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Research Article

COMPUTATIONAL SCREENING AND MOLECULAR DOCKING OF LICHEN SECONDARY METABOLITES AGAINST SEVERE ACUTE RESPIRATORY SYNDROME-COV-2 MAIN PROTEASE AND SPIKE PROTEIN

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ABSTRACT

Objective: At present, the coronavirus disease (COVID)-19 pandemic is increasing global health concerns. This coronavirus outbreak is caused by severe acute respiratory syndrome coronavirus (SARS-CoV)-2. Since, no specific antiviral for treatment against COVID-19, so identification of new therapeutics is an urgent need. The objective of this study is to the analysis of lichen compounds against main protease and spike protein targets of SARS-CoV-2 using *in silico* approach.

Methods: A total of 108 lichen compounds were subjected to ADMET analysis and 14 compounds were selected based on the ADMET properties and Lipinski's rule of five. Molecular docking was performed for screening of selected individual lichen metabolites against the main protease and spike proteins of SARS-CoV-2 by Schrodinger Glide module software.

Results: Among the lead compounds, fallacinol showed the highest binding energy value of −11.83 kcal/mol against spike protein, 4-O-Demethylbarbatic acid exhibited the highest dock score of −11.67 kcal/mol against main protease.

Conclusion: This study finding suggests that lichen substances may be potential inhibitors of SARS-CoV-2.

Keywords: Coronavirus disease-19, Severe acute respiratory syndrome coronavirus-2, Docking, Lichen Compounds, Main protease, Spike protein.

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INTRODUCTION

Coronavirus disease (COVID-19) was emerged from Wuhan city, China, in December 2019 as an epidemic, this disease mainly targets the human respiratory system [1,2]. According to the World Health Organization, 202,608,306 confirmed cases and 4,293,591 deaths were reported globally as of August 9, 2021 [3]. This virus mainly spread through droplets produced from sneezing, coughing, talking, and close contact with the infected person [4,5]. COVID-19 patients are treated using symptomatic therapy due to the unavailability of approved specific drugs [6]. Hence, there is an urgent need to discover drugs for the clinical management of COVID-19.

Severe acute respiratory syndrome coronavirus (SARS-CoV)-2 contains positive-sense single-stranded RNA (+ssRNA) as genetic material and this virus produces nearly 800 KD polypeptides. These polypeptides encode main protease (M^{pro}) and RNA-dependent RNA polymerase (RdRp), spike protein (S protein) other structural proteins [7,8]. Main protease is an essential enzyme for viral replication, involved in cleaving polypeptides and mediating replication and transcription. Hence, main protease (M^{pro}) is one of the key targets to stop viral replication. Spike protein (S protein) is a surface protein that helps for virus attachment with angiotensin-converting enzyme 2 (ACE 2) receptors. Thus, spike (S) protein is considered as one of the main target for COVID-19 therapeutics [9].

Lichens are a symbiotic association of fungi and algae; occur in a variety of habitats and natural environmental conditions. Lichen metabolites were reported to exhibit intense analgesic, antipyretic [10], anti-inflammatory [11], antimicrobial [12], antiviral [13], and cytotoxic activities [14]. The current scenario of molecular docking and computational studies opens new possibilities of drug screening and may assist in the development of COVID-19 treatment [15].

The aim of the present study was made to screening the lichen substances to identifying the potential drug to inhibit SARS-CoV-2 main protease and spike protein by molecular docking method.

METHODS

Accession of target protein

The COVID-19 main protease (M^{pro}) and spike proteins (S protein) were selected as target proteins. The X-ray crystal structure of the above proteins was retrieved from the Protein Data Bank database (PDB ID: 6lu7 and 6M0J) for this virtual screening study [https://www.rcsb.org/pdb/home/home.do].

Ligand selection

A total of 108 lichen metabolites were selected and retrieved that the compounds were from the PubChem database as SDF format and it was subsequently converted into PDB format using Open Babel free software. The retrieved structure energy was minimized and hydrogen atoms were added and charges were assigned using Gasteiger.

ADME prediction

The ADME (Adsorption, Distribution, Metabolism, and Excretion) properties were analyzed for the compounds to test its drug-likeness using QikProp, a Schrodinger module. The ADME properties are important to find the pharmacodynamics of selected molecules that could be used as drug.

Molecular docking

Finally, the 12 lichen compounds which are exhibiting drug-likeness were taken to account for docking studies using the Glide module. The interactions of selected proteins and lichen compounds were observed using PyMOL software [16,17].

