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Molecular docking study of potential phytochemicals of *Tinospora cordifolia* (Giloy) and *Glycyrrhiza glabra* (Mulethi) and their effect on the complex SARS-CoV2 Mpro& RdRp

Jaya Pandey[1], Sarad Kumar Mishra[2]

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Author Affiliation:
[1]Department of Biotechnology, Deen Dayal Upadhyaya Gorakhpur University, Gorakhpur, Uttar Pradesh, India, 273009,
Email: jayapandey242@gmail.com
[2]Department of Biotechnology, Deen Dayal Upadhyaya Gorakhpur University, Gorakhpur, Uttar Pradesh, India, 273009,
Email: saradmishra5@gmail.com

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ABSTRACT

SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) previously convened 2019 novel coronavirus is the responsible for coronavirus disease 2019 (COVID-19), a disease lately state a global public health crisis by the World Health Organization (WHO). At the moment there are no available drugs and vaccines for the treatment or prevention of COVID-19. SARS-CoV-2 main protease (Mpro) and RdRp are crucial determinants in the virus infectious process and have been recognized as key targets for therapeutics designs. In the present *In-silico* study, a library of 20 phytochemicals from 2 plants *Tinospora cordifolia* & *Glycyrrhiza glabra* with antiviral activity obtained from Indian Medicinal Plants, Phytochemistry and Therapeutics (IMPPAT) Database was screened 20 phytochemicals for activity against 6lu7 and RdRp with the PyRX software. Four lead compounds with 8 binding energies within the range of -7 to -9.8 Kcal/mol were selected for molecular docking analyses against 6lu7 and RdRp. The ADMET analysis of 20 phytochemical properties showed that lead compounds less hepatotoxicity and mutagenicity effects while they show variable immunotoxicity, carcinogenicity and cytotoxicity. The compounds showed that best-fit value effective against SARS-CoV-2 main protease 6lu7 & RdRp targets, respectively. Our information suggests a repurposing candidate drug may have multi target activity against SARS-CoV-2; so further *in-vitro* and *in-vivo* evaluations are recommended.

Keywords: Drug discovery, Molecular docking, SARS-CoV-2, Plants-derived phytochemicals, main protease, RNA dependent RNA polymerase, *Tinospora cordifolia*, *Glycyrrhiza glabra.*

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1. INTRODUCTION

The world population is on the verge of collapse due to the emergence of a global pandemic known as Coronavirus Disease 2019 (COVID-19). A novel

