



RESEARCH ARTICLE

An *in silico* molecular strategy to uncover medication against SARS CoV-2 from coastal grass *Spinifex littoreus* (Burm f.) Merr.

J Vedhamani & I Paul Ajithkumar*

Department of Botany, Bishop Heber College (Autonomous), Affiliated to Bharathidasan University, Tiruchirappalli 620 017, India

*Email: paulajith@bhc.edu.in



ARTICLE HISTORY

Received: 27 September 2024 Accepted: 07 January 2025 Available online Version 1.0: 28 February 2025



Additional information

Peer review: Publisher thanks Sectional Editor and the other anonymous reviewers for their contribution to the peer review of this work.

Reprints & permissions information is available at https://horizonepublishing.com/journals/index.php/PST/open_access_policy

Publisher's Note: Horizon e-Publishing Group remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Indexing: Plant Science Today, published by Horizon e-Publishing Group, is covered by Scopus, Web of Science, BIOSIS Previews, Clarivate Analytics, NAAS, UGC Care, etc See https://horizonepublishing.com/journals/index.php/PST/indexing_abstracting

Copyright: © The Author(s). This is an openaccess article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited (https://creativecommons.org/licenses/ by/4.0/)

CITE THIS ARTICLE

Vedhamani J , Ajithkumar IP. An *in silico* molecular strategy to uncover medication against SARS CoV-2 from coastal grass *Spinifex littoreus* (Burm f.) Merr. Plant Science Today (Early Access). https:/doi.org/10.14719/pst.5315

Abstract

The coronavirus (COVID-19) caused a global public health disaster and every outbreak is believed to have a natural cure. Hence, this investigation aims to identify a suitable target to inhibit viral multiplication using Spinifex littoreus and to control the binding of human ACE2 receptors with the viral protein through molecular docking. This investigation aids in finding a SARS-CoV-2 antagonist in the coastal grass S. littoreus. Through GC-MS analysis, 22 different phytochemical compounds were screened from the methanolic and chloroform extracts of S. littoreus. Using Swiss ADME software, the drug-likeness properties of the screened compounds were examined. Of the 22 screened compounds, only seven adhere to Lipinski's rule of five. The compound 1-methylene-2b-hydroxymethyl-3,3-dimethyl-4b -(3-methylbut-2-enyl)-cyclohexane was docked against 3CLPRO and the spike (S) glycoprotein of SARS-CoV-2. The free binding energies of the target proteins are -6.12 kcal/mol and -6.0 kcal/mol, respectively. A stronger ligand -protein interaction results in lower binding energy. These findings could contribute to the development of a new medication for the treatment of SARS-CoV-2.

Keywords

3CL protease; drug-likeness; molecular docking; spike glycoprotein; *Spinifex littoreus*

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreaks and the global COVID-19 pandemic posed significant financial and medical challenges on an international scale (1). To effectively combat SARS-CoV-2, a thorough understanding of its life cycle and interactions with host cells is essential. SARS-CoV-2 is an enveloped virus that possesses single-stranded RNA, positive-sense RNA (+ssRNA) (2). The International Committee on Taxonomy of Viruses has classified it as a β -coronavirus. Coronaviruses have a larger genome than any other RNA virus, ranging from 27 to 32 kb. Recent sequencing predicts the genome size of SARS-CoV-2 to be approximately 29.9 kb (3). The membrane protein (M), spike protein (S) and envelope protein (E) are the three structural proteins associated with the nucleocapsid protein (N), which forms the capsid around the genome. The envelope further encloses the genome (4). The spike glycoprotein (S protein) mediates the entry of the coronavirus into host cells (5). The coronavirus lifecycle depends on the 3chymotrypsin-like cysteine protease (3CLPRO), which is crucial for viral replication and polyprotein processing (6).

VEDHAMANI & AJITHKUMAR 2

Therefore, this study aims to identify the most effective inhibitory component against the spike glycoprotein and 3CL protease of SARS-CoV-2 among phytoconstituents found in plants. Researchers continue to be intrigued by plants due to their complex chemical composition and diverse therapeutic applications (7). In this study, we selected the phytoconstituents of the coastal grass of *S. littoreus* (Burm f.) Merr. for molecular docking against the SARS-CoV-2 spike glycoprotein and 3CL protease.

