on several human viruses such as H1N1-type IV, highly pathogenic avian IV (HPAIV) of the H5- and H7-types as well as swine-origin IV (S-OIV, H1NI)(Pleschka et al., 2009). The molecular docking studies of cinnamoyl-echinadiol phytochemical as a drug candidate with activity against therapeutic targets of SARS-CoV-2 supports its use in herbal preparation for the treatment of COVID-19. The results of our analyses show glabridin (an isoflavone), a phytochemical obtained from liquorice, a plant found in most African traditional medicine inhibited papain-like protease a therapeutic target in SARS-CoV-2, this is the first report of glabridin inhibition of papain-like protease. Islam et al through docking studies showed that glabridin is a potent inhibitor of SARS-CoV-2 3C-like protease (main protease)(Islam et al., 2020). This shows that glabridin, when developed as a drug compound, can inhibit multiple therapeutic targets in SARS-CoV-2. The benefits of such a drug compound are the slow development of drug resistance when multiple viral targets are interfered with; possible reduced toxicity associated with drugs where drugs attracted to different targets are used in one single time; and the elimination of drug-drug interactions (DDIs) where two drugs with varied targets are used simultaneously. It is also possible glabridin may inhibit SARS-CoV-2 spike glycoprotein, other authors have shown experimentally its ability to block hepatitis B virus entry in the cell-based assay(Miyakawa et al., 2018). Herein we also first report docking studies showing neral (citral) phytochemical from lemongrass as a potent inhibitor of SARS-CoV-2 3C-like protease (main protease). The bioactive compounds of lemongrass have been shown to have antiviral activity on the arbovirus dengue virus(Rosmalena et al., 2019) and nonenveloped enterovirus norovirus(Gilling et al., 2014).

## 5.0 Conclusion

In this study, 25 phytochemical hit molecules obtained from 13 different plant species contained in African traditional medicine pharmacopoeia with reported antiviral efficacy were screened through computer-aided drug discovery (CADD) with the molecular docking tool AutoDock Vina. Six lead molecules showed the highest binding affinity and strong interactions with three therapeutic targets (Papain-like protease, 3C-Like protease and spike glycoprotein) of SARS-CoV-2. These compounds displayed appreciable non-covalent interactions such as Hydrogen bonding, Van der Waals forces, electrostatic and hydrophobic interactions. Lipinski's rule indicated the pharmacokinetic efficacy of these lead compounds, especially against papain-like protease. ADMET analyses of three compounds: glabridin from Licorice, cinnamoyl-echinadiol from *Echinacea purpurea* and neral from lemongrass show their potentials as drugs candidate effective against COVID-19. Further study into the absorption, distribution, metabolism, excretion, toxicity (ADMET) of these lead compounds in addition to in vitro and

in vivo experiments are needed to validate utilization and sourcing of COVID-19 therapeutic interventions from these plants.

