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# Plant Based Molecules for the Management of Covid-19

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## Abstract

COVID-19 pandemic has put forward a serious challenge to the global research community to find a therapeutic solution for the disease. Nations are collaborating to fast track the development of the vaccine, but with a very limited or no success. Considering Corona virus being a RNA virus, development of vaccine will have its own challenges and may take more time than the desire or expected time. Natural Products and phytoactives from the plants, which are commonly used globally for the management of various viral diseases, can offer the ray of hope as natural supportive modalities. In the current study, 20 ligands of plant origin were selected after thorough literature survey and were studied for their potential antiviral characteristics using *in silico* techniques. The study focuses on Main Protease ($M^{pro}$) and SARS corona virus main peptidase. These ligands were screened for being the potential drug targets and most of the selected compounds have shown significant binding energies suggesting that these can be further explored to find an effective anti-viral treatment.

**Keywords:** COVID-19; Natural products; SARS; $M^{pro}$

## Introduction

In December 2019, outbreaks of series of respiratory disorder with symptoms similar to pneumonia were reported in Wuhan, central China. The patients reported symptoms like cough, fever, and fatigue. By January, 20 as many as 41 patients admitted in the hospital were suffering from pneumonia as confirmed by their abnormal Chest CT scan. The medical conditions observed in these patients were viral induced Acute Respiratory Distress Syndrome (ARDS), acute cardiac injury, RNAemia along with secondary infections [1]. Since then, COVID-19 has spread across the globe, so much so that WHO declared it as world health emergency and Pandemic. COVID-19 has reached to almost 213 countries and territories, accounting for more than 29,762,965 cases along with recoveries of about 21,564,008 and the death toll around 939,942 as of 16$^{th}$ Sep 2020 [2]. Although, mechanism or factors by which SARS-COV-2 causes ARDS is still not fully understood and researcher are still exploring different pathways, butfactors like advanced age, co-morbidities like diabetes, chronic kidney disease, heart disease, cancer etc may increase severity of the illness from COVID-19 [3].

Corona viruses are large, enveloped positive sense RNA viruses that belong to Coronaviridae family, and order Nidovirales. These are extensively disseminated in mammals together with humans and can also infect avian species. Their genome encodes various structural proteins that are responsible for host infection, membrane fusion, viral assembly, morphogenesis and release of virus particles [4]. The structural proteins are the S (Spike), E (Envelope), M (Membrane), and N (Nucleocapsid) proteins; the N protein holds the RNA genome, and the S, E, and M proteins together create the viral envelope. The clove shaped, trimeric S proteins that protrude from the virus envelope contains Receptor Binding Domain (RBD) and are the key machinery that facilitates virus entry into the host cell [5]. Once Corona virus enters host cell system, it takes over cell's molecular machinery and more copies of long chain protein pp1a and pp1ab are produced by translating virus RNA. The viral genome behaves as a messenger RNA for the synthesis of polyproteins. Viral Proteases cut long chain proteins into small pieces, activate them and play very critical role in the replication and propagation of the deadly virus [6].The ACE -2 receptors (Angiotensin converting Enzyme) are the important binding sites in human for the spread of infection by the SARS-CoV-2 [7]. The Main Protease, also called $M^{pro}$ or 3CLpro acts as molecular scissor and is responsible for the processing of all the non-structural proteins translated from viral RNA. It was reported that $M^{pro}$ is the key factor in proteolytic mutations of the virus [8]. The effective inhibition of $M^{pro}$ could provide us efficient drug molecule/anti-viral compounds against the deadly virus. At the moment there is no definite therapy available for COVID-19, various vaccine trials have been initiated across the globe. The development and effectiveness of vaccine is still long way to go, so at the moment preventive and supportive therapeutic strategies are being implied to prevent spread of the infection.