The grass S. littoreus thrives in extremely harsh climatic conditions. To withstand ecological stress, the plant undergoes various morphological and physiological adaptations, such as leaf tissue succulence and solute accumulation, to grow, survive and colonize sand dunes (8). This leads the plants to produce specific secondary metabolites to carry out physiological activities. The ethnomedical history of *S. littoreus* indicates that root extract has been traditionally administered orally to treat digestive disorders in Purba Medinipur district of West Bengal, India (9). A root decoction is also used to treat joint and muscle pain (10). Further, the therapeutical potential of this plant has been studied to understand its antimicrobial, antioxidant, anti-inflammatory analgesic properties (11-13). In this study, we aimed to identify the best ligand candidate for targeting the SARS-CoV-2 spike glycoprotein and 3CL main protease through the in silico molecular docking approach.

Materials and Methods

Drug-like characteristics and pharmacokinetic studies

Swiss ADME software was used to analyze the physicochemical and pharmacokinetic properties of 1-methylene-2b-hydroxymethyl-3, 3-dimethyl-4b-(3methylbut -2-enyl)-cyclohexane. It is a free web tool that analyses chemical compounds based on their SMILES notations (http://www.swissadme.ch) (14).

Molecular docking study

Preparation of ligand: According to the GC-MS results of S. littoreus, the phytocompound 1-methylene-2b, hydroxymethyl-3, dimethyl-4b,(3-methylbut-2-enyl)cyclohexane (PubChem CID: 550196), the optimized 3D ligand molecule (Fig. 1), was downloaded in PDB format from https://pubchem.ncbi.nlm.nih.gov. The number of rotatable bonds in the 1-methylene-2b-hydroxymethyl-3,3 -dimethyl-4b-(3-methylbut-2-enyl)-cyclohexane molecule is four. The AutoDock MGL program was used to process the downloaded PDB file which was then saved in PDBQT format. With the aid of AutoDock Vina, this file was subsequently used for docking (15).

Target protein preparation: The chosen target proteins were spike glycoprotein (PDB ID:6VXX) and stable SARS-CoV-2 3CLPRO (PDB ID: 7JVZ), which were isolated using the X-ray diffraction method. Each protein contained a single chain (A) with a resolution of 2.5 Å. The receptor structure of the spike glycoprotein is in a closed state, which limits its ability to bind to ligands (16). The goal of the current research is to determine whether the selected

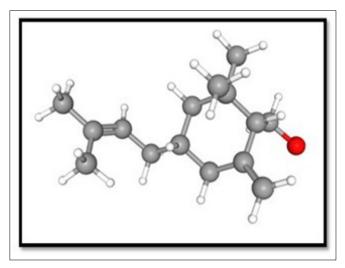


Fig. 1. 3D structure of 1-methylene-2b-hydroxymethyl-3,3-dimethyl-4b-(3-methylbut-2-enyl)-cyclohexane.

ligand can bind to the 6VXX spike glycoprotein. The PDB format files for the chosen target proteins were retrieved from the RCSB Protein Data Bank. The 3D structures of 3CLPRO (PDB ID: 7JVZ) and spike glycoprotein (6VXX) are shown in (Fig. 2, 3). The target proteins were optimized by removing water molecules and heteroatoms. The optimized human stable SARS CoV-2 3CLPRO and spike glycoprotein, each containing a single chain (A), were subjected to the molecular docking studies (2).

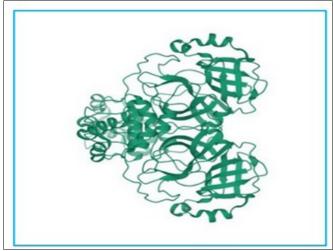


Fig. 2. SARS CoV-2 3CL protease (PDB ID: 7JVZ).

