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Calotropin a potent bioactive from milk of *Calotropis gigantean* against 2019-N-Cov M^{pro}/$3CL^{pro}$ and Spike Protein

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Abstract: SARS-CoV-2 (COVID-19), a positive sense ssRNA virus, adherent of family of "corona" virus, is disseminating its appendages worldwide because of paucity of drugs at the moment. Due to its vital role in virus replication, M^{pro} and Spike (S) proteins have currently been considered as an appropriate target for designing of drug. The current study focused on the inhibitory activity of calotropin, a component of milk extracted from *Calotropis gigantean*, against M^{pro} and Spike proteins from SARS-CoV-2. So far, there is no work commenced on in-silico study of this compound against M^{pro} and Spike proteins of SARS-CoV-2. In the current analysis, we had used Patchdock analysis to study molecular docking. Protein Interactions Calculator was practiced to analyze interactions among proteins. In-silico Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) profile was also studied. Docking score specified actual binding of component calotropin towards COVID 19 M^{pro} and S-protein. Interactions consequences specified that, M^{pro} and S-protein protein/calotropin complexes involve in interactions (hydrogen and hydrophobic). Besides, our analysis also threw light on the significant outcome that the S2domains of COVID 19 "S" glycoproteins possibly make interaction with calotropin. In silico ADMET analysis provided guidelines and possibility for identification of effective anti COVID 19 drug. Consequently, calotropin could signify probable herbal therapy to be used as inhibitor of COVID 19. Though, additional research is obligatory to explore their probable therapeutic use.

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1. Introduction

A new corona virus, 2019-n-CoV, caused a pandemic of respiratory disease (COVID-19) in Wuhan city, has since spread worldwide [**Herbert, 2020**]. The virus has been called as SARS CoV2, as the RNA genome of virus is 82% similar to the SARS coronavirus. Presently, no particular treatment for COVID 19 is accessible and research concerning the therapy of COVID-19 is undergoing [Wang and Yang, 2020]. Nevertheless, the processes that have been applied remain restricted to supportive and defensive therapies, intended to avoid additional obstacles and damage to organs. Certain primary investigations have scrutinized possible blends that comprise anti-malarial drug hydroxychloroquine, and Anti Human Immuno deficieny virus (HIV) vaccines could be used for treating COVID19 infections [Li et al., 2020]. Besides using antiviral drugs, clinicians are utilizing MERS CoV and SARS CoV neutralizing antibodies with a specific target on the domain "S1 and M^{pro}/$3CL^{pro}$" of proteins of the COVID 19 [Huang et al. 2020]. SARS-CoV-2 M^{pro},/chymotrypsin-like protease also called as $3CL^{pro}$ from, represents a key target among coronaviruses [Song et al, 2018, Zhou et al., 2015]. The M^{pro} /$3CL^{pro}$ main protease is a 33.8-kDa protease that plays a central role in mediating viral replication and transcription functions all the way through wide-ranging proteolytic processing of two replicase polyproteins, pp1a (486 kDa) and pp1ab (790 kDa). M^{pro}/$3CL^{pro}$ 3D structure is highly alike to that of the SARS-CoV M^{pro}/$3CL^{pro}$, based on its 96% sequence identity. Due to its likely role in polyprotein processing and virus maturation, M^{pro}/$3CL^{pro}$ is measured to be a appropriate target for viral inhibitor development. Like other corona viruses, the outer membrane spike glycoprotein "S", is the major protein involved in interaction with specific targets of host cell (for instance adhesion factors, Ezrin, CD26, ACE2 and cyclophilins). All these targets are significant for adhesion and virulence. As far as entry of corona viruses is concerned, it is facilitated via transmembrane "S" glycoprotein that produces homo-trimer projecting from surface of virus [Millet et al., 2012]. The SARS-Cov "S" glycoprotein comprises a conserved Receptor Binding Domain (RBD) which identifies receptors of host cell such as

Ezrin, CD26, ACE2 and cyclophilins. It is 1200 amino acids long protein belongs to class1viral fusion proteins and involves in binding with cell's receptor, pathogenesis and tissue tropism [Millet et al., 2012]. In the course of infection, the trimeric "S" protein is treated via proteases of host cell at the S1 or S2 cleavage site. Subsequent cleavage, also called it as priming, the protein is separated into two terminals: one is 'S1' ectodomain (N terminal) that identifies similar surface receptor of cell and other is 'S2' membrane anchored protein (C terminal) involved in entry of virus [Millet et al., 2012]. Therefore, by virtue of its key role, SARS-Cov 'S' protein is considered as an appropriate objective for developing viral inhibitor. Inhibition of SARS-Cov'S' protein activity would block replication of virus. Since in humans, not at all any proteases with comparable cleavage specific are recognized, so inhibitors are improbable to be considered as toxic.

