RESEARCH ARTICLE

Molecular docking analysis of selected phytochemicals on two SARS-CoV-2 targets [version 1; peer review: 1 approved, 1 approved with reservations]

Potential lead compounds against two target sites of SARS-CoV-2 obtained from plants

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Abstract

Background: The coronavirus spike (S) glycoprotein and M protease are two key targets that have been identified for vaccines and drug development against COVID-19.

Methods: Virtual screening of some compounds of plant origin that have shown antiviral activities were carried out on the two targets, the M protease (PDB ID 6LU7) and S glycoprotein (PDB ID 6VSB), by docking with PyRx software. The binding affinities were compared with other compounds and drugs already identified as potential ligands for the M protease and S glycoprotein, as well as chloroquine and hydroxychloroquine. The docked compounds with best binding affinities were also filtered for drug likeness using the SwissADME and PROTOX platforms on the basis of physicochemical properties and toxicity, respectively.

Results: The docking results revealed that scopadulcic acid and dammarenicolic acid had the best binding affinity for the S glycoprotein and M^{pro} protein targets, respectively. Silybinin, through molecular docking, also demonstrated good binding affinity for both protein targets making it a potential candidate for further evaluation as repurposed candidate for SARS-CoV-2, with likelihood of having multitarget activity as it showed activities for both targets.

Conclusions: The study proposes that scopadulcic acid and dammarenicolic acid be further evaluated *in vivo* for drug formulation

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Approval Status

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Any reports and responses or comments on the article can be found at the end of the article.

against SARS-COV-2 and possible repurposing of Silybinin for the management of COVID-19.

Keywords

SARS-CoV-2, Molecular docking, COVID-19

This article is included in the **Chemical Information Science** gateway.

This article is included in the **Emerging Diseases and Outbreaks** gateway.

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Introduction

Since 2003, three coronaviruses have been associated with pneumonia, the first was severe acute respiratory syndrome coronavirus (SARS-CoV-1)¹ which affected 8,098 people causing 774 deaths between 2002 and 2003², the second was Middle-East respiratory syndrome coronavirus (MERS-CoV)³ and the third is SARS-CoV-2 which, as at 8th July, 2020, has affected 11,669,259 globally and is responsible for 539,906 deaths. SARS-CoV-2 is a human pathogen which has been declared a global pandemic by the World Health Organization⁴ and is responsible for the Coronavirus disease 2019 (COVID-19) (1). The bats have been identified as the possible reservoir and origin for both the SARS-CoV-2 and SARS-CoV-1³. Unfortunately, there has been no known cure for COVID-19 to date.³

The entry into the host cell by the coronaviruses is usually mediated by the spike (S) glycoprotein³. This glycoprotein interacts with the angiotensin-converting enzyme 2 (ACE2), enabling the virus penetration into the host. The main protease (M protease, also known as 3CL protease) has also been found to be essential for processing of translated polyproteins for the SARS-CoV-2 virus. The two targets, the S glycoprotein, Sgp and M^{Pro} proteins have therefore been considered as important drug targets against the SARS-CoV-2 virus.⁵ For this study, these two drug targets were selected and used to virtually screen some phytochemicals for possible activity against the SARS-CoV-2 virus.

Possibly, potent inhibitors of these two targets will be able to interfere with the SARS-CoV-2 replication process and thus serves as potential drugs for the management of the COVID-19. Hence, this work is aimed at identifying some potential lead compounds of plant origin that can serve as candidates for testing against the SARS-CoV-2 virus.

Methods

Mining of compounds from Pubchem

Plant compounds reported in the literatures that have been demonstrated to have antiviral activities (list of all the compounds analyzed is available as *Extended data*⁶) were selected, alongside also hydroxychloroquine, remdesivir and favipiravir, which have been used in the treatment and management of COVID-19 and mined from the PubChem database.