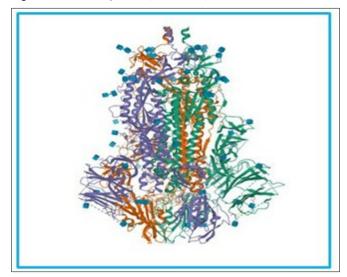


Fig. 3. SARS CoV-2 spike glycoprotein (6VXX).

Computation of docking: The optimized ligand molecule 1-methylene-2b-hydroxymethyl-3,3-dimethyl-4b- (3-methylbut -2-enyl)-cyclohexane was docked with the SARS-CoV-2 3CLPRO (PDB ID: 7JVZ) and spike glycoprotein (PDB ID: 6VXX) using AutoDock 4.2.6 software (16). Dynamic docking was carried out using PDB-formatted versions of the chosen ligands, rigid macromolecules and flexible residues. To perform molecular docking analysis, a Lamarckian genetic algorithm (LGA) with a maximum of 2.5 million energy evaluations was used. Using the AutoDock 4.2.6 tool, the binding energy for the docked complex's topmost conformation was predicted. The primary conformation of the docked complex was comprehended using BIOVIA Discovery Studio (17).

Results

Computation of drug-likeness

Together with toxicity and therapeutic efficacy, many drug development failures are attributed to poor pharmacokinetics and bioavailability (18). The drug-likeness properties of all screened compounds were computed using Swiss ADME. The results obtained from this computation indicate that only seven out of 22 compounds obey Lipinski's rule of 5. Lipinski's Rule of Five includes molecular weight, LogP, number of hydrogen (H†) donors and number of hydrogen (H†)acceptors, which are linked to a drug's bioavailability (19). Among these, LogP is a vital component of Lipinski's Rule of Five, as it indicates the drug-likeness of a

novel synthetic compound. According to Lipinski's Rule of Five, an oral medication must possess a LogP value <5 (20). The following compounds were ranked in order based on their Log P values: Undecanal (3.72), 1-octonal,2-butyl (3.72), 1-methylene-2b-hydroxymethyl-3, 3-dimethyl-4b (3methylbut -2-enyl)-cyclohexane (3.94), phenol, 2, 4-bis(1,1-dimethyl) (3.99), 5-ethyl-1-nonane (4.17), alpha-bisabolol (4.23) and 2-methyl-3-(3-methyl-but-2-enyl)-2-(4-methyl-pent-3-enyl)-oxetan (4.49). The pharmacokinetic and bioavailability scores of all the screened phytocompounds were calculated and provided in Table 1.

Molecular docking

The computational docking of the active region of 3CLPRO main protease and spike glycoprotein with 1-methylene-2bhydroxymethyl-3, 3-dimethyl-4b-(3-methylbut-2-enyl)cyclohexane was performed using the AutoDock tool, which providentially generated the binding modes according to their lowest energy state. The active binding of 1-methylene-2bhydroxymethyl-3, 3-dimethyl-4b-(3-methylbut-2-enyl)-cyclohexane with 3CLPROmain protease and spike glycoprotein was pictured in (Fig. 4). The binding energy of the ligand:target complex is -6.12 kcal/mol in 3CLPRO main protease and -6.0 kcal/mole for spike glycoprotein (Fig. 5). Regarding the interaction with amino acids, the spike glycoprotein (PDB ID: 6VXX) forms three conventional hydrogen bonds with the amino acids LYS (A) 1028, ASP (A) 1041 and PHE (A) 1042, at distances of 2.38 Å, 2.51 Å and 2.32 Å, respectively. With ALA (B) 1026 and LEU (A) 1024, it forms a hydrophobic alkyl bond at a distance of 5.09 Å and 3.91 Å, respectively. There are three hydrogen bonds on the aromatic edge side, along with

 $\textbf{Table 1.} \ \textbf{Swiss ADME} \ \textbf{studies of phytochemicals of} \ \textit{Spinifex littoreus}$

