



In-Silico Identification of Natural Compounds from Traditional Medicine as Potential Drug Leads against SARS-CoV-2 Through Virtual Screening

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Abstract The novel coronavirus strain SARS-CoV-2 is the virus responsible for the recent global health crisis, as it causes the coronavirus disease-19 (COVID-19) in humans. Due to its high rate of spreading and significant fatality rates, the situation has escalated to a pandemic, which is the cause of immense disruption in daily life. In this study, we have taken a docking-based virtual screening approach to select natural molecules (from plants) with possible therapeutic potential. For this purpose, AUTODOCK Vina-based determination of binding affinity values (blind and active-site oriented) was obtained to short-list molecules with possible inhibitory potential against the main Mpro in SARS-CoV-2 (PDB ID 6Y2F -the monomeric form). The 4 molecules selected were Chebuloside (−8.2; −8.2), Acetoside (−8.0; −8.0), Corilagin (−8.1; −7.7) and Arjunolic Acid (−8.0; −7.6) (blind and active-site oriented docking scores (Kcal/mol) in parenthesis, respectively). Further, a comparative search, with FDA-approved drugs, has shown that Ouabain was comparable to Chebuloside with a similarity score of 0.227. This in silico finding with respect to Ouabain is significant, since this polycyclic glycoside has been shown to treat COVID-19 positive patients with a cardiovascular disease. Hydrocortisone was similar to Arjunolic acid with a score of 0.539. Again, this likeness is

worthy of mention, since hydrocortisone has been used earlier for the treatment of SARS-CoV1 and MERS. However, further experimentation and validation of the results, in suitable biological model systems, are necessary to gain more insight and relevance as well as provide corroborative evidence for our *in-silico* findings.

Keywords COVID-19 · Docking · Drug likeliness screening · Medicinal plant · Bioinformatics

Introduction

Under the electron microscope, the CoVs (RNA viruses with a positive strand) appear to have a crown-like appearance. This molecular feature is attributable to be due to the spike glycoproteins on the viral envelope. The viruses in the *Coronaviridae* family belong to the order *Nidovirales*. Several viruses from this family have been known to cause many enteric, neurological, hepatic and respiratory diseases in diverse species (camels, cats, bats, etc.), while a select few are capable of infecting humans. [1] The current global pandemic, due to significant increases in the occurrence and rapid transmission of the novel coronavirus—SARS-CoV-2, has resulted in infections in over 213 countries. This outbreak has been thought to have originated in Hubei and Wuhan City in China in December of 2019. Due to the high rates of spreading and significant fatality rates, the World Health Organization convened an emergency committee and declared it a global health emergency in January 2020. It was dubbed a pandemic in March 2020, with several countries going into lockdown in an effort to contain its spread [2]. Also, this infection has posed an enormous economic and

Significance statement: The virtual screening performed examines the possibility of using compounds from traditional medicinal plants as possible drug leads for COVID-19.

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psychological burden on the public health maintenance systems globally as well as being a major factor contributing to the decline in productivity levels.

The SARS-CoV-2, referred to as COVID-19, belongs to the genera *Betacoronavirus* (betaCoV), under the subfamily *Orthocoronavirinae*. The CoVs belonging to this genera predominantly manifest as respiratory and extra-respiratory pathogenesis with variable severity. The recent genomic studies have revealed that the SARS-CoV-2 may have evolved from the betaCoV RaTG13 strain present in bats, showing approximately 96% similarity. [3]

SARS-CoV-2 has a diameter of 60–140 nm, and its form is spherical and often pleomorphic. The number of nucleotides and amino acids in the single-stranded RNA genome of this corona virus is 29891 and 9860, respectively [1]. The number of open reading frames (ORFs) in the genome of CoVs is generally around 6–11. The first ORF (ORF1a/b) corresponds to two polyproteins, namely—pp1a and pp1ab, as well as the 16 non-structural proteins (NSPs) and is encoded by about 67% of the viral RNA genome. The rest of the ORFs code for the remaining accessory and structural proteins. The envelope (E), spike (S), membrane (M) and nucleocapsid (N) represent four structural proteins, along with the other accessory proteins [4]. The spike and membrane proteins play a key role in the assembly of the virus during replication, while the accessory proteins are crucial as triggers to initiate and facilitate entry processes.