Herbs, plant extracts and other extracts of natural origin are used as effective therapies and treatments for various diseases and infections including viral infection. Ayurveda and ethno medicine are widely accepted and used globally. These alternate systems of medicine use plants, their decoctions & extract as source of bioactive ingredients. These can be a valuable resource at this moment of pandemic. Chen and Nakamura reported effectiveness of Chinese herbs in controlling spread of SARS outbreak in 2003 [9]. In a research study conducted by screening of 100 medicinal plants native to British coloumbia, Canada against various corona viruses, extract from two plants belonging to rosaceae family i.e *Rosa nutkana* C. Presl and *Amelunchier alnifolia* (Nutt.) Nutt showed anti-viral activity against an enteric coronavirus of bovine origin [10]. In another study it was reported, that the extract prepared from *African Trifolium* species blocked SARS-CoV entry [11]. A Taiwanese team reported strong anti-SARS-CoV (FFM 1 isolate) activity of the tender leaf extracts of Toona *Sinensis Roem* (TSL) (syn. Cedrela sinensis Juss, Meliaceae) [12].

Phytoactives from the various plants have been examined for the $M^{pro}$ proteases inhibition by *in silico* methodology. Authors of the current study evaluated various plants like *Andrographis paniculata, Azadirachta indica, Pomegranate peel extract, Zingiber officinale, Pterocarpus marsupium, Hamamelis virginiana, Biota orientalis, Clerodendrum serratum* and studied the *in silico* activity of the active compounds

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from these plants for their activity against $M^{pro}$ protease. The in-silico activity of Andrographolide, Andrograpanin, Corilagin, Azadirachtin, Nimbin, Nimbolinin A, Gingerol, Gingerenone A, (6)-Shogaol, cis-(8)-Shogaol, Zingerone, Pterostilbene, Pinusolidic acid, Clerodermic acid, Ellagitannins, Gallotannin, Geraniin, Cyclovalone, Hamamelitannin and Gallic acid against COVID-19 $M^{pro}$ (PDB ID: 6LU7) and SARS coronavirus main peptidase (PDB ID: 2GTB) was examined.

## Materials and Methods

### Protein receptor preparation

COVID-19 $M^{pro}$ (PDB ID: 6LU7) and SARS coronavirus main peptidase (PDB ID: 2GTB) structures were taken from the PDB (https://www.rcsb.org/), in PDB format [13]. The 6LU7 protein contains two chains, A and B, which form a homodimer. The 2GTB protein contains one chain, A. The native ligand for 6LU7 is 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, whereas the 2GTB native ligand is (5s,8s,14r)-ethyl 11-(3-amino-3-oxopropyl)-8-benzyl-14-hydroxy-5-isobutyl-3,6,9,12-tetraoxo-1-phenyl-2-oxa-4,7,10,11-tetraazapentade can -15-oate.

### Ligand preparations and computational docking

The ligands of the above constituents were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/), in SDF format. PubChem is a database which stores chemical substances and biological activities. The active site of a protein was determined using LIGPLOT v.4.5.3 and Biovia Discovery Studio 4.5 for COVID19 $M^{pro}$ (PDB ID: 6LU7) and SARS coronavirus main peptidase (PDB ID: 2GTB). Ligand optimization was done using the Marvin tools of ChemAxon. The ligands of the above active contituents were docked with three-dimensional structures of the protein target using AutoDock 4.2. The reported active sites of 6LU7 and 2GTB are mention in (Table 1).

| PBD ID | Active Sites | Formula weight |
|---|---|---|
| 6LU7 | THR24, THR26, PHE140, ASN142, GLY143, CYS145, HIS163, HIS164, GLU166, HIS172 | |
| | | 33825.5 |
| 2GTB | LYS5, ALA7, THR25, HIS41, MET49, TYR54, VAL125, TYR126, GLY127, PHE140, LEU141, ASN142, GLY143, SER144, CYS145, HIS163, HIS164, MET165, GLU166, LEU167, PRO168, HIS172, ASP187, ARG188, GLN189, GLN192, ALA198, LYS236, TYR237, GLN273 | 33947.7 |

**Table 1:** The Binding sites for 6LU7 and 2GTB [14].

## Results and Discussion

COVID-19, a severe acute respiratory viral infection caused by transmission of SARS-CoV-2 through entry of infected aerosols from respiratory droplets, cough or sneeze into the lungs. The most common symptoms may include cough, fatigue, fever, shortness of breath, with complications of organ failure and death in severe and critical cases [15].