S. No.	Nam of the compound Physicochemical properties							Phar	Bioavailability score		
		MW	Log P	HBD	НВА	Rotatable bonds	TPSA	GI absorption	BBB permeation	Skin permeation (log Kp (cm/s))	
1	Phenol,2,4-bis(1,1-dimethyl)	206.32	3.99*	1	1	2	20.23	High	Yes	-4.07	0.55
2	3-tetradecene, (Z)	196.37	5.48	0	0	10	0	Low	No	-2.62	0.55
3	3-octadecene, (E)	252.48	7.04	0	0	14	0	Low	No	-1.43	0.55
4	N-Hexadecanoic acid	256.42	5.55	1	2	14	37.3	High	Yes	-2.77	0.85
5	N-tetracosanol	354.65	8.58	1	1	22	20.23	Low	No	-0.33	0.55
6	1-hexacosanol	382.71	9.36	1	1	24	20.23	Low	No	0.26	0.55
7	1-octonal,2-butyl	186.33	3.76*	1	1	9	20.23	High	Yes	-4	0.55
8	Hexadecane	226.44	6.49	0	0	13	0	Low	No	-1.8	0.55
9	DI-N-Octyl phthalate	390.56	6.72	0	4	18	52.6	High	No	-2.93	0.55
10	Nonadecane	268.52	7.66	0	0	16	0	Low	No	-0.9	0.55
11	1-Methylene-2b-hydroxymethyl- 3,3-dimethyl-4b-(3-methylbut-2- enyl)-cyclohexa	222.37	3.94*	1	1	3	20.23	High	Yes	-4.78	0.55
12	2-methyl-3-(3-methyl-but-2-enyl)- 2-(4-methyl-pent-3-enyl)-oxetane	222.37	4.49*	0	1	5	9.23	High	Yes	-4.36	0.55
13	Tetracontane,3,5,24-trimethy	605.16	16.59	0	0	37	0	Low	No	6.08	0.17
14	1,2-benzenedicarboxylic acid, butyl octyl ester.	334.45	5.16	0	4	14	52.6	High	Yes	-4.13	0.55
15	Alpha-bisabolol	222.37	4.23*	1	1	4	20.23	High	Yes	-4.97	0.55
16	Hexatriacontan	506.97	14.29	0	0	33	0	Low	No	4.18	0.17
17	1-iodo-2-methylundeca	296.23	5.2	0	0	9	0	Low	No	-3.01	0.55
18	5-ethyl-1-nonan	154.29	4.17*	0	0	7	0	Low	Yes	-3.43	0.55
19	Octadecan	268.48	6.45	0	1	16	17.07	Low	No	-2.16	0.55
20	Pentafluropropionic acid, octadecyl ester	416.51	10.09	0	7	20	26.3	Low	No	-1.32	0.55
21	Hexadecanal	240.42	5.67	0	1	14	17.07	High	No	-2.76	0.55
22	Undecanal	170.29	3.72*	0	1	9	17.07	High	Yes	-4.26	0.55

MW - molecular weight; HBD - hydrogen bond donor; HBA - hydrogen bond acceptor; TPSA - topological polar surface area; GI - aastro-intestinal absorption; BBB - blood brain barrier permeation. *Values indicate acceptable LogP value i.e. <5.

VEDHAMANI & AJITHKUMAR
4

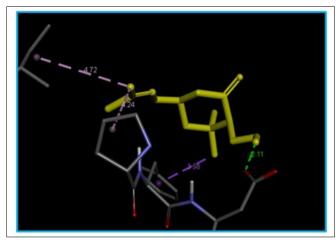


Fig. 4. 3D docking pose of the 1-methylene-2b-hydroxymethyl-3,3-dimethyl-4b-(3-methylbut-2-Enyl)-cyclohexane with SARS CoV-2 3CL protease.

additional bonds between the aromatic edge and face side. Both LYS (A) 1028 and ASP (A) 1041 are in the H-bond acceptor region, while LYS (A) 1028 is in the H-bond donor region. The interpolated charge at the neutral zone is where all hydrogen bonds and hydrophobic alkyl bonds are located. PHE (A) 1024 is in the hydrophobic zone of -1.00, while LYS (A) 1028 is in the hydrophobic region of (-2.00), along with ASP (A) 1041. A hydrophobic alkyl bond exists between LEU (A) 1024 in the hydrophobic 3.00 area and ALA (B) 1026 in the hydrophobic -1.00 region. Between theacidic and basic ionizability zones, there are hydrophobic alkyl and hydrogen bonds. Hydrophobic alkyl bonds formed by LEU (A) 1024 and ALA (B) 1026 are in the 17.5 SAS region, while H-bond interactions involving LYS (A) 1028, PHE (A) 1042 and H-bond ASP (A) 1041 are in the 10.00 SAS region.