single-stranded RNA virus from the coronaviridae family's beta-coronavirus genus is responsible for this pandemic. This virus is designated as Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV-2) and relates to the same coronavirus family as the SARS coronavirus (SARS-CoV). That has phylogenetic and structural similarities to the coronavirus that generates severe acute respiratory syndrome (approximately 80% nucleotide identity and 89.10 percent nucleotide similarity) (SARS-CoV). Meanwhile, on December 31st, 2019 in Wuhan, China, an infection was uncovered. Mammalian and avian diseases are caused by them. The most prevalent symptoms are respiratory infections and pneumonia-like symptoms. In humans, some instances of the common cold are considered minor infections. Coronavirus is named after the Latin word corona, which means "crown" or "wreath" in Latin. The term was originally coined by June Almeida and David Tyrrell, who were the first to observe and investigate human coronaviruses. The name comes from an electron microscope study of virions (the virus's infective phase), which feature a fringe of enormous, bulbous surface projections that indicate the extent similar of the solar corona or halo (Abraham S et al.1990). This morphology or outer appearance is created by the viral spike peplomers, which are proteins on the outer surface of the corona virus. Coronaviruses are representatives of the orthocoronavirinae subfamily of the coronaviridae family. They are enclosed viruses having a single-stranded positive-sense RNA genome and a helical symmetry nucleocapsid. Corona virus has a genomic size of 26 to 32 kb, trying to make it one of the largest viral pathogens. A 5′ methylated cap and a 3′ polyadenylated tail are present in the genome. The main proteases/spike protein and RdRp of SARS-CoV-2 were investigated as possible macromolecular targets for COVID-19 control employing active phytocompounds from Ayurvedic texts. Ayurveda, also known as 'The Science of Life,' is a traditional Indian medicine cantered on the holistic notion of life, health, and healing. Ayurvedic scripture describes a variety of rejuvenative treatments that provide biological sustenance to body tissues. It describes a variety of medicinal plants that have a wide range of therapeutic potential in the treatment of respiratory problems; some of the most notable, but not limited to, are *Glycyrrhiza glabra* (mulaithi), *Tinospora cordifolia* (Giloy) used in present study (Adhikari B et al.2021). They're all immunomodulators, which means they help the body fight infections. They have similar shape and chemical structures: Human and cow coronaviruses, for example, are antigenically related. Animals, on the other extreme, have not been shown to propagate human coronaviruses. In most cases, airborne droplets infect the nasal mucosa. Local replication of the virus in ciliated epithelial cells causes cell damage and inflammation. Immunity begins to wane after a year or two. According to research in both organ cultures and human volunteers, coronaviruses are extremely selective, growing only in differentiated respiratory epithelial cells. Infected cells acquire vacuolated, their cilia are destroyed, and they may produce syncytia. Inflammatory mediators are produced in response to cell injury, which stimulate nasal discharge and encourage local inflammation and swelling. Sneezing is induced, the airway is obstructed, and the mucosa temperature goes up as a reaction of these responses. Treatment of common colds is symptomatic; no vaccines or specific drugs are available. Hygiene measures are help slow-down the spread of disease. The most effective candidates in this regard tend to be naturally occurring substances with high bioavailability and low cytotoxicity. Since ancient times, humans have depended on natural substances, notably phytochemicals, to cure a variety of diseases and problems. Antioxidant, anti-inflammatory, anticancer, antibacterial, antifungal, and antiviral properties are only some of the biological properties. Some of the active phytochemical present in *Tinospora cordifolia* (Giloy) & *Glycyrrhiza glabra* (Mulethi) has been shown to inhibit the replication of severe acute respiratory syndrome and also reduce the expression of nucleoprotein (SARS Cov-2 nucleoprotein enhances the infectivity of spike protein). Existing FDA-approved pharmaceuticals like chloroquine (CQ) and hydroxychloroquine (HCQ) are currently being redirected in this regard, either alone or in combination with other known drugs. The researchers employed molecular docking to determine the most effective natural chemicals (flavonoids) that can bind to the functional domains in this in silico investigation of the SARS-CoV-2 spike protein (SARS-CoV-2S) and RdRp (RNA-dependent RNA polymerase), to find the most effective natural chemicals (flavonoids) that can bind to the functional domains of the SARS-CoV-2 spike, commonly known as nsp12. RdRp activity is supported by magnesium ions and essential for the nonstructural proteins nsp7 and nsp8 for complete activity. Conserved polymerase motifs (AG) form the active site of the SARS-CoV-2 RdRp, with motif A and motif C containing the divalent-cation-binding amino acid D618. We discovered that roughly ten of these compounds may successfully attach to the C-terminal area of either the S1 or S2 domains of SARS-CoV-2S, and that they have a more stable binding connection than HCQ. These natural compounds bind to the S1 and S2 domains of the SARS-CoV-2S protein, preventing it from binding to the hACE2 receptor or internalising during infection (Merarchi et al., 2021).

2. MATERIALS & METHODS

Preparation of target protein and ligand molecules

The Protein Data Bank (https://www.rcsb.org/) of the RCSB (Research Collaboratory for Structural Bioinformatics) was performed to retrieve the three-dimensional crystal structures of COVID-19 (SARS-CoV-2) Mpro (PDB ID-6LU7) and RdRp (PDB ID- 6XQB).

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The 'Prepare protein' methodology in Discovery studio 4.0 was used to prepare the proteins (DS 4.0). PyMOL software was used to inspect the downloaded 3D structures for incorrect bonds, side-chain abnormalities, and missing hydrogens. In Biovia Discovery Studio 2020, all water molecules, complex compounds, ions, and protein ligands were eliminated (Biovia 2020). The AutoDock-MGL Tool was used to upload the improved PDB structures. To summarise, polar hydrogens were added to the PDBQT files, and they were created using standard approaches. The active site of the generated protein was also estimated using DS 4.0. The active sites of the proteins were determined using Biovia Discovery Studio 2020 and the Computed Atlas for Surface Topography of Proteins (CASTp) (http://sts.bioe.uic.edu/castp/index.html?2011). The active sites for the closed and open conformational states of spike protein were selected based on the receptor-binding domain, which binds to the ACE2 receptors on the membrane of the human host cell. The binding site for 3CLpro protein was chosen based on the position of cocrystallized inhibitor N3, which was generated using computer-aided drug design and has shown selective inhibition of SARS and MERS with strong binding affinity in the binding pockets of 3CLpro/Mpro & RdRp crystal structures (Mandal & Mandal, 2021; Ambrose et al., 2021). The optimized ligands and proteins in PDBQT format were selected to molecular docking with the support of AutoDock Vina software. AutoDock Vina predicts the interaction between protein and ligand by employment its scoring function (binding affinity). For documentation of potential inhibitors of SARS-CoV-2 Main protease and RdRp, a total of 20 active phytochemicals (Table 1) were retrieved from the Indian Medicinal Plants, Phytochemistry and Therapeutics (IMPPAT) compound database (https://cb.imsc.res.in/imppat/home). DS 4.0 was then used to perform ligand optimization, energy minimization, and conversion of the recovered ligands to 3D PDB.