Protein preparation

Two proteins including crystal structure of the SARS-CoV-2 main protease (PDB ID 6LU7)⁷ in complex with an inhibitor N3 and the S glycoprotein in complex with N-acetyl-D-glucosamine (NAG) (PDB ID 6VSB) were downloaded from the Protein Data Bank (www.rcsb.org). The proteins were prepared by removing water molecules and co-crystallized ligands (highlighting the water molecules and co-crystallized ligands and deleting) on the proteins using Discovery Studio version 2017R2 (19). The UCSF Chimera molecular modeling package is an open access equivalent that could be used to perform the same function⁸.

Molecular docking and visualization

The already prepared protein and ligands were loaded on to the PyRx docking software (PyRx-Python Prescription 0.8), where molecular docking was done in the AutodockVina mode. Visualization to see how the ligands fitted and bound into the binding pockets on the protein and also the interactions between the protein and the ligands was done using Discovery Studio version 2017R2 (19) by first loading the saved PDBqt output file of the target protein from PyRx and then inserting the output of the binding modes of the different ligands and then viewed under the Receptor-Ligand interaction platform of Discovery Studio software.

Physicochemical properties and toxicity prediction of compounds

The Physicochemical properties and drugability of selected compounds were predicted using the free online versions of SwissADME⁹ and Molinspiration¹⁰ platforms and their predicted toxicity profile also compared using the PROTOX toxicity prediction platform¹¹. In each case the ligands were loaded onto the platforms as SMILES structures obtained from PubChem.

Results

Ligands composition and filtering

A library of 22 compounds of plant origin known to have antiviral activity was obtained from the PubChem database (see *Extended data*⁶). Though the compounds are chemically diverse, they consist of largely flavonoids and terpenes. Some compounds from the citrus family were found among the library, though they could not make it among the top six selected compounds that demonstrated good binding affinities for the two targets. Most of the compounds has showed similar binding affinities to the selected protein targets (6LU7 (M protease) and 6VSB (S glycoprotein)) compared to the training sets of known ligands to the selected targets (see *Table 1*).

However, the top six compounds with most favorable binding affinity were selected for each of the targets. The outcomes of the binding affinities of the selected compounds on the 6LU7 and 6VSB targets are presented in *Table 2* and *Table 3*, respectively.

Molecular docking analysis

The binding affinities of the top six compounds (*Table 1*) on the 6VSB target are comparable to each other, i.e. they all lie within a close range of 9 to 9.6 kcal/mol indicating that they might likely have equal or comparable potential as lead compounds for the 6VSB S glycoprotein.

One of the compounds sylibinin¹² is an FDA approved drug, which showed up as active on both M protease and S glycoprotein will make a good candidate of repurposing. Finding Quercetin as a potential inhibitor of the M protease Protein (6LU7) of SARS-CoV-2 corresponds with an earlier report¹³.

Physicochemical screening of ligands

Looking at the octanol–water coefficient (cLogP) of the compounds, there was no correlation observed between the

Table 1. Comparison of Binding affinities of library to some known ligands and the co-crystallized ligand.

Protein target	Co-crystallized ligand	Ligands used in treatment (kcal/mol)	Phytochemicals (kcal/mol)
6LU7		Remdesivir -7.1	Dammarenolic acid -7.2
		Favipiravir -5.3	Quercetin -7.1
		Chloroquine -5.2	Solanidine -7.0
			Silymarin -6.9
			Silvestrol -6.7
			Shikonin -6.6
6VSB		Remdesivir -7.3	Scopadulcic acid -9.6
		Favipiravir -5.3	Baicalin -9.4
		Chloroquine -5.2	Legalon -9.2
			Solanidine -9.1
			Naringenin -9.0
			Oleanane -9.0
			Silymarin -8.6

Table 2. Binding affinities of the compounds on the 6vsb and their Interaction with the binding site.