The surfaces interaction between spike glycoprotein and 1-methylene-2b-hydroxymethyl-3,3-

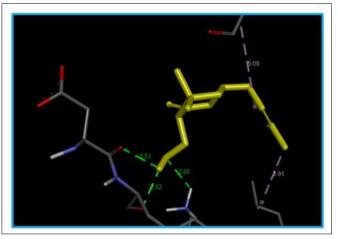


Fig. 5. 3D docking pose of the 1-methylene-2b-hydroxymethyl-3,3-dimethyl-4b-(3-methylbut-2-enyl)-cyclohexane with SARS CoV-2 spike glycoprotein.

dimethyl-4b-(3-methylbut-2-enyl)-cyclohexane (Fig. 6). The 3CL main protease (PDB ID: 7JVZ) with ASP (A) 295 at a distance of 2.11 Å. Additionally, at distances of 4.72 Å and 4.24 Å, it forms a hydrophobic alkyl bond with ILE (A) 249 and PRO (A) 293, respectively. The complex and PHE (A) 294 establish a hydrophobic pi-sigma bond at a distance of 3.98A°. The surfaces interaction of 1-methylene-2bhydroxymethyl—3, 3-dimethyl-4b - (3-methylbut-2-enyl)-cyclohexane and the 3CL main protease Fig.7. The amino acid interactions of spike glycoprotein and 3CL main protease with 1-methylene-2b-hydroxymethyl-3,3-dimethyl-4b-(3methylbut-2-enyl)-cyclohexane (Fig. 8). The aromatic edge side contains ASP (A) 295, ILE (A) 248 and PRO (A) 293, while the aromatic face side includes PHE (A) 294. In the Hbond acceptor region, ASP (A) 295 forms a hydrogen bond. Hydrophobic pi-sigma and alkyl bonds are in the interpolated charge region of (0.000), while ASP (A) 295 I positioned in the interpolated charge region of (-0.033). Other bonds are in the neutral area, while the H-bond (ASP

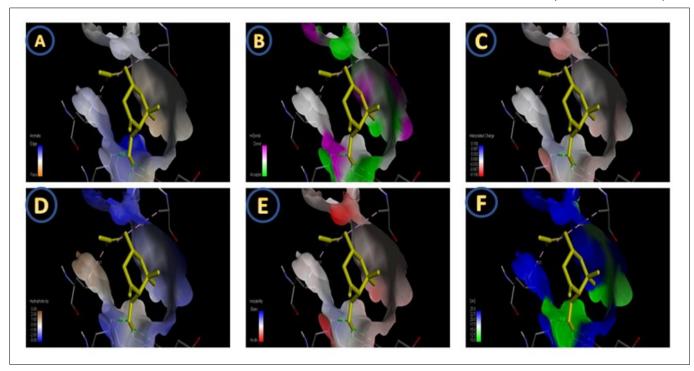


Fig. 6. Surface interactions of spike glycoprotein and 1- methylene -2b- hydroxymethyl -3,3- dimethyl -4b- (3-methylbut-2-enyl) -cyclohexane: A – Aromatic ring of target protein with ligand; B - H-bond donor and acceptor region around target protein and ligand; C - Interpolated charge region around target protein and ligand; D - Hydrophobicity region around target protein and ligand; E - Ionizability region around target protein and ligand; F – Solvent accessibility surface region around target protein and ligand.