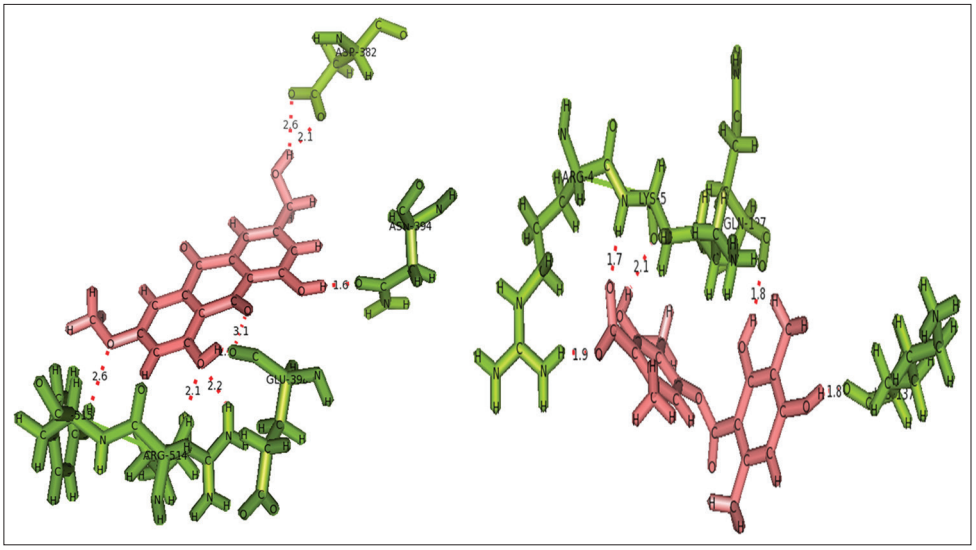

Fig. 1: (a) Interaction of fallacinol with spike protein (6M0J). (b) Interaction of 4-O-Demethylbarbatic acid with main protease (6lu7)

Table 1: Interactions of selected lichen compounds with SARS-CoV-2 target proteins

Ligand (PubChem ID)	G-score (kcal/mol)	Bond length (Å)	No. of hydrogen bonds	Interacting residues
Main protease **(PDB ID: 6lu7)**				
4-O-Demethylbarbatic acid (10450302)	−11.67	1.8	5	LYS-137 (O-H)
		2.1		LYS-5 (O-H)
		1.7		LYS-5 (H-O)
		1.8		GLN-127 (O-H)
		1.9		ARG-4 (H-O)
Emodin (3220)	−11.56	1.8	4	LYS-5 (O-H)
		2.5		LYS- 137 (O-H)
		3.1		GLN-127 (O-O)
		2.1		GLN-127 (H-O)
Diploschistic acid (12309260)	−11.36	1.9	3	GLN-110 (O-H)
		2.3		GLN-110 (O-H)
		1.7		ASP-153 (O-H)
Evernic acid (10829)	−10.73	1.9	4	GLN-110 (O-H)
		1.9		ASP153 (O-H)
		2.1		LYS-102 (H-O)
		2.3		LYS-102 (H-O)
Fallacinol (3083633)	−10.25	1.9	4	LYS-137 (O-H)
		3.1		LYS-5 (O-O)
		2.1		GLN-127 (H-O)
		2.5		ARG-4 (H-O)
Lecanoric acid (99613)	−10.66	1.8	2	ASP-153 (O-H)
		2.1		GLN-110 (O-H)
Olivetolic acid (2826719)	−9.27	1.8	3	LYS-5 (H-O)
		1.9		GLU-288 (O-H)
		1.9		ASP-289 (O-H)
Strepsilin (12443050)	−8.13	2.0	1	LYS-137 (O-H)
Norlichexanthone (5281657)	−8.3	1.9	2	LYS-137 (O-H)
		2.1		LYS-5 (H-O)
Haematommone (11066989	−7.24	2.7	2	LYS-5 (H-O)
		2.1		GLU-290 (O-H)
Pannaric acid (12313948)	−7.11	1.6	4	LYS-5 (H-O)
		2.0		LYS-5 (H-O)
		2.5		LYS-5 (H-O)
		1.6		ARG-4 (H-O)
Citreorosein (361512)	−6.89	2.2	3	LYS-137 (O-H)
		1.7		ASP-289 (O-H)
		1.8		GLU-288 (O-H)
Protocetraric acid (5489486)	−6.65	1.6	2	ASP-289 (O-H)
		1.8		LYS-5 (H-O)
Convirensic acid (101657446)	−6.02	2.5	3	LYS-137 (O-H)
		2.0		ARG-4 (H-O)
		1.9		GLU-288 (O-H)

(Contd...)