The role of the main protease in the pathogenesis of SARS-CoV-2 is highly significant. Its function is to proteolytically (enzymatically) cleave pp1a and pp1ab polyproteins, which subsequently makes them functional. Without the occurrence of this important cleavage event, important viral replication-associated proteins like RdRp and nsp13 will not fully function. Along with its essential role in viral replication, the Mpro is highly conserved/expressed selectively in SARS-CoV-2 and lacks any similar structures in humans making it an ideal antiviral drug target [5].

SARS-CoV-2 also dubbed as the Wuhan-Hu-1 coronavirus (WHCV), exhibits marked similarity to the human SARS-CoV (approximately 82%), at the phylogenetic and genomic levels [6]. This aspect indicates its capability of direct human to human transmission, especially due to the high similarity seen in the S-glycoprotein and receptor-binding domain (RBD). Based on the epidemiological investigations, COVID-19 has an incubation period of 1–14 days. However, it is contagious even during the latency period.

With the exponential spreading of SARS-CoV-2, there is an increasing demand for drugs to treat these infections. Compounds from traditional medicinal plants have proved to have antiviral properties in the past. AYUSH (Ayurveda,

Yoga and Naturopathy, Unani, Siddha and Homoeopathy), Government of India, has recommended a formulation made up of ingredients from 15 plants [7]. Since this treatment was based on empirical findings, we decided to screen and identify key bioactive components (possibly major contributors) present in the extracts of the respective medicinal plants in the aforesaid Ayurvedic formulation. Hence, an extensive literature study was performed to obtain compounds from plants and a few other traditional medicinal plants as mentioned in Table S1 [8–25]. We have then used virtual screening as a tool to select plant compounds that can serve as possible leads for the development of anti-SARS-CoV-2 drugs.

Material and Methods

Ligand Selection, Retrieval and Preparation

A detailed literature survey for the identification and listing of active compounds in the plants was conducted (Table S1). The study enabled selection of ligands for docking against the main protease. 175 compounds were selected and their respective chemical structures and Ids were retrieved from PubChem [29]. The ligands were then imported into the OpenBabel suite of PyRx (<http://%28https//pyrx.sourceforge.io/>). Energy minimization, under default parameters, was done for all the ligands. They were further converted to the appropriate docking format using the make ligand option available in PyRx.

Protein Retrieval and Preparation

The monomeric form of the structure of the main Mpro of SARS-CoV-2 with PDB ID 6Y2F [26] was retrieved from RCSB-PDB. The protein was prepared by removing water and nonspecific molecules using the online USCF Chimera tool. The protein molecule was further prepared by energy minimization in USCF Chimera. It was then loaded to PyRx and was prepared for docking using the make macromolecule option in PyRx.

Protein Binding Pocket Identification

Before undertaking docking analysis, CASTp (Computed Atlas of Surface Topography of proteins) [27] was used to identify the major binding pockets in the protein- Mpro. Data obtained thereby were corroborated with published experimental findings to confirm, validate and lend more credence to our *in-silico* approach.