## Declarations

### Author Contributions:

Conceptualization: Goni Abraham Dogo and John Chinyere Aguiyi; Data Curation: Uchechukwu Oheari; Formal Analysis, Uchechukwu Oheari; Funding Acquisition, John Chinyere Aguiyi; Investigation, Goni Abraham Dogo and Uzal Umar; Methodology, Goni Abraham Dogo, Uchechukwu Oheari and Aboi Madaki; Project administration, Goni Abraham Dogo; Supervision, John Chinyere Aguiyi; Visualization, Uzal Umar; Writing – original draft, Goni Abraham Dogo, Aboi Madaki, John Chinyere and Uchechukwu. All authors have read and agreed to the published version of the manuscript.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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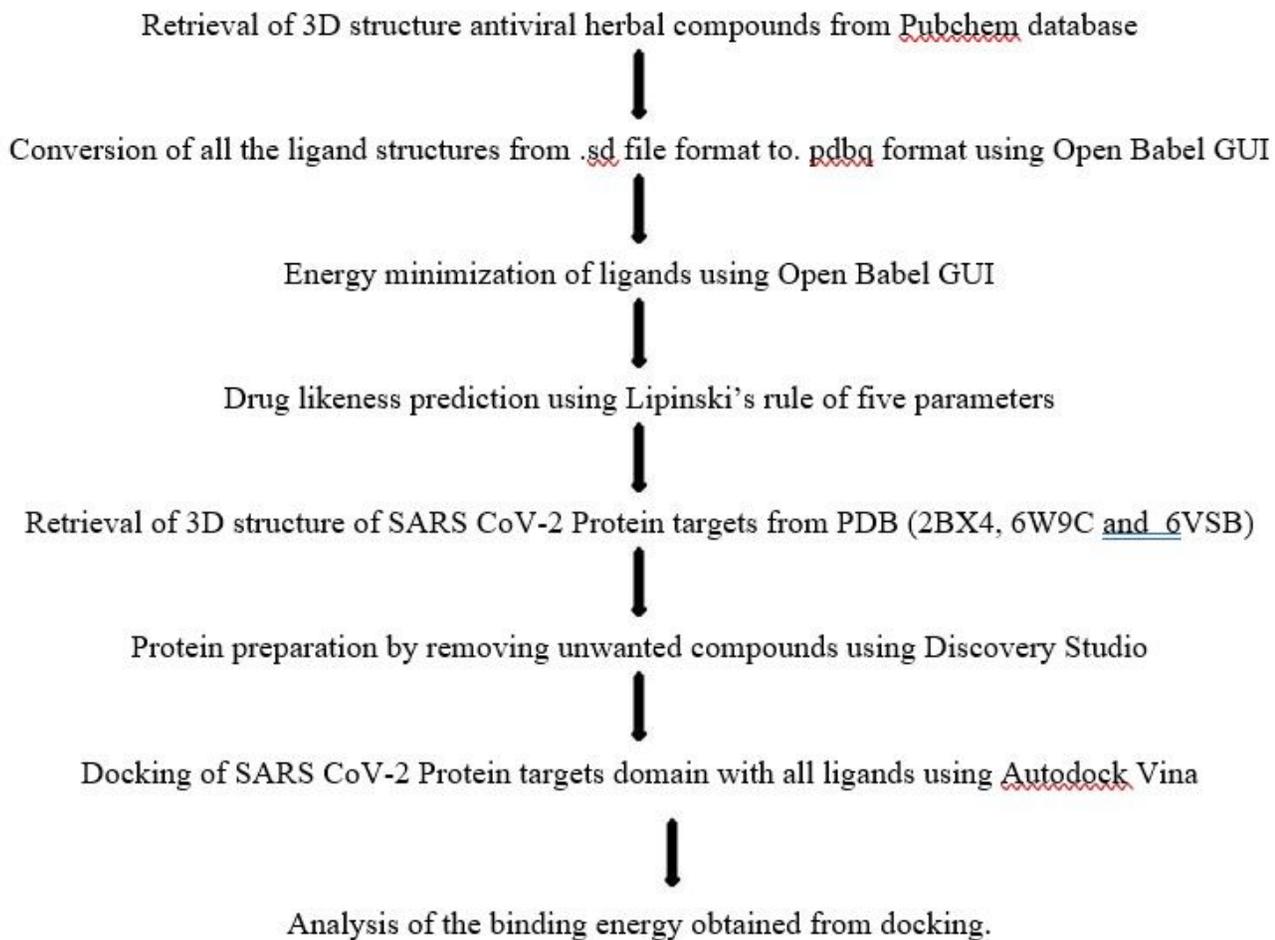
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## Tables

Due to technical limitations, tables are only available as a download in the supplemental files section

## Figures



**Figure 1**

Flow Chart for the collection and sorting of antiviral herbal compounds from NCBI.