Table 1: ***(Continued)***

Ligand (PubChem ID)	G-score (kcal/mol)	Bond length (Å)	No. of hydrogen bonds	Interacting residues
Spike protein **(PDB ID: 6M0J)**				
Fallacinol (3083633)	−11.83	1.6	8	ASN-394 (O-H)
		2.6		ASP-382 (O-H)
		2.1		ASP-382 (O-H)
		2.6		TYR-515 (H-O)
		2.2		ARG-514 (H-O)
		2.1		ARG-514 (H-O)
		1.9		GLU-398 (O-H)
		3.1		GLU-398 (O-O)
Pannaric acid (12313948)	−11.78	3.1	7	HIS- 345 (N-H)
		1.9		TYR -127 (H-O)
		2.8		TYR -127 (H-O)
		2.0		TYR -515 (H-O)
		2.1		ARG-273 (H-O)
		2.1		ARG-273 (H-O)
		1.7		ARG-273 (H-O)
Diploschistic acid (12309260)	−11.74	2.6	7	HIS -505 (H-O)
		1.8		ARG-273 (H-O)
		1.7		ARG-273 (H-O)
		1.9		GLU-402 (O-H)
		2.2		HIS -378 (H-O)
		2.0		GLU-375 (O-H)
		1.8		ALA-348 (H-O)
Lecanoric acid (99613)	−11.58	2.2	5	GLU-375 (O-H)
		2.6		HIS -505 (H-O)
		1.9		ARG-273 (H-O)
		2.1		ARG-273 (H-O)
		2.1		ALA-348 (O-H)
Haematommone (11066989)	−11.37	1.8	5	GLU-398 (O-H)
		1.7		ARG-514 (H-O)
		2.6		ARG-514 (H-O)
		2.1		ALA-348 (O-H)
		2.1		GLU-375 (O-H)
Convirensic acid (101657446)	−10.03	2.0	5	GLU -406 (O-H)
		2.0		GLU -402 (O-H)
		1.7		GLU -402 (O-H)
		2.0		ARG-518 (H-O)
		1.7		ARG-518 (H-O)
Evernic acid (10829)	−10.65	2.1	5	ARG-514 (H-O)
		2.3		ASN-394 (O-H)
		1.7		LYS -562 (H-O)
		2.8		LYS -562 (H-O)
		2.7		GLY-395 (O-H)
Strepsilin (12443050)	−10.57	1.7	6	GLU -398 (O-H)
		2.8		ARG-514 (H-O)
		2.1		ARG-514 (H-O)
		2.2		ARG-514 (H-O)
		2.5		TYR-515 (H-O)
		2.0		ALA-348 (O-H)
Citreorosein (361512)	−10.49	2.0	4	ALA-348 (O-H)
		1.8		GLU -398 (O-H)
		2.0		ARG-514 (H-O)
		2.5		TYR-515 (H-O)
Emodin (3220)		2.2	5	TYR-515 (H-O)
		1.8		ARG-514 (H-O)
		3.0		GLU -398 (O-O)
		2.0		GLU -398 (O-H)
		2.4		ASN-394 (O-H)
4-O-Demethylbarbatic acid (10450302)	−9.98	1.8	6	GLU -395 (O-H)
		2.1		GLU -402 (O-H)
		2.1		ARG-514 (H-O)
		2.1		ARG-514 (H-O)
		1.9		ARG-514 (H-O)
		1.8		GLU -398 (O-H)

(Contd...)

Table 1: ***(Continued)***

Ligand (PubChem ID)	G-score (kcal/mol)	Bond length (Å)	No. of hydrogen bonds	Interacting residues
Norlichexanthone (5281657	−9.65	2.6	6	ASP-382 (O-H)
		1.9		ASP-382 (O-H)
		2.0		GLU-402 (O-H)
		3.2		GLU-402 (O-O)
		1.8		GLU -398 (O-H)
		1.7		ARG-514 (H-O)
Olivetolic acid (2826719)	−8.5	1.7	4	ARG-514 (H-O)
		1.7		ARG-514 (H-O)
		2.2		TYR-515 (H-O)
		2.0		GLU -398 (O-H)
Protocetraric acid (5489486)	−7.6	2.1	4	GLN-442 (H-O)
		2.2		ARG-518 (H-O)
		1.9		GLU-406 (O-H)
		2.7		SER-409 (H-O)