SARS-CoV-2 has four structural proteins, known as the S (Spike), E (Envelope), M (Membrane), and N (Nucleocapsid) proteins; the N protein holds the RNA genome, and the S, E, and M proteins together create the viral envelope. Scientists isolated SARS-CoV-2 and sequenced the genome SARS-CoV-2 on January 7, 2020 [16]. The $M^{pro}$ protease is a key protein required for the proteolytic maturation of the virus. Inhibiting the activity of this enzyme would block viral replication (Figures 1 and 2). Thus, targeting $M^{pro}$ protease has the potential to provide effective treatment against SARS-CoV-2 by inhibition of the viral polypeptide cleavage [17].

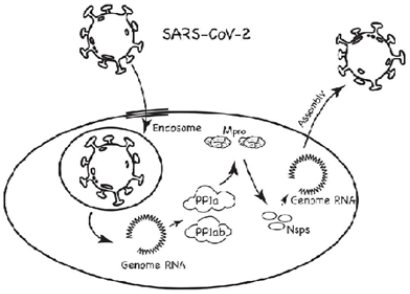



**Figure 1:** Viral replication of SARS-CoV2 with $M^{pro}$ protein.

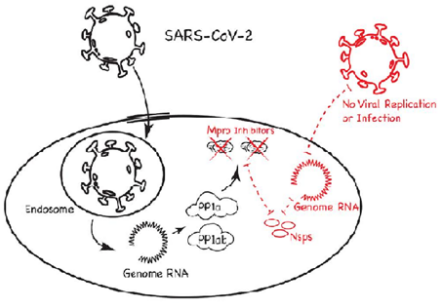
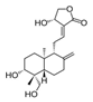
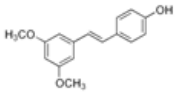
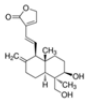
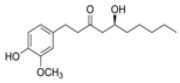
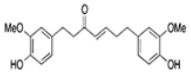
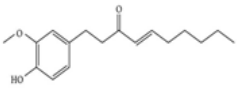
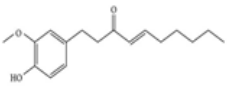
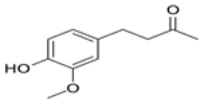
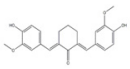
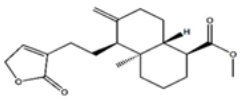
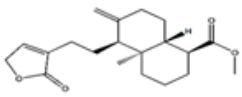



**Figure 2:** Inhibition of $M^{pro}$ protein leading to no viral replication of SARS-CoV-2.

Andrographolide is the potent bioactive component of Andrographis paniculata Nees. It is reported to have range of bioactivities like immunostimulatory, antibacterial, and antiviral. Its clinical trial on HIV positive patients reported a significant increase in the average CD4+ lymphocyte level. It repressed HIV-induced cell cycle dis-regulation, enhancing CD4+ lymphocyte levels in the enrolled patients [18]. Wiart et al. reported that Andrographolide have viricidal activity against herpes simplex virus 1 (HSV-1) [19]. In another study by Lin et al. it was observed that the *A. paniculata* ethanol extract and andrographolide reduced the expression of Epstein-Barr Virus (EBV) [20]. An in vitro study reported anti-influenza activity of *A. paniculata* in canine kidney cell line infected with H1N1, H9N2, or H5N1 [21]. Andrographolide and its derivatives also showed anti-HIV activity by inhibiting gp120-mediated cell fusion of HL2/3 cells, expressing gp120 on its surface with TZM-bl cells-expressing CD4 and co-receptors CCR5 and CXCR4 [22]. It is also reported to inhibit replication of chiken guunya virus [23]. In the current study, Andrographolide showed binding energy of -9.4 for 2 GTB and -9.8 for 6LU7, suggesting it to be a good candidate for development of antiviral product. Enmozhi et al. concluded its good solubility, pharmacodynamics property and target accuracy [24].