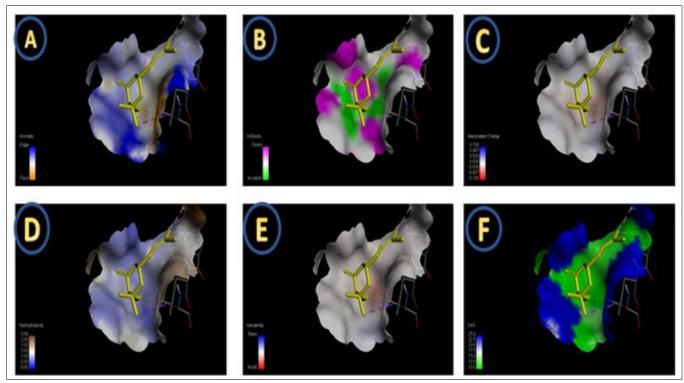


Fig. 7. Surface interactions of 3CL main protease and 1- methylene -2b- hydroxymethyl -3,3- dimethyl -4b- (3-methylbut-2-enyl) -cyclohexane: A - Aromatic ring of target protein with ligand; B - H-bond donor and acceptor region around target protein and ligand; C-Interpolated charge region around target protein and ligand; D - Hydrophobicity region around target protein and ligand; E - Ionizability region around target protein and ligand; F - Solvent accessibility surface region around target protein and ligand.

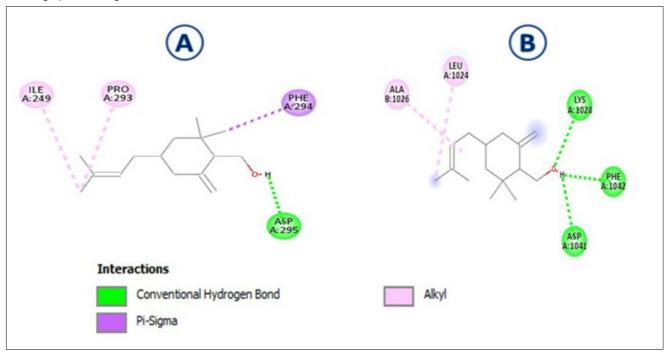


Fig. 8. 2D representation describing the amino acid interactions of 1- methylene -2b- hydroxymethyl -3,3- dimethyl -4b- (3-methylbut-2-enyl) -cyclohexane with the active site of (A) 3CL main protease and (B) spike glycoprotein.

(A) 295) I is in the hydrophobic region of (-2.00) and the hydrophobic alkyl bond with ILE (A) 249 is in the region of (3.00). Other bonds are in the Ionizability neutral charge while the hydrogen bond (ASP (A) 295) is in the Ionizability acidic zone. H-bond (ASP (A) 295) and other bonds are both located in the SAS region, with values of 10.00 and 25.00, respectively.

Discussion

In late 2019, COVID - 19 became a global concern due to its pandemic nature. Since then, extensive research has been conducted to identify a potential remedy for SARS-CoV-2. Traditional medications systems take a long time to develop new drugs and the process is expensive making it challenging to adapt these drugs for clinical treatment in a timely manner. Additionally, SARS-CoV-2 is highly infectious and genetically variable (21, 22). The advancement of virtual screening offers the benefits of low-cost and efficient-screening and presents a more direct and logical approach