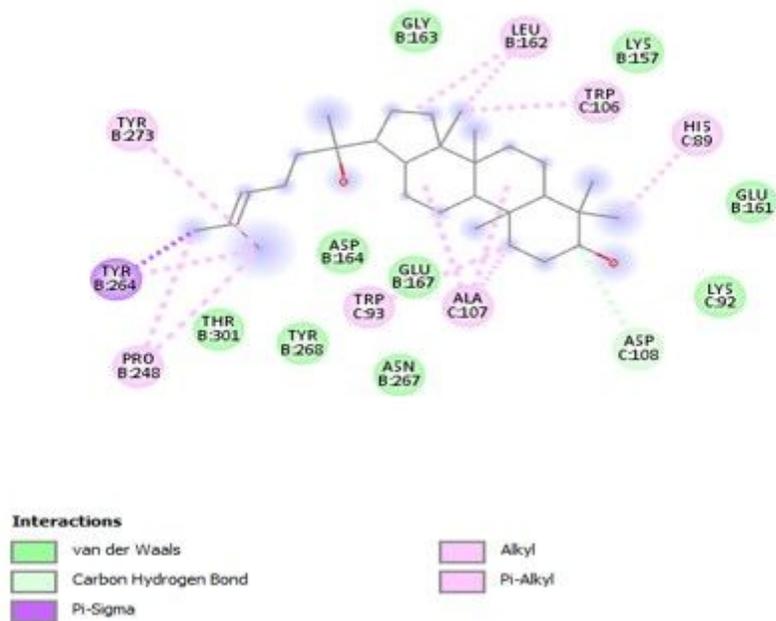


Figure 2

Papain-like protease in complex with ginsenosides

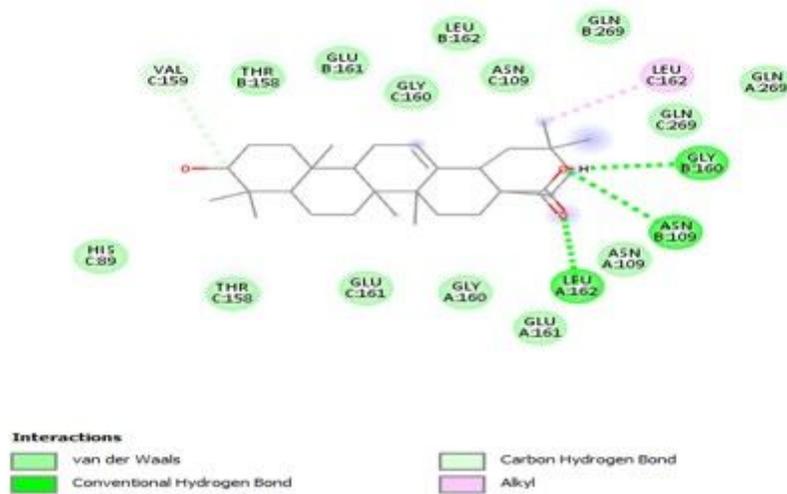


Figure 3

Papain-like protease in complex with Ursolic acid

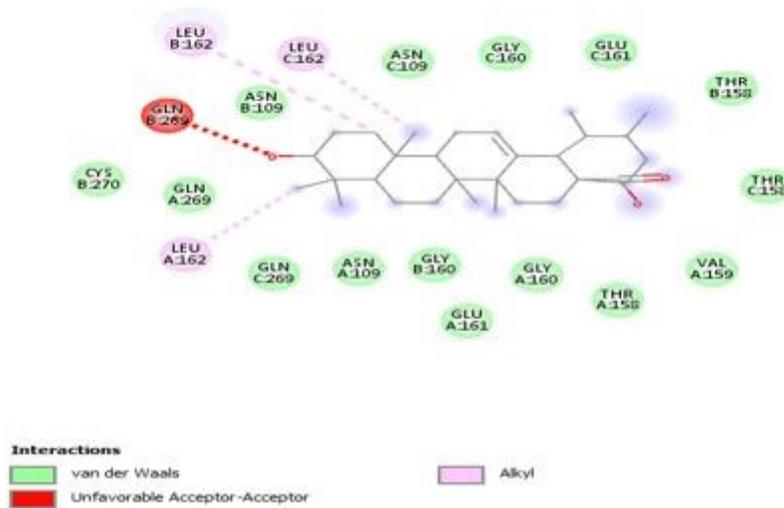


Figure 4

Papain-like protease in complex with Oleanolic acid

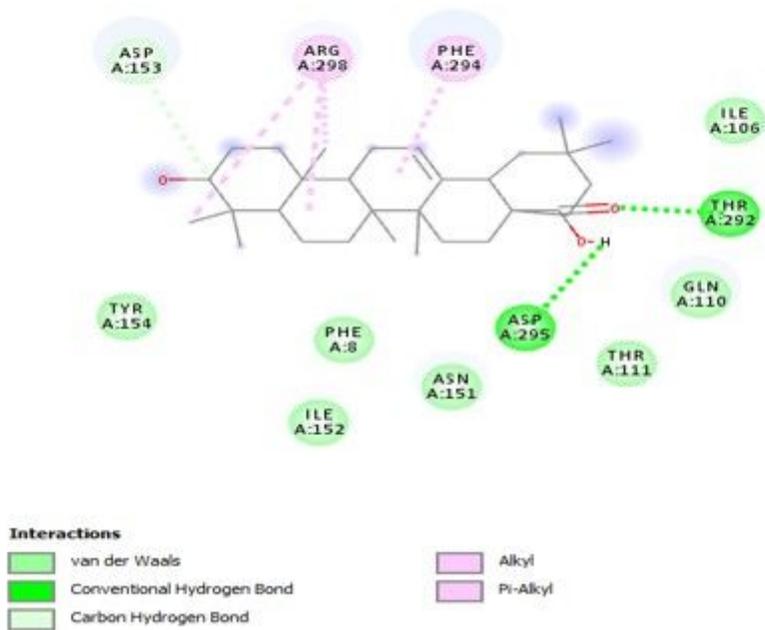
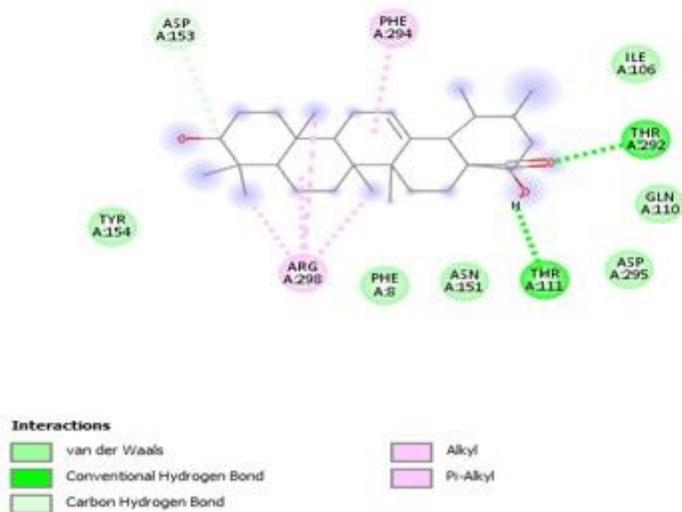


Figure 5

3C-Like Protease in complex with Ursolic



**Figure 6**

3C-Like Protease in complex with Neral

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [TableSJBS.docx](#)