SARS-CoV: Severe acute respiratory syndrome coronavirus

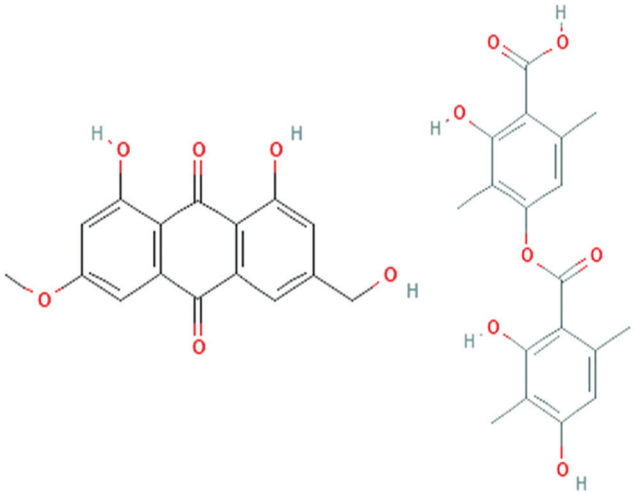

Fig. 2: (a) Chemical structure if fallacinol (b) chemical structure 4-O-Demethylbarbatic acid

RESULTS

Molecular docking studies of lichen secondary metabolites (14 compounds) were carried out with SARS-CoV-2 proteins**.** The interactions of lichen metabolites with main protease and spike protein of SARS-CoV-2 tabulated with G-Score, number of hydrogen bonds, bond length, and the interacting residues (Table 1). The amino acid residues of the proteins (6lu7 and 6M0J) were determined by LIGSITE tool. The residues are Lys-5, Lys-137, Gln-110, Gln-127, Glu-288, Glu-290, Arg-4, Asp-153, Lys-102, Asp-289 and Asn-394, Asp-382, Tyr-127,Tyr-515, Arg-273, Arg-514, Arg-518, Glu-375 Glu-398, Glu-402, Glu-406, His-345, His-378, His-505, Ala-348, Gln-442, and Ser-409. Among the lichen compounds, fallacinol and 4-O-Demethylbarbatic acid exhibited the least G score (−11.83 kcal/mol and −11.67 kcal/mol) against spike protein and main protease respectively with 8 and 5 hydrogen bonds. The residues Asn-394, Asp-382, Tyr-515, Arg-514, and Glu-398 of spike protein and Lys-137, Lys-5, Gln-127, and Arg-4 of the main protease are predicted as active sites and had interactions with above said ligands, respectively. The bond lengths were observed as 2.6, 2.1, 2.6, 2.2, 2.1, 1.9, 3.1 Å and 1.8, 2.1, 1.7, 1.8, 1.9 Å with respect to the above residues of both proteins. The interaction of fallacinol and 4-O-Demethylbarbatic acid with SARS-CoV-2 proteins shown in Fig. 1 and 2D structures of fallacinol and 4-O-Demethylbarbatic acid are shown in Fig. 2.

The compounds emodin and diploschistic acid were also showed significant binding affinity (−11.56 kcal/mol and −11.36 kcal/mol) against the main protease with 4 and 3 hydrogen bonds, respectively. Pannaric acid, diploschistic acid, lecanoric acid, and haematommone have shown good binding affinity of −11.78 kcal/mol, −11.74 kcal/mol, −11.58 kcal/mol, and −11.37 kcal/mol, respectively, with spike protein, each formed 7, 7, 5, and 5 hydrogen bonds. The above compounds have shown ADME properties and drug-likeness was also noteworthy.

Note: Split pea green color represents the amino acid residues of the protein and deep salmon red color indicates the ligands.

DISCUSSION

The *in silico* method such as docking is an effective strategy and widely used method for understanding the molecular aspects of proteins and protein-ligand interactions in the drug discovery process [18]. Identification of effective drugs for treating COVID-19 patients is an urgent need of global pandemic COVID-19. The various discoveries made through computational studies possess significance in regard the discovery of a potential drug, as the success of the derived molecules is obvious. The present study indicates the efficient binding of lichen compounds such as fallacinol and 4-O-Demethylbarbatic acid with the active amino acid residues of the main protease and spike protein of SARS-CoV-2 with the least G-Score.

CONCLUSION

This study finding suggested that the use of naturally occurring lichen substances could serve as efficient therapeutics for the treatment of COVID-19. Through this structural bioinformatics approach, some of the lichen compounds are potential against the protein targets (main protease and spike protein) of SARS-CoV-2.

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AUTHORS' CONTRIBUTIONS

Each author has given considerable and equal contributions to this research.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHORS FUNDING

Not applicable.

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