Table 1 – List of phytochemival found in *T.cordifolia* & *G.glabra* for docking analysis.

S.No.	Phytochemicals found in *T. cordifolia* (Giloy)	Phytochemicals found in *Glycyrrhiza glabra* (Mulethi)
1)	Phytosterols	Glycyrrhizic acid
2)	Berberine	1-PENTADECANOL
3)	Xanosporic acid	Apiin
4)	Chasmanthin	Aurone
5)	Columbin	Chalcone
6)	Cordifolide A	Coumarin
7)	Palmarin	Formononetin
8)	Tembetarine	Docosyl caffeate
9)	Tinosporinone	Enoxolone
10)	Tinosponone	24-Hydroxyglycyrrhetic acid

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Molecular Docking

The goal of molecular docking is to identify the best match between two molecules. Docking is a strategy for predicting one ligand's preferred orientation in an active region of a receptor to produce a stable compound. The docking analysis was carried out using the Pyrx program. Mpro and RdRp each have their own grid boxes.

Drug-likeness and ADMET prediction

The best docked compounds from *Glycyrrhiza glabra & Tinospora cordifolia* were taken for drug-likeness test and ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) profile prediction with the help of web based server Lipinski rule of five (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp) and admetSAR server (http://lmmd.ecust.edu.cn/admetsar1/predict/).

3. RESULTS AND DISCUSSION

According to a molecular docking study, different active phytochemicals identified in T. cordifolia (Giloy) and Glycyrrhiza glabra (Mulethi) demonstrated significant binding affinity for SARS-CoV-2 Mpro and RdrP (Figure 1 & 2). Total 20 active phytocompounds selected from 2 Indian medicinal plants represents the list with significant binding energy (>7.0 kcal/mol) for SARS-CoV-2 (Main protease) & RdRp. In our study, the protein that we chose has a significant role in viral pathogenesis as it is involved in replication, transcription, and translation and has shown to be potential for an antiviral drug target. For docking in Autodock Vina, a text file is generated that contains the name of the receptor along with the grid dimensions where the grid size was set as x=20, y=20, and x=20, and the grid center values were x = 26.283, y = 12.5998, and z = 58.9657 for 6lu7 and x = 97.8192 y = 96.0379 and z = 100.5061 for RdRp.

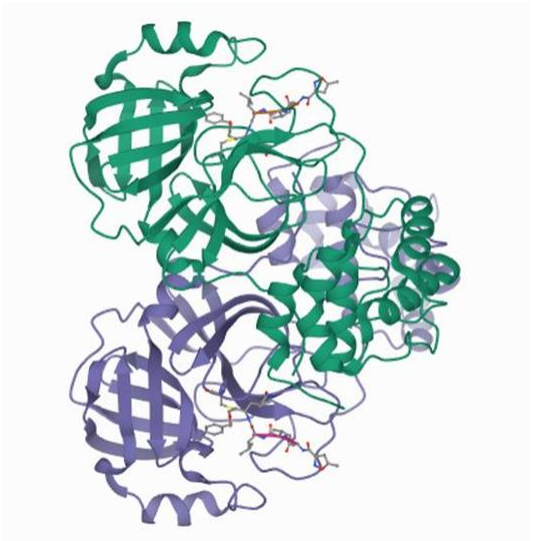

Figure 1 - Main protease of SARS-CoV-2 with the inhibitor N3.