VEDHAMANI & AJITHKUMAR 6

to drug discovery (23, 24). Through these scientific advancements, numerous bioactive compounds have been identified as potential inhibitors of SARS-CoV-2. This current investigation aids in the identification of a potent anticoronaviral compound from a coastal grass S. littoreus. The plant was collected and extracted using both polar (methanol) and non-polar (chloroform) solvents and the phytochemicals were screened through GC-MS, which revealed the presence of secondary metabolites like alkaloids, flavonoids, tannins, terpenoids and saponins. The presence of alkaloids, flavonoids, saponins and phenol in S. littoreus (25). All the screened compounds were further processed with Swiss ADME to determine pharmacokinetic and physicochemical properties. The outcome of this analysis showed only 7 out of 22 screened compounds obeyed the Lipinski's rule of Five. The importance of the ADME studies in evaluating drug-likeness properties in their research on bicyclo (aryl methyl) benzamides (26). According to GC-MS results, both polar and non-polar solvents eluted the compound 1- methylene -2b- hydroxymethyl -3,3- dimethyl -4b- (3-methylbut-2-enyl) cyclohexane as the first hit. Since this compound exhibited favorable pharmacokinetics physicochemical and properties, it was docked against 3CLPRO and the spike glycoprotein of SARS-CoV-2. The in-silico docking of the screened compound with 3CLPRO main protease and spike glycoprotein exhibits good binding affinities i.e., -6.12 kcal/ mol and -6.0 kcal/mol, respectively. Among these two target proteins, 3CLPRO exhibited the strongest binding affinity, with the highest free binding energy score (-6.12 kcal/mol). Methyl linolenate docked with spike glycoprotein (6VXX) and reported a binding affinity of -5.3 kcal/mol (14). Molecular docking for hydroxychloroquine with 3CLPRO (7JVZ) the docking score was -5.80 kcal/mol (27). The 3CLPRO is the main protease of SARS-CoV-2 and plays a pivotal role in binding with the human cellular receptor of ACE-2 (28). Since the compound 1-methylene-2b-hydroxymethyl-3, 3dimethyl-4b-(3-methylbut-2-enyl)-cyclohexane binds with 3CLPRO it could inhibit the host-pathogen binding (29). The amino acid interaction between the ligand and target highlighted the bonding formation at the aromatic face side, H-bond acceptor region and interpolated charge region. These interactions enhance the binding of ligands to the target and inhibit the infection (30).

Conclusion

In this investigation, an *in silico* molecular docking method was employed to develop a potential medication for severe acute respiratory syndrome (SARS) caused by coronavirus. The bioactive compound 1-methylene-2b-hydroxymethyl-3,3-dimethyl-4b-(3methylbut-2-enyl)-cyclohexane of coastal grass *S. littoreus* potential drug-likeness properties and inhibitory effects against SARS-CoV-2 proteins, specifically 3CLPRO and spike glycoprotein. Thus 1-methylene-2b-hydroxymethyl-3,3-dimethyl-4b-3-methylbut-2-enyl) cyclohexane holds as a strong anti-coronavirus agent. However, further investigation into its efficacy against SARS-CoV-2 *in vitro* and *in vivo*, is necessary for potential clinical application and patient safety.

Acknowledgements

The authors sincerely thank VIT-SIF Lab, SAS, Chemistry Division for NMR and GC-MS Analysis, Vellore Institute of Technology, Vellore for providing a GC-MS analysis facility. The authors are grateful to the DST-FIST (DST/FST/College -2024/1613) for providing financial assistance to the Department of Botany, Bishop Heber College. Also, our sincere thanks to Bishop Heber College Management for the support rendered throughout the research.

Authors' contributions

IPA and JV participated in the design of the study. JV carried out all the experiments and drafted the manuscript. IPA supervised all the work and finalized the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interests to declare.

Ethical issues: None

References

- Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol. 2021;19(3):141–54. https:// doi.org/10.1038/s41579-020-00459-7
- Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, et al. The protein data bank. Nucleic Acids Res. 2000;28(1):235–42. https://doi.org/10.1093/nar/28.1.235
- 3. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. Lancet. 2020;395 (10224):565–74. https://doi.org/10.1038/s41579-020-00459-7
- Brian DA, Baric RS. Coronavirus genome structure and replication.
 Curr Top Microbiol Immunol. 2005;287:1–30. https://doi.org/10.1007/3-540-26765-4_1
- Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et.al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003;426(6965):450–54. https:// www.nature.com/articles/nature02145
- Krichel B, Falke S, Hilgenfeld R, Redecke L, Uetrecht C. Processing of the SARS-CoV pp1a/ab nsp7-10 region. Biochem J. 2020;477 (5):1009–19. https://doi.org/10.1042/BCJ20200029
- Phillipson JD. Phytochemistry and medicinal plants. Phytochem. 2001;56(3):237–43. https://doi.org/10.1016/S0031-9422(00)00456-8
- Larcher W. Physiological plant ecology: Ecophysiology and stress physiology of functional groups. (4th Ed), Springer: New York; 2003. https://dx.doi.org/10.1007/978-3-662-05214-3
- Sen UK, Bhakat RK. Ethnobotanical study on sand-dune based medicinal plants and traditional therapies in coastal Purba Medinipur district, West Bengal, India. European J Med Plants. 2018;26(2):1–9. http://dx.doi.org/10.9734/EJMP/2018/46231
- Neamsuvan O, Singdam P, Yingcharoen K, Sengnon N. A survey of medicinal plants in mangrove and beach forests from sating Phra Peninsula, Songkhla Province, Thailand. J Med Plants Res. 2012;6 (12):2421–37. http://www.academicjournals.org/JMPR
- 11. Thirunavukkarasu P, Ramanathan T, Ramkumar L, Balasubramanian T. Antimicrobial effect of a coastal sand dune