From ancient time, medicinal plants are beneficial in the field of drug therapeutics as they are safer alternatives being utilized by humans for centuries [Vora et al., 2019]. Previously, many of the new drug formulations are derived from natural products. Our present study focuses on the *in-silico* analysis of Calotropin from milk of *Calotropis gigantean.* Calotropis, a member of Apocynaceae family, is a poisonous plant native to Cambodia, Malaysia, India, Bangladesh, Indonesia, Philippines, Thailand, Sri Lanka, China, Pakistan, Nepal, and tropical Africa [Vora et al., 2019]. It is a large shrub growing to 4 m (13 ft) tall. The stem and leaves when incised yield thick milky juice which is rich in bioactive molecule calotropin. Milk of this plant has been used in various system of medicine for the past 2000 years. Bioactive components from leaves, flowers, fruits and roots of *Calotropis gigantean* are used as anticancer, pesticide, insecticide, fungicide and Nematicidal/Schistosomicidal/Antihelminthic Activity, but little is known about its antiviral potential.

Traditionally, the discovery of new therapeutic drugs is a tedious and expensive process which generally takes 12-14 years with a lot of money to bring drug into market. With the purpose of overcoming these problems a lot many multidisciplinary approaches are used to discover new drug. In the field of drug discovery, medicinal plants are advantageous as they are utilized as a safe herbal alternative by humans for centuries. Over the years many approaches have used to design drug and released into commercial market for use. Among all, structure-based drug design (SBDD) is most commonly used , which based on 3-D structure protein target to propose a suitable ligand that can pose as its potential inhibitor [Singh et al., 2016]. In SBDD, Molecular docking is a key technique that can be applied in designing drug making process. Molecular docking has facilitated researchers to virtually monitor a collection of bio-actives against the receptor target protein and analyze binding conformations and affinities of the compounds to the receptor [Barcellos et al., 2019]. In drug discovery processes, *in silico* designing of drug is a practice of computer based modeling which is very useful [Antonio et al., 2020]. The sources of several of the active constituents of medicines and novel drugs are obtained from natural products [Islam et al., 2020]. We hypothesize that calotropin from *Calotropis gigantean* has the capability to prevent infection of COVID-19. However, in the present study, we investigated calotropin as potential inhibitor candidates for COVID-19 M^{pro} and SARS-Cov S proteins. Therefore the research objective of the present study was *in-silico* analysis and comparative molecular docking studies pertain to calotropin in relation with M^{pro} and SARS-Cov S proteins. The findings of the present study will provide other researchers with opportunities to identify the right drug to combat COVID-19.

Fig 1: Pictorial image of *Calotropis gigantea*

2. Materials and Methods

2.1 Ligand modelling

The instinctive ligand for M^{pro} and S-protein structures was calotropin. SMILES (simplified molecular-input line-entry system) was retrieved for calotropin molecule and converted to their corresponding 3D structures by using UCSF-chimera and saved in .pdb format

2.2 Protein receptor preparation and Molecular Docking

X ray crystal structures of COVID-19 M^{pro} (PDB ID: 1uk3) and Spike protein (PDB ID: 6VXX)

co-crystallized with inhibitors were retrieved from PDB web cite (https://www.rcsb.org/). The target enzymes were cleaned, prepared energy minimized before docking study. Before the docking studies, the protein structures were first prepared using the dock prep set up in chimera software. The dock preparation is an optimization part that corrects atomic and bond length, structure, charges anomalies. Original inhibitors and water molecules were detached from the spike protein structure and any missing hydrogen atoms were added . PatchDock tool was used for docking study of the compounds over COVID-19 M^{pro}/$3CL^{pro}$ and S-proteins (https://bioinfo3d.cs.tau.ac.il/PatchDock/). For this both ligand (calotropin) and receptors molecules in .pdb file formats were uploaded to PatchDock server and job was executed. The best generated docked structure was downloaded and saved as .pdb file. The docked complex structure output formats were submitted into Biovia Discovery Studio Visualizer 2020 and Chimera tools in order to study 3D conformations, surface analysis and to map the interaction of the resulting docked complexes (https://projects.biotec.tu-dresden.de/plip-web/plip/index).