Pterostilbene are plant stilbenoids that are natural dimethylated analogue of resveratrol [25]. They are considered to be good for health. It was reported to completely block HIV-1 infection primarily at the reverse transcription step in resting CD4 T cells, that at a low micro molar concentration [26]. It was also reported that Pterostilbenehas drug likeness and anti-oxidant property [27]. We observed binding energy of -7.8 for 2GTB and -6.8 for 6LU7. Pandey et al. reported that Pterostilbene interacted with C terminus of S 1 domain with binding energy of -6.7 kcal/mol (Table 2) [28].

| Sr. No. | Name | | PubChem CID | 2GTB | 6LU7 |
|---|---|---|---|---|---|
| 1 | Andrographolide |  | 44593583 | -9.4 | -9.8 |
| 2 | Pterostilbene |  | 5281727 | -7.8 | -6.8 |
| 3 | Andrograpanin |  | 11666871 | -10.5 | -8.8 |
| 4 | Gingerol |  | 442793 | -6.8 | -6.2 |
| 5 | Gingerenone A |  | 5281775 | -8.1 | -7.8 |
| 6 | (6)-Shogaol, cis-(8)-Shogaol, Zingerone |  | 5281794 | -6.6 | -6.1 |
| 7 | cis-(8)-Shogaol |  | 6442560 | -6.7 | -9.4 |
| 8 | Zingerone |  | 31211 | -6.6 | -5.6 |
| 9 | Cyclovalone |  | 11366 | -7.9 | -8.6 |
| 10 | Pinusolidic acid |  | 25880646 | -9.7 | -8.6 |
| 11 | Clerodermic acid |  | 16745295 | -9 | -9 |

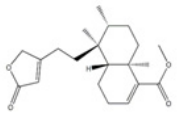
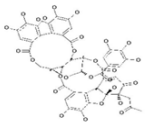
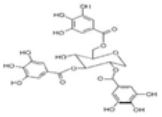
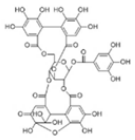
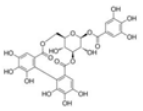
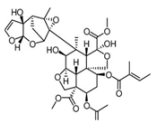
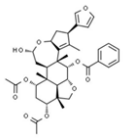
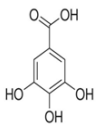
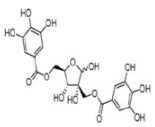
| | | | | | |
|---|---|---|---|---|---|
| 12 | Ellagitannins |  | 53790482 | -8.2 | -7.9 |
| 13 | Gallotannin |  | 12795683 | -9.8 | -10.2 |
| 14 | Geraniin |  | 3001497 | -13.7 | -15.4 |
| 15 | Corilagin |  | 73568 | -11.2 | -11.4 |
| 16 | Azadirachtin |  | 5281303 | -10.1 | 10.1 |
| 17 | Nimbolinin A |  | 6443004 | -10 | -10.8 |
| 18 | Nimbin |  | 108058 | -8.7 | -9.4 |
| 19 | Gallic acid |  | 370 | -6.4 | -6.1 |
| 20 | Hamamelitannin |  | 253775 | -9.2 | -9 |

**Table 2:** The binding energy of the selected constituents against COVID-19 $M^{pro}$ (PDB ID: 6LU7) and SARS coronavirus main peptidase (PDB ID:2GTB).

Ginger is reported to have potent inhibitory effects on acute and chronic inflammation, and suppressed activation of macrophage through anti-inflammatory pathway. Ahkam et al. reported that gingerol, geraniol, shogaol, zingiberene, zingiberenol, and zingerone from Ginger have good potential as antiviral agents with good oral bioavailability and flexibility [29]. Chang et al. reported that significant antiviral activity of fresh ginger against Human Respiratory Syncytial Virus (HRSV). They reported that ginger is effective against HRSV-induced plaque formation on airway epithelium by blocking viral attachment and internalization [30]. Khaerunnisa et al. reported that binding energy obtained by docking of 6LU7 with zingerol and, gingerol as -5.40 and-5.38 kcal/mol [31]. During the present evaluation, we observed binding energy for ligand gingerol 2GTB and 6LU7 as -6.8 and 6.2 kcal/mol respectively. Binding energy with Gingerenone A as a ligand for 2GTB and 6LU7 was -8.1 and -7.8 kcal/mol. (6)-Shogaol, cis-(8)-Shogaol, Zingerone ligands had binding energy of -6.6, -6.7, -6.6 kcal/mol respectively for 2 GTB and -6.1, -9.4, -5.6 kcal/mol respectively for 6LU7. Sharma et al. studied ADME related properties

for compounds like Gingerenone, Shogaol and reported that these follow Lipinski's rule of five and are good drug candidates [32].