Table 1 Consolidated virtual screening results

Compound name	Pubchem ID	Binding affinity from docking run 1	Binding affinity from docking run 2 (active site oriented)	Drug likeliness score
Chebuloaside II	44,567,150	- 8.2	- 8.2	0.66
Acteoside	5,281,800	- 8	- 8	0.51
Ursolic acid	64,945	- 8	- 7.8	0.66
Luteolin	5,280,445	- 7.8	- 7.8	0.38
Arjunglucoside I	14,658,050	- 8.2	- 7.7	0.63
Corilagin	73,568	- 8.1	- 7.7	0.64
Daucosterol	5,742,590	- 7.9	- 7.7	0.5
Eucalyptin	76,573	- 7.6	- 7.7	- 0.13
Arjunolic acid	73,641	- 8	- 7.6	0.64
Oleanolic acid	10,494	- 8.4	- 7.6	0.37
Arjunetin	21,152,828	- 8.6	- 7.5	0.58
Kaempferol-3-rutinoside	5,318,767	- 7.6	- 7.5	0.9
Coleon U Quinone	9,974,772	- 7.5	- 7.5	- 0.23
Beta-sitosterol	222,284	- 8.1	- 7.4	0.78
Vitexin	5,280,441	- 7.5	- 7.4	0.6
Apigenin	5,280,443	- 7.3	- 7.3	0.39
Horminone	2,751,795	- 7.3	- 7.3	0.04
Cordioside	101,915,817	- 8.2	- 7.2	0.37
Pelargonidin	440,832	- 7.1	- 7.2	- 0.57
24-Ethylcholesta-5,24-dien-3beta-ol	5,283,643	- 7.8	- 7.1	0.96
Ecdysterone	5,459,840	- 7.5	- 7.1	1.37
Dehydrocostus lactone	73,174	- 7.1	- 7.1	- 1.37
Ergosterol Peroxide	5,351,516	- 8.6	- 7.1	- 0.5
Berberine	2353	- 8	- 7	0.77
Stigmasterol	5,280,794	- 7.8	- 7	0.62
TinosporinB	122,206,356	- 8.4	- 6.9	- 0.99
Tinosporinone	42,607,646	- 6.8	- 6.9	- 0.05
Moupinamide	5,280,537	- 6.9	- 6.9	- 0.23
Palmatoside G	184,515	- 7.9	- 6.8	0.12
Constunolide	5,380,858	- 6.8	- 6.8	- 1.82
Rutin	5,280,805	- 7.9	- 6.8	0.91
Ellagic Acid	5,281,855	- 7.3	- 6.8	- 1.11
Betulin	72,326	- 7.8	- 6.7	- 0.13
palmatine	19,009	- 7.5	- 6.7	0.69
Jatrorrhizine	72,323	- 7.4	- 6.7	- 0.47
Tamarixetin	5,281,699	- 7.2	- 6.7	0.29
Tinocordiside	102,504,931	- 6.9	- 6.7	0.49
Sweroside	161,036	- 6.8	- 6.7	0.63
Piperolactam A	3,081,016	- 8.3	- 6.7	- 0.74
Isocolumbin	24,721,165	- 8.4	- 6.5	- 0.52

Virtual Screening

The ligands were virtually screened by docking of each of them with the Mpro in the Autodock Vina (

<http://www3.interscience.wiley.com/journal/122439542/abstract>) suite of PyRx. Two docking runs were undertaken. In the first one, grid dimensions were maximized (X:50.7889,Y:66.6742,55.5860) with centre