Serial Number	Ligands	Binding affinity (kcal/Mol)	Hydrogen bond interaction with residues	Hydrophobic bond interaction with residues
1.	Scopadulcic Acid	-9.6	GLN B: 913	TYR C:904, GLY B:1093, VAL B:911, ARG B: 1107, ASN B:907, THR B:912, ASN B:1119, GLN B:1113, GLY B: 910, GLN B:1106, GLU B:1092, PHE A:1121, ARG A:1091
2.	Baicalin	-9.4	ARG B:1039, ARG A:1039, ARG C:1039, ALA B:1020, ASN C:1023	ALA C:1026, LEU B:1024, GLN C:784, SER C:1030, ASP B:1041, LEU C:1024, THR C:1027, PHE B:1042, PHE C:1042, PHE A:1042, THR B:1027, SER B:1021, GLU C:780.
3.	Sylibinin	-9.2	GLU A:954, ARG B:765	GLU A:1017, ARG A:1014, ALA B:766, LYS B:776, LYS A:947, LEU A:948, PRO A:728, VAL A:951, ILE A:1018, ALA B:766, GLN A:957, GLN B:762, GLN A:1010, ILE A:1013, LEU B:1012, ARG B:1019, GLU B:773.
4.	Solanidine	-9.1		TYR A:369, TYR C:489, ARG C:454, PRO C:491, TYR C:421, ASN C:460, LEU C:461
5.	Naringenin	-9.0	GLU C:1092, ARG C:1107, ASN C:1108, GLY C:910, ILE C:909	ASN C:907, THR C:912, GLN C:1113, ARG B:1091, GLU B:1092, GLY C:1093, GLN C:1106, TYR A:904
6.	Oleanane	-9		LEU A:1141, ASP C:1118, LEU C:1141, PRO A:1140, ASP A:1118, THR A:1117, THR B:1116, ASP B:1118, PRO B:1140, GLU B:1144, ASP A:1139, GLU A:1144

lipophilicity and the interaction with the receptors. However, for the compounds acting on 6LU7 (Serial numbers 3, 4, 7, 8, 9 and 10 in Table 4), interaction with the receptor is correlated

with low lipophilicity, with the exception of solanidine and dammarenolic acid, which have high cLogP values, although both compounds also use their polar functional groups in

Table 3. Binding affinities of the compounds on the 6LU7 and their interaction with the binding site.

S/N	Ligands	Binding affinity (kcal/Mol)	Hydrogen bond interaction with residues	Hydrophobic bond interaction with residues
1.	Dammarenolic acid	-7.2	THR A: 111, GLN A: 110, GLN A: 107	VAL A:104, ARG A: 105, ILE A: 106, THR A: 292, PHE A: 112, GLN A: 127, ASP A: 295, ASN A: 152, PHE A: 294, PHE A: 294, PHE A: 8, ASP A: 153, SER A: 158, ILE A: 152
2.	Quercetin	-7.1	-----	-----
3.	Solanidine	-7.0	-----	VAL A: 104, LYS A: 102, SER A: 158, ASP A: 153, ILE A: 152, ASN A: 151, ASN A: 151, PHE A: 8, ARG A: 105, GLN A: 107, ILE A: 106
4.	Silybinin	-6.8	ARG A: 105, ASP A: 176	ASN A: 180, GLU A: 178, PHE A: 103, VAL A: 104, SER A: 158, ASN A: 151, THR A: 111, GLN A: 110, ILE A: 106, GLN A: 107
5.	Loliolide	-6.7	-----	-----
6.	Shikonin	-6.6	THR A: 111, SER A: 158	PHE A: 294, PHE A: 8, GLN A: 110, ILE A: 106, ASN A: 151, PHE A: 112, LYS A: 102, ASP A: 153, VAL A: 104

Table 4. Comparison of the calculated cLogP values for the selected compounds.

S/N	Compound	SwissADME cLog P	Molinspiration cLog p	Mean calculated cLogP
1.	Scopodulcic acid	4.57	5.01	4.79
2.	Baicalin	0.22	0.55	0.39
3.	Sylibinin	1.59	1.47	1.53
4.	Solanidine	5.01	5.93	5.47
5.	Naringenin	1.84	2.12	1.98
6.	Oleanane	8.57	8.86	8.72
7.	Dammarenolic acid	6.74	8.08	7.41
8.	Quercetin	1.23	1.68	1.46
9.	Loliolide	1.53	1.84	1.69
10.	Shikonin	2.08	2.02	2.05

cLogP: octanol-water coefficient.

interacting with the receptor. Baicalin (Figure 1) and naringenin showed good hydrogen bond interaction with the 6VSB receptor due to their polarity.