Pomegranate peel is sometimes considered an agro-waste, but it is indeed as a source of different flavonoids with antibacterial, antiviral, antioxidant, anti-inflammatory and antineoplastic bioactivities. Corilagin is an ellagitannin found in the peel and also in the peel, bark or heartwood of pomegranates [33]. Gallotannin and Ellagitannins from pomegranate peel crude extract specifically blocked the HCV NS3/4A protease activity in an in vitro study and also certain polyphenols have shown significant antiviral effects against foodborne viral surrogates, FCV-F9, MNV-1, and bacteriophage MS2 [34].

Geraniin possesses antioxidant, antimicrobial, anticancer, cytoprotective, immune-modulatory, analgesic properties and antiviral activity. Choi et al. reported that geraniin possess potent antiviral activity against influenza-A strain and influenza virus-B strain. It inhibited neuraminidase activity following viral infection in Madin – Darby canine kidney cells [35]. NA inhibitors such as zanamivir and oseltamivir are predominantly prescribed against most of the influenza virus infections [36]. Ahmad et al. reported geraniin has antiviral activity against dengue virus (DENV-2) [37]. Geraniin as a ligand showed significant binding energy of -13.7 and -15.4 kcal/mol for 2GTB and 6LU7. It is large molecule, that may make it difficult to enter viron and it can be a promising viral entry inhibitor.

Azadirachta indica has wide range constituents including Azadirachtin, Nimbin and Nimbolinin A, which possess strong biological and pharmacological activities such as antibacterial, antifungal, anti-inflammatory and most importantly antiviral activity. Various reports have documented that neem extracts significantly inhibited the polio virus, HIV, coxackie B group virus, and dengue virus at early step of viral genome replication including Herpes simplex virus type-1 (HSV-1) [38].In the current study ligands such as Azadirachtin, Nimbolinin A and Nimbin binding energy for 2GTB were -10.1, -10.0, and -8.7 kcal/mol respectively and for 6LU7 were -10.1, -10.8 and -9.4 kcal/mol. These ligands docked with SARS-CoV-2 proteases and are considered as drug potentials for preventing spike protease attaching cellular membrane and ACE2 interaction. These results are consistent with reported literature.

Hamamelitannin an active constituent of Hamamelis virginiana is the best performing antiviral candidate, identified against both influenza A virus (IAV) and human papillomavirus (HPV) [39]. Another constituent from the same plant, Gallic acid is known for its antioxidant activity, anticancer, antibacterial and antifungal properties. Gallic acid has virucidal effect on herpes simplex virus particles, along with partial inhibition of the virus attachment to cells and its subsequent cell-to-cell spread activity [40].

Cyclovalone, a synthetic curcumin derivative in which the keto-enolic system is replaced by a cyclohexanone ring, acts as a choleretic and cholagogic agent which stimulates the formation and secretion of bile, and also has an anti-inflammatory effect. Pinusolidic acid from Biota orientalis has shown to be a promising compound fro for their inhibitory activity against of SARS-CoV 3CLpro through molecular modelling [41]. Clerodermic acid, constituent from Clerodendrum serratum Linn, has shown to be effective against yellow fever virus [42].

## Conclusion

In conclusion, it can be deemed from the above data that the natural molecules derived from plants can have a recognisable activity against $M^{pro}$ Protease and can be considered for future development. Based on the data available from the literature and the binding affinity of the phytoactives against COVID-19 $M^{pro}$ and SARS coronavirus main peptidase (more than or equal to -9), it can be concluded that Andrographolide, Corilagin, Azadirachtin, Nimbin, Nimbolinin A, cis-(8)-Shogaol, Pinusolidic acid, Clerodermic acid, Gallotannin, Geraniin and Hamamelitannin suggests more promising activity for use against COVID-19 as compared to other phytoactives.

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