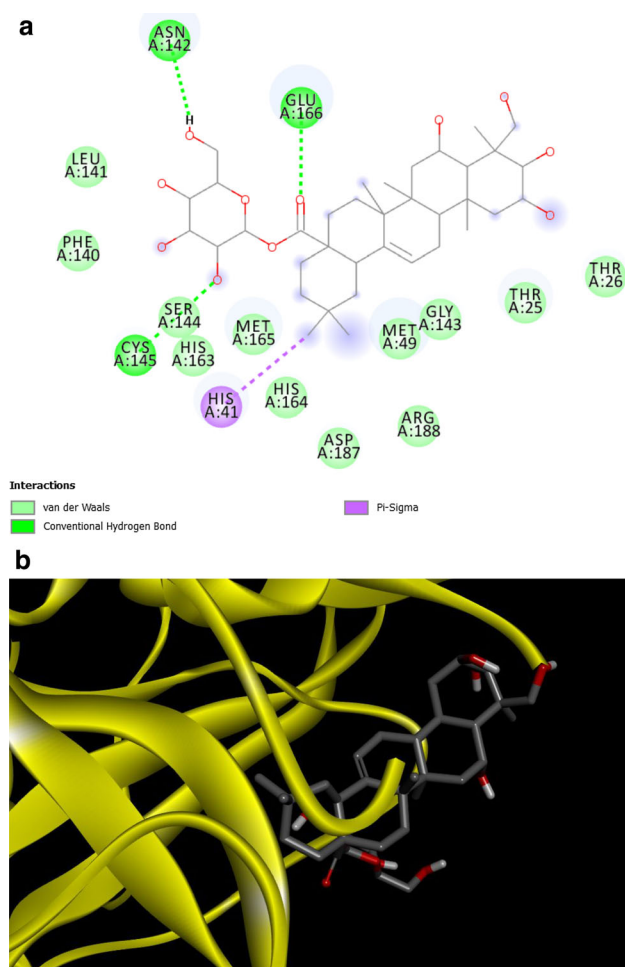


Fig. 1 **a** Interactions between Main Protease and Chebuloside, **b** ribbon format—MPro and chebuloside

(X:4.7290,Y:0.7953,Z:1.0522) such that the ligand was allowed to bind to any part of the protein. For the second docking run, the grid box was minimized (Dimensions—X:25.9265,Y:25.1807,Z:38.0944 and Centre—X:11.20939,Y:8.9589,Z:15.0892) to cover only the active sites of the protein molecule—HIS41, CYS145, GLY143 and SER144 [28]. This “blind-docking” versus “targeted approach” was taken to better obtain a more precise binding affinity value based on active site-based interactions. The exhaustiveness was set at 12 and 8, respectively, for the two runs, and the docking of plant-derived active compounds with the SARS-CoV-2 Mpro was performed.

Drug Likelihood Screening

MolSoft (<https://molsoft.com/mprop/>), an *in-silico* tool, was used to check the drug likelihood score. Molsoft is a tool which calculates the drug likelihood of a compound using parameters such as logP and logS. This was done to

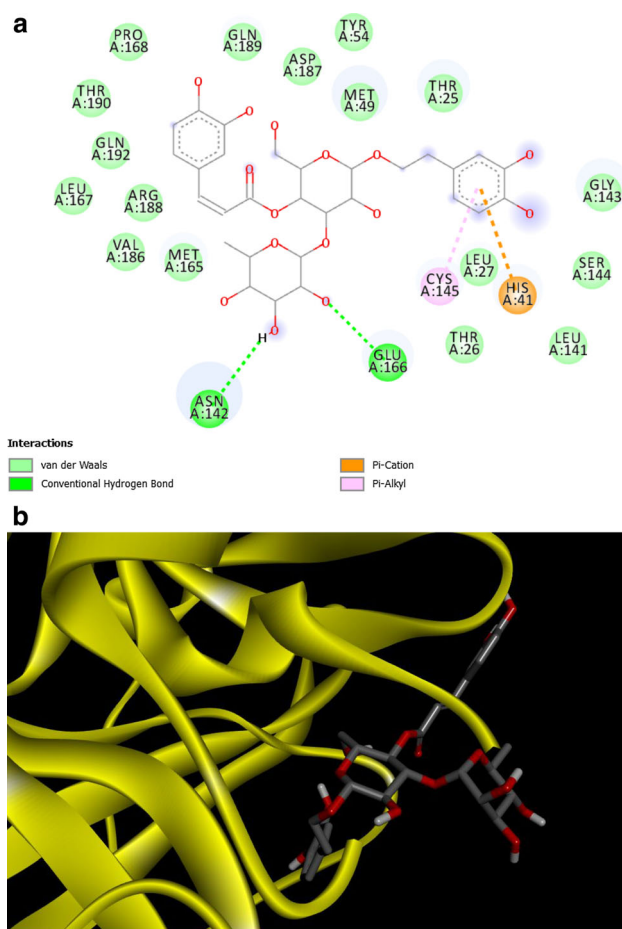


Fig. 2 **a** Interactions between Main Protease and Acetoside, **b** ribbon format—MPro and acetoside

further assess the ability of selected natural compounds to act as drug lead compounds.