2.3 Binding Mode of Docked Complexes

Plip tool was use to find out residues involved in 3-D interactions(https://projects.biotec.tu-dresden.de/plip-web/plip/index/). 2-D interactions were also calculated using discovery studio 2020 client software.

2.3 Drug-likeness and toxicity

Calotropin was retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/) with PubChem CID 16142. Lipinski's rule of five was used to calculate drug like properties. SWISSADME prediction tool was used to find Lipinski's rule of five (http://www.swissadme.ch/) and to find out ADMET (Absorption, Metabolism, Toxicity and Excretion) properties. Bioactivity analysis was carried out using molinspiration tool (https://www.molinspiration.com/cgi-bin/properties). Bioactivity was based on following score: if the bioactivity score is (>0), then it is active, if (-5.0-0.0) then moderately active, if (< -5.0) then inactive.

2.4 Active sites prediction in 3D modeled receptor

CASTp (The Computed Atlas of Surface Topography of proteins) web tool was used to predict active sites residues in the spike 3D modelled protein. CASTp is an online tool used in identification and dimension of cavities on 3D protein structures. Default value of 1.4 Angstroms was used as probe radius.

3. Result Analysis

Coronaviruses (CoVs) are a group of viruses that infects humans and animals. CoVs infections affect animals by several means such as: cold, fever, digestive, respiratory and liver systems of animals and humans [Gildenhuys, 2020]. It is the main protease (M^{pro}/$3CL^{pro}$) and Spike proteins (S) that is found in the CoV associated with the severe acute respiratory syndrome (SARS), which can be accessed in PDB and was suggested to be a potential drug target for 2019-nCov [Liu and Wang, 2020]. In the present study, we performed in silico analysis of calotropis milk component 'calotropin' against M^{pro}/$3CL^{pro}$ and Spike proteins of COVID-19. In modern drug discovery process, molecular docking is a widely used computational method to predict the binding mode and binding affinity of ligands with the target receptor protein [Lu, 2020]. The efficacy of the docked complex was estimated on the basis of two important criteria's: The lowest binding energy and the interaction of the ligand with the active site amino acids residues. A ligand experiences either hydrophobic interactions or H-bonding or both while docking in the active site. The results of docking can be used to find the best inhibitors for specific target proteins and thus to design new drugs. In many viruses, proteases play essential roles in viral replication; therefore, proteases are often used as protein targets during the development of antiviral therapeutics. In CoV, the M^{pro}/$3CL^{pro}$ protein is involved in virus proteolytic maturation and has been examined as a potential target protein by inhibiting the cleavage of the viral polyprotein to prevent the spread of infection [Huang et al., 2020, Sharma and Kaur, 2020]. The invention of the M^{pro}/$3CL^{pro}$ protease structure in COVID-19 provides a nice path to identify potential drug candidates to prevent infection. As cited by Liu and Wang , 2019, proteases represent key targets for the inhibition virus replication, and the protein sequences of the SARS-CoV M^{pro}/$3CL^{pro}$ and the 2019-nCoV M^{pro}/$3CL^{pro}$ are 96% identical, hence host proteases can be used as potential therapeutic targets.

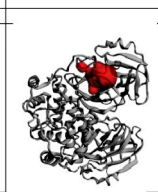
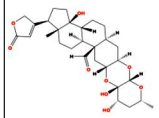
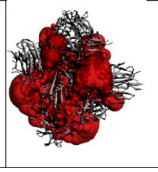
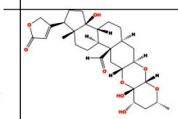
Molecular docking using PatchDock docking tool that was used to find out interaction of inhibitor i.e calotropin with M^{pro}/$3CL^{pro}$ protein revealed 20 different poses based on the highest dock score indicated maximum binding affinity. Docking pose and molecular interactions of calotropin with M^{pro}/$3CL^{pro}$ protein are shown in Fig. 2. Calotropin was successfully docked with M^{pro}/$3CL^{pro}$ protein binding pocket in domains I and II with good scores (Fig. 1, Table 1). The interaction of Calotropin in the binding pocket of M^{pro}/$3CL^{pro}$ was mediated by four hydrophobic interactions via THR23, LEU25 at