Drug likeness and predicted toxicity profiles of ligands

Filtering the compounds for drug likeness on the basis of Linpinski's and/or Veber's rule showed that all the compounds have drug-like properties except baicalin, which failed the two filtering scales applied (Table 5). This implies that baicalin is not worth considering further without any structural modification. The predicted toxicity profile of the selected compounds shows (Table 6) that all the compounds are likely to be relatively

safe, which makes them good potential candidates for anti-infectives because the chances of achieving selective toxicity is high. Baicalin is thus most likely the safest.

Discussion

Two compounds among the top six selected for each target, solanidine and sylibinin, were observed to have good binding affinity on both the 6VSB and the 6FLU7 proteins. This makes them potential multitarget acting inhibitors on the SARS-CoV-2. Solanidine is a steroidal glycoalkaloid found in potatoes¹⁴. Although toxic to humans and animals, solanidine has been reported to be effective against herpes viruses (HSV), herpes

Figure 1. Best binding pose and interaction of (A) scopodulcic acid and (B) baicalin on the spike glycoprotein.

Table 5. Drug likeness.

S/N	Compound	Mol. Wt(g/mol)	TPSA	HBA	HBD	RB	cLogP	Lipinski filter	Veber filter
1.	Scopodulcic acid	438.56	80.67	5	1	4	4.79	+	+
2.	Baicalin	446.36	187.12	11	6	4	0.77	-	-
3.	Sylibinin	482.44	155.14	10	5	4	3.06	+	-
4.	Solanidine	397.64	23.47	2	1	0	5.47	+	-
5.	Naringenin	272.25	86.99	5	3	1	1.98	+	+
6.	Oleanane	412.75	0.00	0	0	0	8.72	+	+
7.	Dammarenolic acid	458.72	57.53	3	2	1	7.41	+	+
8.	Quercetin	302.24	131.36	7	5	1	1.46	+	+
9.	Loliolide	196.24	46.53	3	1	0	1.69	+	+
10.	Shikonin	288.3	94.83	5	3	3	2.05	+	+

Mol. Wt.: molecular weight; TPSA: total polar surface area; HBA: number of hydrogen bond acceptors; HBD: number of hydrogen bond donors; RB: number of rotatable bonds; cLogP: mean of calculated logP values.

genitalis and herpes zoster¹⁵. Its activity against HSV is attributed to the presence of a sugar moiety¹⁶. *In silico* drug screening using PROTOX II showed that solanidine is very likely to be cytotoxic and immunotoxic. PROTOX II is a cost- and

time-saving approach for testing and determining the toxicity of a compound to be considered a drug of choice¹⁷. PROTOX II predicts the toxicity outcome of a potential drug of choice, it incorporates machine-learning models which use a combination

Table 6. Predicted toxicity profile of the compounds using PROTOX II.

S/N	Compound	Hepatotoxicity	Immunotoxicity	Carcinogenicity	Mutagenicity	Cytotoxicity	Possible toxicity targets
1.	Scopodulcic acid	-	++	-	-	-	AR, AO, PGS
2.	Baicalin	--	--	+	-	--	AO, PGS
3.	Silybinin	--	++	-	--	--	PGS
4.	Solanidine	--	++	-	--	+	AR, PGS
5.	Naringenin	-	--	-	--	+	AR, PGS
6.	Oleanane	--	--	++	--	--	
7.	Dammarenolic acid	-	-	--	--	--	AR, AO PGS
8.	Quercetin	-	+	--	-	--	AO, AR, PGS
9.	Loliolide	-	+	--	-	--	AO, PGS
10.	Shikonin	-	-	++	-	+	PG

--: inactive; -: less inactive; +: active; ++: more active; AR: androgen receptor; AO: amine oxidase A; PGS: prostaglandin G/H synthase 1.

of fragment propensities, molecular similarity, pharmacophores, to predict toxicity endpoints, such as acute toxicity, cytotoxicity, carcinogenicity, hepatotoxicity, immunotoxicity, mutagenicity and toxicity targets¹⁸

A safe drug must not be toxic to its host target. Based on the PROTOX II evaluation of toxicity, dammarenolic acid emerges as the compound of choice with the least toxicity. Dammarenolic acid has been reported as effective antiviral agents dammarenolic acid potently inhibited the *in vitro* replication of other retroviruses, including simian immunodeficiency virus and murine leukemic virus in vector-based antiviral screening studies and has been proposed as a potential lead compound in the development of anti-retrovirals¹⁸. The compound is cytotoxic and demonstrate potential against respiratory syncytial virus¹⁹. We therefore propose that the evaluation of dammarenolic acid might hold the key to a safe and effective anti-SARS-CoV-2 drug considering its drugability and low toxicity.