Using a command prompt, the command was given to dock the 10 ligand molecules at a time. At the end of the docking, an output file is generated that shows the binding affinity of the ligand. 20 ligand molecules were docked with the protein and among them, 4 ligands showing the best interaction with the protein molecule were chosen. These 20 ligands include Phytosterols, Berberine, Xanosporic acid, Chasmanthin, Columbin, Cordifolide A, Palmarin, Tembetarine, Tinosporinone, Tinosponone present in *T.cordifolia* & Glycyrrhizic acid, 1-PENTADECANOL, Apiin, Aurone, Chalcone, Coumarin, Formononetin, Docosylcaffeate, E noxolone, 24-Hydroxyglycyrrhetic acid present in *G.glabra*.

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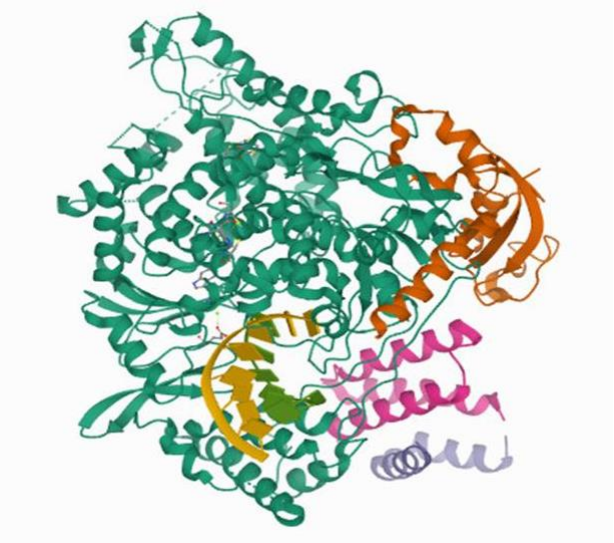

Figure 2 - SARS-CoV-2 RdRp/RNA complex in three dimensions.

***Tinospora cordifolia* (Giloy) inhibitors for SARS-CoV-2 Mpro and RdRp**

The two compounds from Tinospora cordifolia (Giloy), berberine (CID:2353) and cordiofolide A (CID:102451916), demonstrated substantial binding affinity for SARSCoV-2 Mpro and RdRp when compared to other phytochemicals. For RdRp and Mpro, cordiofolide A had the maximum binding energy of -9.1 kcal/mol and -7.8 kcal/mol, respectively. Berberine was discovered to be another inhibitor, with binding energies of - 8.8 kcal/mol for RdRp and -7.2 kcal/mol for Mpro, respectively (Table 2).

Table 2 - Compounds found in *T.cordifolia* with the highest binding that can be a potent drug against SARS- COV 2 M^{pro} & RdRp

S.I NO.	Phytochemicals from *Tinospora cordifolia*(Giloy)	M^{pro}Binding affnity (kcal/ mol)	RdRp Binding affnity (kcal/ mol)
Positive control	Remdesivir	-7.90	-7.60
1.	Phytoserol	-7.5	-7.8
2.	Berberine	**-7.2**	**-8.8**
3.	Xanosporic acid	-7.8	-0.0
4.	Chasmanthin	-7.2	-7.9
5.	Columbin	-6.9	-7.8
6.	Cordiofolide A	**-7.8**	**-9.1**
7.	Palmarin	-7.1	-8.5
8.	Tembetarine	-6.3	-8.3
9.	Tinosporinone	-5.7	-8.2
10.	Tinosponone	-6.6	-7.4

***Glycyrrhiza glabra* (Mulaithi) inhibitors for SARS-CoV-2 Mpro and RdRp**

The two compounds from Glycyrrhiza glabra (Mulaithi), glycyrrhizic acid (CID:122130752) and enoxolone (CID:10114), demonstrated the highest binding affinity for Mpro and RdRp when compared to other phytochemicals. RdRp and Mpro had

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binding energies of -8.8 kcal/mol and -9.8 kcal/mol, respectively, for glycyrrhizic acid. For RdRp and Mpro, Enoxolone had the maximum binding energy of -9.8 kcal/mol and -8.8 kcal/mol, respectively (Table 3).