atomic distances of 3.79 Å, 3.89 (Fig. 3). Hydrogen bond interaction were observed with GLY141 (1.88 Å), SER142 (327 Å), MET613(312 Å), GLU164 (2.20Å). CAST-P server also revealed the presence of PHE18, LEU139, ASN140, GLY141, SER142, CYS143, PRO166 as active site residues in the major cavity of SARS-CoV-2 M^{pro}/$3CL^{pro}$ protein. With CASTp active site prediction, a major pocket was identified with Area (SA) of 2282 and Volume (SA) of 2292 (Table 2). In M^{pro}, domains I (residues 10-99) and II (100-182) are six-stranded antiparallel β-barrels that harbor the substrate-binding site between them. Domain III (residues 198-303), a globular cluster of five helices, is implicated in regulating dimerization of the M^{pro}, mainly by a salt-bridge interaction between both protomers [Lu, 2019]. SARS-CoV-2 M^{pro} forms tight dimer with contact interface, chiefly between domain II of protomer A and the N-finger (NH2-terminal residues) of protomer B, with the two molecules oriented perpendicular to one another (Fig. 2). Dimerization is essential for M^{pro}/$3CL^{pro}$ enzyme catalytic activity, because the N-finger of each of the two protomers interacts and shapes the S1 pocket of the substrate-binding site. To attain this interaction site, the N-finger is squeezed in between domains II and III of the parent monomer and domain II of the other monomer. Further, calotropin was also docked to 'S' protein of SARS-CoV-2. Enveloped viruses get enter into their respective host cells through membrane fusion process that is facilitated via a precise fusion, or "S" protein (virus encoded), and embedded in the envelope of the virus [Millet et al., 2012]. Such proteins are presently clustered into three diverse structural classes, with the so called class I fusion proteins usually primed for fusion activation through proteolytic cleavage. It is the S-protein present in the CoV related with the Severe Acute Respiratory Syndrome (SARS), which could be gain access to in PDB and was proposed to be a possible drug target for 2019-nCov [Song et al., 2018]. In several viruses, S-protein play crucial roles in entry of virus into host cells; therefore, S-proteins are frequently used as protein targets throughout the development of antiviral therapeutics. The coronavirus spike proteins (S) play an important role in the initial steps of viral infection, with the S1 domain responsible for receptors binding and the S2 domain region (aa570–aa1278),facilitating membrane fusion. As cited by earlier, S-proteins signify key targets for the inhibition of viral replication, and the protein sequences of the SARS-CoV S-protein and the 2019-nCoV S-protein are 91% identical, hence host proteases could be exploited as probable therapeutic targets [Joshi, et al., 2020].

Table 1. Binding Energy and full fitness values of Docked complex and interaction values

Target	Dock pose	Dock score	Interacting residues (4 A°)	
			H-bond interactions	Hydrophobic interactions
M^{pro}	1	5648	GLY141, SER142, MET613, GLU164	THR23, LEU25
Spike	1	6664	PHE377, ASP405, ARG408,408	TYR369, ALA272, GLU406, LYS417,417

Table 2: Protein target structure, native ligand and active site amino acids

Pdb id	Macromolecule	Native ligand	Interacting Active site residues	Cavity	
				Area	Volume
1UK3			PHE18,LEU139,ASN140, GLY141,SER142,CYS143, PRO166	2082	2292
6VVX			PHE377, ASP405, ARG408,466, TYR369, GLU406, LYS417,462	38354	70195