This study proposes a potential re-purposing of silybinin for the management of COVID19 diseases. Silybinin (silymarin) possesses antiviral ability against hepatitis C virus (HCV)^{20,21}. It has been reported to have activities against a wide range of viral groups including flaviviruses (HCV and dengue virus), togaviruses (Chikungunya virus and Mayaro virus), influenza virus, human immunodeficiency virus, and hepatitis B virus²⁰. In an *in vivo* and *in vitro* study, Silymarin has been proposed to inhibit HCV entry, RNA synthesis, viral protein expression and prevent infectious virus production; it can also block cell-to-cell spread of the virus²². *In silico* analysis of silybinin in this present study has shown that it can likely inhibit

SARS-CoV-2 S glycoprotein and M^{pro} targets, making it a drug to be considered with a possible multi-target activity against the SARS-CoV-2 virus.

Conclusions

From the 22 phytochemicals that were virtually screened, scopodulcic acid and dammarenolic acid showed the best binding energies with the S glycoprotein and M^{pro}, respectively. This makes them potential lead compounds for development into candidates against the SARS-CoV-2. Furthermore, the FDA-approved drug silybinin (Legalon) had good binding affinity for the two targets, so could be evaluated further for possible repurposing against the SARS-CoV-2 virus.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Extended data

Harvard Dataverse: Replication Data for: Molecular docking analysis of some phytochemicals on two SARS-CoV-2 targets. <https://doi.org/10.7910/DVN/BB0QQK>⁶.

The file within this project contains the compounds obtained from the PubChem database that were analyzed in this study.

Extended data are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

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The current study titled "Molecular docking analysis of selected phytochemicals on two SARS-CoV-2 targets", deals with an important subject. Investigation of promising anti-SARS-CoV-2 agents is a recent universal need. Computational technique can accelerate the drug discovery. Major revisions are needed for this study.

- Update what mention in the first paragraph of introduction section "the third is SARS-CoV-2 which, as at 8th July, 2020, has affected 11,669,259 globally and is responsible for 539,906 deaths".
- Figures exhibiting the best fit docking of all the tested compounds should be inserted in the supplementary file with short comment(s) explaining the interactions (hydrogen bonding, π -interactions, etc.)
- Experimental data for the most successful agents discovered are the perfect support for the hypothesized/computational studies. This point is considered the major revision requested.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Organic, medicinal chemistry with special interest in computational chemistry

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 04 June 2021

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The work by Ubani *et al.*, on molecular docking analysis of phytochemicals on SARS-CoV-2 is well presented. I recommend and endorse the study. However, few points can be improved, they are as follows:

1. In the abstract the abbreviation for M protease can be mentioned, it is mentioned but not corresponding to M protease.
2. Generally, the molecular dynamic simulation is said to be the best indicator/predictor of biological activity. Why this was not performed? or is it not the limitation of the study?
3. Why only 22 compounds from plant origin are selected? How it is shortlisted? What was the rationale? Because there are more than 22 natural plant product having antiviral properties. Why only silybin, why not curcumin, which is also FDA approved. (Mohan *et al.* (2020¹))
4. The ligand protein interaction can be further discussed. In the discussion, at least top five compounds can be discussed.
5. Why not just try the silybin in clinical trial?

References

1. Mohan S, Elhassan Taha MM, Makeen HA, Alhazmi HA, et al.: Bioactive Natural Antivirals: An

Updated Review of the Available Plants and Isolated Molecules. *Molecules*. 2020; **25** (21). [PubMed Abstract](#) | [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pharmacy and Pharmacology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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