Visualization of Ligand-Protein Bonds

The docked complexes of the plant-derived compounds with Mpro were visualized using Discovery Studio 2020 (Dassault Systèmes BIOVIA, [Discovery Studio], [20.1.0.19295], San Diego: Dassault Systèmes, [2020]). The 2D interaction plot of bonds between compound and Mpro active sites was obtained.

Similarity Screening

The compounds with high binding affinities and drug likelihood scores were then checked for to select drugs that have already been approved by FDA using the SWISS similarity tool.

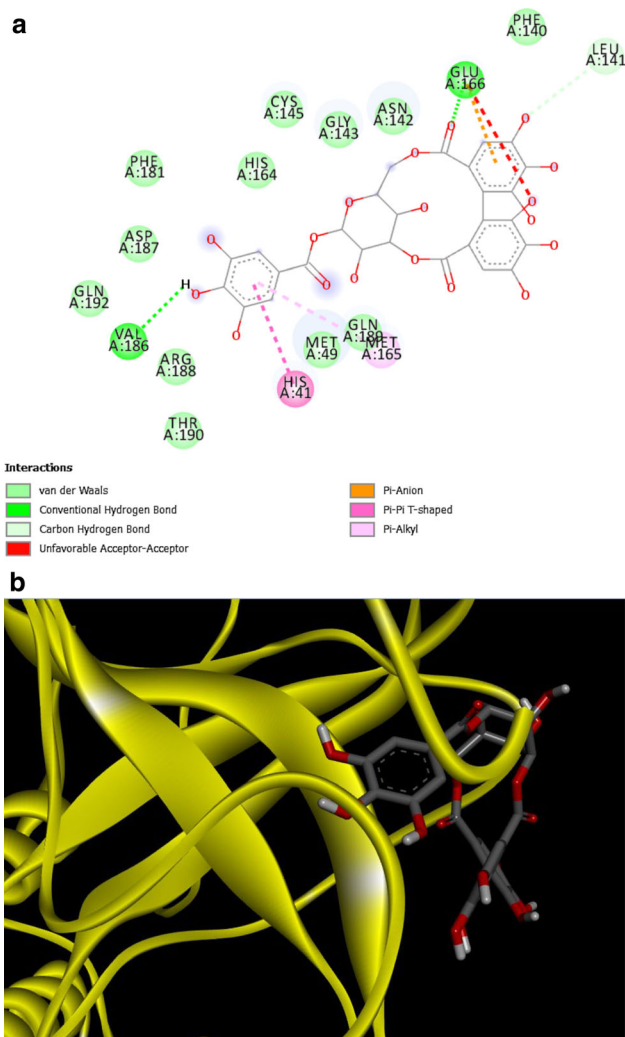


Fig. 3 a Interactions between Main Protease and Corilagin, b ribbon format—MPro and corilagin

Results and Discussion

From the docking run results, the docked pose with best binding affinity was chosen for each ligand. The 30 ligands with the highest binding affinities from docking run 2 (active site-oriented) are summarized in Table 1 and chosen for further analysis. The drug likeliness scores of chosen compounds are also given in Table 1.

Five compounds were then selected based on the highest binding affinities (active site oriented) and their bonds, visualized using Discovery Studio visualizer. The 2D images of bonds between the active sites and the selected compounds, namely Chebuloside, Acetoside, Corilagin, Arjunolic Acid and Beta Sitosterol are provided in Figs. 1, 2, 3, 4 and 5, respectively (depicting receptor-ligand interactions in terms of the chemical bonds as well in the form of a ribbon diagram). Chebuloside has a hydrogen bond with CYS145, ASN142, GLU166, Pi-Sigma bond