Molecular docking using patchDock docking tool that was used to find out interactions of inhibitor calotropin with S-protein revealed 19 diverse poses based on the dock score and area with maximum score values showed maximum binding affinity. Docking pose and molecular interactions of calotropin are shown in Figure 4. Calotropin was successfully docked with S-protein binding pocket in S2 domains (Figure 4, Table 1). S-protein includes 2 functional subunits accountable for binding to the host cell receptor (S1 unit) and fusion of the viral and cellular membrane (S2) subunit [Song et al., 2018].The interaction of calotropin in the binding pocket of S2-protein domain was mediated by hydrophobic interactions via TYR369, ALA372, GLU406 and LYS417 at atomic distances

of 3.70 Å, 3.92 Å, 3.80 Å and 3.99 Å, respectively (Fig. 3 B). In addition, hydrogen bond interactions were observed via PHE377, ASP405, ARG408 at atomic distances of 3.59 Å, 3.30 Å and 3.36 Å, respectively. CAST-P server also revealed the presence of PHE377, ASP405, ARG408,466, TYR369, GLU406, LYS417,462 as active site residues in the major cavity of SARS-CoV-2 S protein. With CASTp active site prediction, a major pocket was identified with Area (SA) of 38354 and

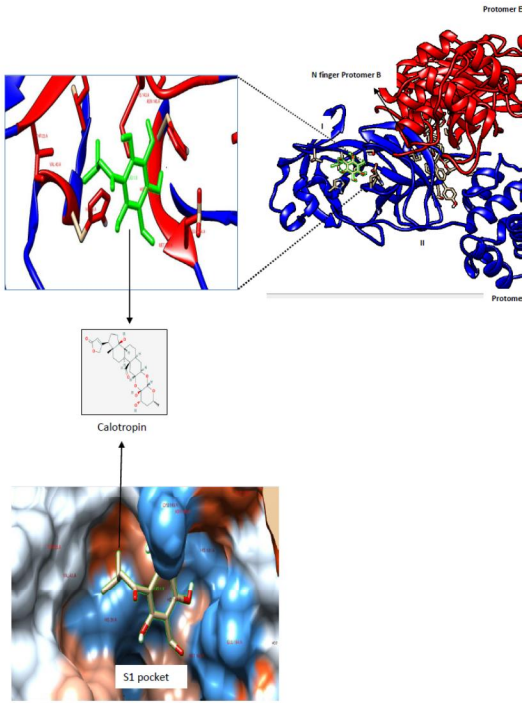


Fig 2: Three-dimensional docked structure of SARS-CoV-2 M^{pro} with Calotropin. One protomer of the dimer is shown in light blue, the other one in red. Domains are labeled by Roman numbers

Volume (SA) of 70195 (Table 2). The calotropin showed full fitness within active site amino acids of S2 domain of S-protein of COVID-19. Coronavirus trafficking into and take over the host cell machinery is predominantly driven by means of the C-terminal S2 domain of spike glycoprotein that interacts with numerous proteins of host cell [ul Qamar et al., 2020, Ashour et al., 2020] It was postulated that COVID-19 S-protein becomes closed upon binding with calotropin which in turn brings conformational changes of the S-protein and stop initiation of the fusion reaction responsible for its insertion into the host cell membrane. We investigated that calotropin as probable inhibitor of the COVID19 S-protein. Further, comparative docking score indicated that Spike protein showed more interaction than M^{pro} protein. It is quite expected as more number of hydrophobic interactions was observed with Spike protein than M^{pro} protein. That why docking score was higher with spike (6664) than M^{pro} protein (5648).

Pharmacokinetic analysis using ADMET properties was studied. Calotropin scanning results are illustrated in Fig 5. Topological polar surface area (TPSA) value was 131°A squared. It indicated good permeability of calotropin cell membranes to enter Blood Brain Barrier (BBB). Pharmacokinetics

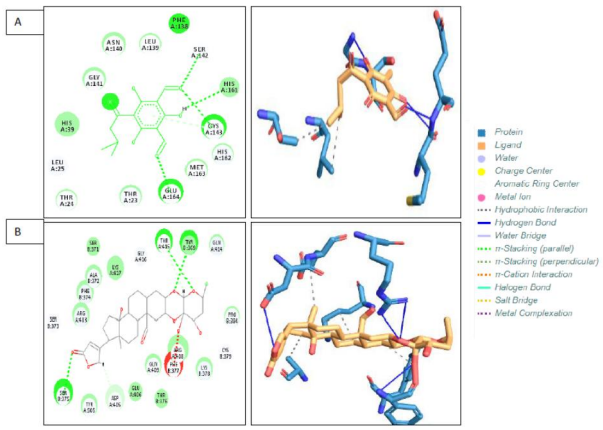


Fig 3: 3D and 2D interactions of calotropin with M^{pro} protein (A) and Spike protein (B)