Table 3 - Compounds found in *G.glabra* with the highest binding that can be a potent drug against SARS – COV 2 M^{pro} & RdRp

S.no	Phytochemicals from *Glycyrrhiza glabra (Mulaithi)*	Mpro Binding affnity (kcal/ mol)	RdRp Binding affnity (kcal/ mol)
Positive control	Remdesivir	-7.90	-7.60
1.	Glycyrrhizic acid	**-9.8**	**-8.8**
2.	1-Pentadecanol	-4.5	-5.4
3.	Appin	-8.5	-8.1
4.	Auron	-6.9	-8.6
5.	Chalcone	-6.3	-7
6.	Coumarin	-5.3	-6.6
7.	24- hydeoxyglycyrrhetic acid	-8.5	0.0
8.	Formononectin	-6.5	-7.5
9.	Docosyl caffeate	-5	-4.5
10.	Enoxolone	**-8.8**	**-9.8**

Lipinski's rule of five has been used to predict drug-likeness for the best docked compounds, and the ADMET molecular property prediction test was carried out via the Swiss ADME server (Table 4). The Lipinski rule of five is a five-parameter thumb rule that helps distinguish between drug-like and non-drug-like compounds by requiring two or more of their criteria to be satisfied (molecular mass, hydrogen bond donor, hydrogen bond acceptor, Log P, and molar refractivity). As a result, the best docked compounds in our investigation from both plants obey more than two Lipinski rule of five features and may thus be classified as drug-like compounds.

Table 4 - Ligand library showing their binding affinity, ADME and Boiled egg presentation (GI absorption BBB Permeation) along with their CID number

Phytochemical name	Pubchem ID	Molecular weight	Lipinski's rule violation	GI Absorption	BBB Permeation
1) Phytosterol	CID:12303662	414.72 g/mol	Yes; 1 violation	Low	No
2) Berberine	CID:2353	336.37 g/mol	Yes; 0 violation	High	Yes

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3) Xanosporic acid	CID:46879540	536.49 g/mol	No; 2 violations	Low	No
4) Chasmanthin	CID:442012	374.39 g/mol	Yes; 0 violation	High	No
5) Columbin	CID:18502774	358.39 g/mol	Yes; 0 violation	High	No
6) Cordifolide A	CID:102451916	598.67 g/mol	No; 2 violations	Low	No
7) Palmarin	CID:442068	374.39 g/mol	Yes; 0 violation	High	No
8) Tembetarine	CID:167718	344.43 g/mol	Yes; 0 violation	High	Yes
9) Tinosponone	CID:15215479	330.38 g/mol	Yes; 0 violation	High	Yes
10) Tinosporinone	CID:42607646	342.35 g/mol	Yes; 0 violation	High	Yes
11) Glycyrrhizic acid	CID:122130752	822.94 g/mol	No; 3 violations:	Low	No
12) 1-PENTADECANOL	CID:12397	228.42 g/mol	Yes; 1 violation	High	Yes
13) Apiin	CID:16211399	564.50 g/mol	No; 3 violations	Low	No
14) Aurone	CID:6537099	222.24 g/mol	Yes; 0 violation	High	Yes
15) Chalcone	CID:637760	208.26 g/mol	Yes; 0 violation	High	Yes

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16) Coumarin	CID:323	146.15 g/mol	Yes; 0 violation	High	Yes
17) 24-Hydroxyglycyrrhetic acid	CID:10128 0182	486.69 g/mol	Yes; 0 violation	High	No
18) Formononetin	CID:5280378	268.27 g/mol	Yes; 0 violation	High	Yes
19) Docosyl caffeate	CID:53169 52	488.75 g/mol	Yes; 1 violation	Low	No
20) Enoxolone	CID:10114	470.69 g/mol	Yes; 1 violation	High	Yes

4. CONCLUSION

Molecules were docked against the receptor protein (Mpro & RdRp) and depending on the score of the binding affinity 4 best molecules were chosen that can be used as a potent drug against SARS- CoV 2. After performing molecular docking to estimate the binding affinities simulation to evaluate the stability of the protein-ligand complexes berberine estimated binding energy -7.8 and -8.8, Cordiofolide A estimated binding energy -7.8 and -9.1, glycyrrhizic acid estimated binding energy -9.8 and -8.8, enoxolone estimated binding energy -8-8 and -9.8 respectively for 6lu7 and RdRp. With our computational approach, found some potential anti-viral compounds that inhibits the M^{pro} (main protease) and RdRp (RNA dependend RNA polymerase) of SARS-CoV 2. This would bring an end to the persistent health risk imposed by the virus. In conclusion to this, we can say that the computational project performed can be treated as a guide for experimental work on viral SARS-CoV-2 Mpro (main protease) & RdRp (RNA dependent RNA polymerase) and antiviral drug design.

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Ethical approval
Not applicable.

Conflict of Interest:
The authors declare that there are no conflicts of interests.

Data and materials availability:
All data associated with this study are present in the paper.

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