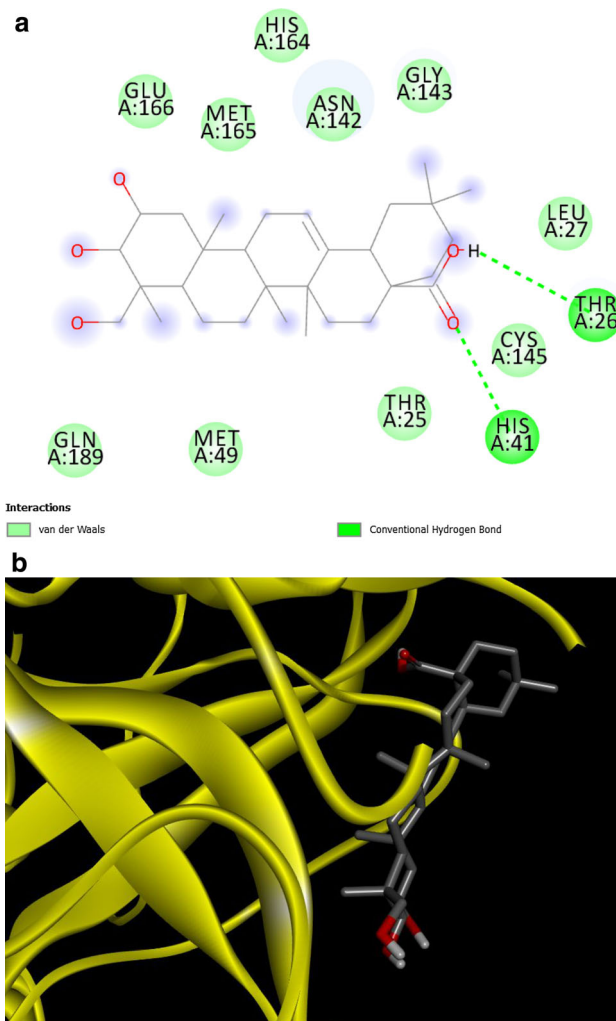


Fig. 4 a Interactions between Protease and Arjunolic Acid, b ribbon format—Mpro and arjunolic acid

with HIS41. Acetoside is connected to CYS145 by Pi-Alkyl and HIS41 by Pi-Cation bonding, GLU166, ASN142 by hydrogen bonding. Corilagin is connected to HIS41 by Pi-Pi T-shaped bonding, to GLU166 and VAL168 by hydrogen bonding, whereas the arjunolic acid has hydrogen bonding with HIS41, THR26. Beta Sitosterol has alkyl binding with CYS145, MET165. Hence, all 5 compounds have bonding with the Mpro active sites HIS41, CYS145. These results are consistent with those reported in other in-silico docking studies, wherein Acetoside [29] and Corilagin [30] have been reported to have good binding affinities with Mpro.

The two main binding pockets were given by CASTp. The first pocket included the Mpro active sites HIS41, CYS145 around which the grid for docking run 2 was built. Based on data available in the literature, binding pocket 2, however, did not contain any active site. It is interesting to note that the results from docking run 1 showed a few