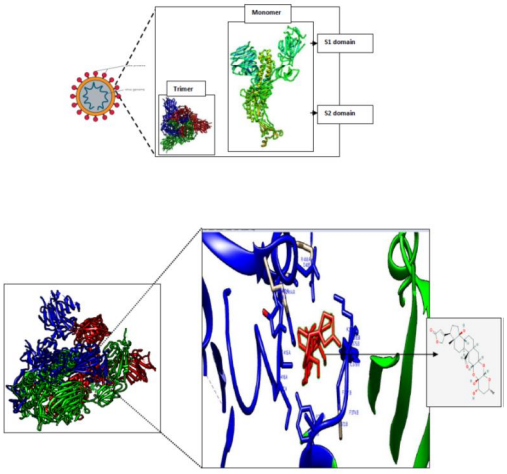


Fig 4: Three-dimensional docked structure of SARS-CoV-2 S-protein with calotropin. Protomers of the trimer is shown in light blue, green and the other one in red. Domains are labeled by S1and S2 Roman numbers.

parameters and ADMET factors are key parameters for success of mostly drugs during

clinical trials [8]. Log Po/w (lipophilicity indicator, octanol-water partition coefficient) was 1.83, indicating calotropin was optimal BBB penetration.

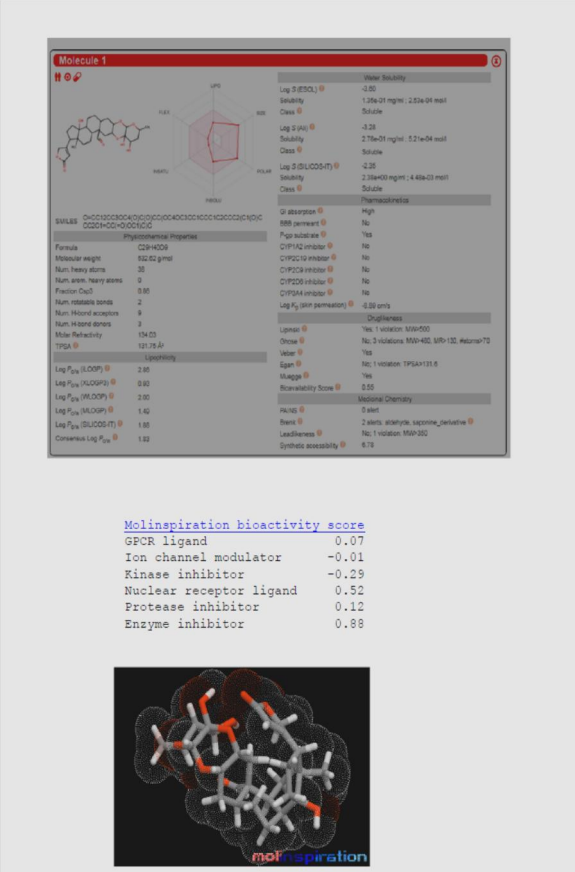


Fig 5: ADMET properties and 3D molecular structures showing Molecular Lipophilicity Potential (MLP)

GI (Gastrointestinal tract absorption) of Calotropin was high (Table 2). In order to exert a toxic effect, drug molecules have to be absorbed from intestinal tract in the body. Further, Calotropin shown non inhibitory activity against cytochrome P series (CYP1-3) of enzymes, involved in liver detoxificatyion of toxins from body. 3D molecular structures showing Molecular Lipophilicity Potential (MLP) and Polar Surface Area (PSA) are also shown in Fig. 5. MLP is convenient property to rationalize numerous molecular ADME characteristics (for example: plasma-protein binding or membrane penetration). Bioactivity of Calotropin as the drug was calculated online by using Molinspiration drug-likeness score. Table 2 depicts Bioactivity score of Calotropin. Ion channel property and kinase inhibitor of Calotropin was high (<0) while enzyme inhibitor and protein inhibitor activities were moderate (>0).

SARS-Cov-2 has emerged as major pandemic worldwide. Present studs revealed molecular docking of calotropin from milk of calotropin plant against COVID-19 M^{pro} and S protein. This study further suggested that calotropin has more potential to act as potential inhibitors of SARS-Cov-2- against S-protein than M^{pro}. However, more *in vivo* and *in vitro* model based studies may pave way these compounds in drug discovery.