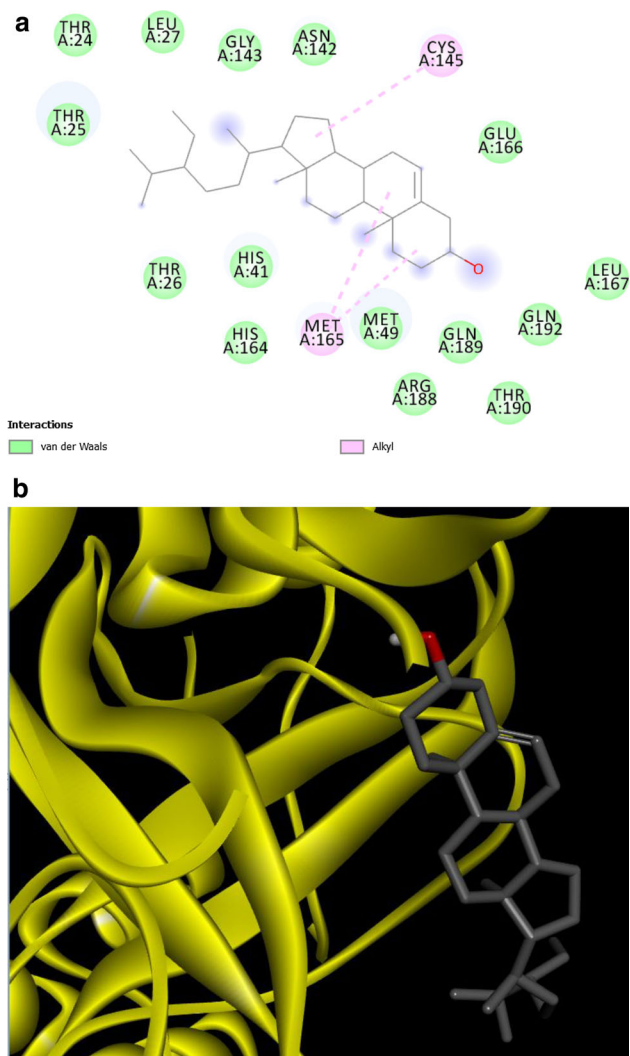


Fig. 5 **a** Interactions between Protease and Beta Sitosterol, **b** ribbon format—MPro and beta sitosterol

compounds namely- Ergosterol Peroxide, Lupeol, Piperolactam A and Corilagin binding with Mpro in the second binding pocket strongly the with high binding affinities—8.5, -8.4, -8.3, -8.1, respectively. Supplementary figure S1 shows bonding between Ergosterol Peroxide and Mpro at ILE200, VAL202, HIS246 (Binding pocket 2). However, due to absence of corroborating experimental data in the existing literature signifying the presence of active sites in binding pocket 2, it is not possible for these results to be considered as significant in the current study. However, conformational-related alterations in binding pocket 1, subsequent to the natural molecule interacting with the Mprotease at binding pocket 2, cannot be ruled out. Hence, our *in-silico* data provides a basis for more experimental work involving the targeting of binding pocket 2 by our natural molecules and evaluating the functional consequences thereafter.

The compounds Chebuloside, Acetoside, Corilagin and Arjunolic acid were chosen to check for similarity with FDA-approved drugs, Beta sitosterol was exempted as it lacked strong bonding with active sites of Mpro. The results of the SWISS similarity tool as lists of FDA-approved drugs similar to Chebuloside and Arjunolic Acid are shown in Tables S2 and S3, respectively. Spinosad and Ouabain were the drugs similar to Chebuloside with similarity scores of 0.269 and 0.227, respectively. In the case of Ouabain, this significant *in silico* finding is consistent with certain reports, wherein Ouabain has been shown to treat COVID-19 positive patients with a cardiovascular disease. Hydrocortisone, Dinoprost Tromethamine was similar to Arjunolic acid with scores 0.539 and 0.523, respectively. Again, this similarity is significant since hydrocortisone has been used earlier for the treatment of SARS-CoV1 and MERS. The tool showed that there are no FDA-approved drugs similar to Acetoside and Corilagin.

Conclusion

This study, involving a preliminary *in silico* screening of known natural compounds from traditional medicine, has revealed that certain compounds such as Chebuloside, Acetoside, Corilagin and Arjunolic acid may serve as possible drug development leads against the SARS-CoV-2. The lists of FDA-approved drugs similar to Chebuloside and Arjunolic acid obtained in this study may help in drug repurposing against SARS-CoV-2, especially in individuals with certain co-morbid conditions. Further validation of our preliminary *in silico* findings with advanced computational tools, supplemented by *in vitro* and *in vivo* experimental data would be pivotal in increasing treatment options and fastening the drug development process against SARS-CoV-2.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40011-021-01292-5>.

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Declarations

Conflict of interest The authors declare they have no conflict of interest.

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