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References

[1]Antonio A.D.S., Wiedemann L.S.M., Veiga-Junior V.F. Natural products' role against COVID-19. RSC Adv, 2020, 10, 23379–23393.

[2]Ashour, H.M. et al. Insights into the recent 2019 novel coronavirus (SARSCoV- 2) in light of past human coronavirus outbreaks. Pathogens, 2020, 9, 186

[3]Barcellos M.P., Santos C.B., Federico L.B., Almeida P.F., da Silva C.H.T.P., Taft C.A. Pharmacophore and structure-based drug design, molecular dynamics and admet/tox studies to design novel potential pad4 inhibitors. J Biomol Struct Dyn, 2019,37,966–981.

[4]Fischer A., Sellner M., Neranjan S. et al. Potential inhibitors for novel coronavirus protease identified by virtual screening of 606 million compounds. Int J Mol Sci., 2020, 21, 3626

[5]Gildenhuys S. Expanding our understanding of the role polyprotein conformation plays in the coronavirus life cycle. Biochem J., 2020, 477,1479–1482.

[6]Herbert M. Coronavirus disease 2019 (COVID-19) Research Literatures. Academ Arena, 2020;12,30-64.

[7]Huang C., Wang Y., Li X., et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, 2020, 395,497–506

[8]Islam M.T., Sarkar C., El-Kersh D.M. et al. Natural products and their derivatives against coronavirus: a review of the non-clinical and pre-clinical data. Phyther Res, 2020, https ://doi.org/10.1002/ ptr.6700

[9]Joshi R.S. et al. Discovery of potential multi-target-directed ligands by targeting host-specific SARS-CoV-2 structurally conserved main protease. J. Biomol. Struct. Dyn. .2020, http://dx.doi.org/10.1080/07391102.2020.1760137

[10]Li X., Wang Y., Agostinis P. et al. Is hydroxychloroquine beneficial for COVID-19 patients? Cell Death Dis., 2020, 11,512

[11]Liu X., Wang, X.J. Potential inhibitors against 2019-nCoV coronavirus M protease from clinically 13 of 14 approved medicine. J. Genet. Genomics, 2020, doi: 10.1016/j.jgg.2020.02.001.

[12]Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). Biosci. Trends, 2020, doi:10.5582/bst.01020

[13]Mahanta S., Chowdhury P., Gogoi N. et al. Potential antiviral activity of approved repurposed drug against main protease of SARS-CoV-2: an *in silico* based approach. J Biomol Struct Dyn., 2020, 0,1–10.

[14]Millet J.K., Kien F., Cheung C.Y. et al. Ezrin interacts with the SARS coronavirus spike protein and restrains infection at the entry stage. Plos One. 2012, 7, e49566.

[15]Sharma A.D., Kaur, I. Molecular docking studies on Jensenone from eucalyptus essential oil as a potential inhibitor of COVID 19 corona virus infection. Research and Reviews in Biotechnology and Biosciences, 2020, 1, 59-66

[16]Singh P., Kumari K., Awasthi S.K., Chandra R. Virtual screening and docking studies of synthesised chalcones: potent anti-malarial drug. Int J Drug Dev Res. 2016, 8, 49–56.

[17]Song W.F., Gui M., Wang X., et al. Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. *PLoS Pathog*, 2018, 14, e1007236.

[18]ul Qamar M.T. et al. Structural basis of SARS-CoV-2 3CLpro and anti-COVID- 19 drug discovery from medicinal plants. J. Pharm. Anal., 2020, 10, 313–319

[19]Vora J., Patel S., Sinha S. et al. Structure based virtual screening, 3D-QSAR, molecular dynamics and ADMET studies for selection of natural inhibitors against structural and non-structural targets of Chikungunya. J Biomol Struct Dyn., 2019, 37,3150–3161.

[20]Wang Z., Yang L. Turning the tide: natural products and natural-product-inspired chemicals as potential counters to SARS-CoV-2 Infection. Front Pharmacol, 2020, 11,1013

[21]Zhou, Y. et al. (2015) Protease inhibitors targeting coronavirus and filovirus entry. Antiviral Res. 116, 76–84.

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