- plant of *Spinifex littoreus* (Burm. f.) Merr. Curr Res J Biol. 2010;2 (4):283–85. https://www.researchgate.net/publication/45266735
- Shakila K. Bioactive flavonoids of *Spinifex littoreus* (Burm. f.) Merr-Investigation by ELISA method. J Stress Physiol Biochem. 2020;16 (4):107–12.
- 13. Yogamoorthi A, Priya ES. Anti-inflammatory and analgesic property of methanolic extract of *Spinifex littoreus* (Burm. f.) Merr. J Environ Biol. 2006;27(2):271.
- Idroes GM, Tallei TE, Idroes R, Riza M. The study of *Calotropis gigantea* leaf metabolites from le Brouk geothermal area Lamteuba-Aceh Besar using molecular docking. In: IOP Conf Series: Earth Environ Sci; 2021. 667(1):012072. https://doi.org/10.1088/1755-1315/667/1/012072
- Shanmathi C, Ponmurugan P, Karthik N, Anita M, Ezhilarasu A, Rohini A. *In silico* analysis of various antiviral compounds against spike protein of COVID-19 using docking methods. Int J Engin Res Technol. 2020;9(11):55–60. https://www.researchgate.net/ publication/352977008
- Saki J, Shadnoush F, Arjmand R, Rahim F. *In-silico* identification of the best compound against *Leishmania infantum*: High throughput screening of all FDA approved drugs. Turkiye Parazitol Derg. 2019;43:158–64. http://doi.org/10.4274/tpd.galenos.2019.6290
- Surti M, Patel M, Adnan M, Moin A, Ashraf SA, Siddiqui AJ, et. al. Ilimaquinone (marine sponge metabolite) as a novel inhibitor of SARS-CoV-2 key target proteins in comparison with suggested COVID-19 drugs: Designing, docking and molecular dynamics simulation study. RSC Adv. 2020;10(62):37707–20. https:// doi.org/10.1039/D0RA06379G
- Daina A, Zoete V. A boiled-egg to predict gastrointestinal absorption and brain penetration of small molecules. ChemMedChem. 2016;11(11):1117–21. https://doi.org/10.1002/ cmdc.201600182
- Tice CM. Selecting the right compounds for screening: Does Lipinski's rule of 5 for pharmaceuticals apply to agrochemicals? Pest Manag Sci. 2001;57(1):3–16. https://doi.org/10.1002/1526-4998(200101)57:1%3C3::AID-PS269%3E3.0.CO;2-6
- 20. Mandlik V, Bejugam PR, Singh S. Application of artificial neural networks in modern drug discovery. In: Artificial neural network for drug design, delivery and disposition. Academic Press. 2016; p.123–39. https://doi.org/10.1016/B978-0-12-801559-9.00006-5
- Brüssow H. The novel coronavirus-a snapshot of current knowledge. Microb Biotechnol. 2020;13(3):607–12. https:// doi.org/10.1111/1751-7915.13557

- Prajapati S, Sharma M, Kumar A, Gupta P, GV NK. An update on novel COVID-19 pandemic: A battle between humans and virus. Eur Rev Med Pharmacol Sci. 2020;24(10):5819–29. https://doi.org/10.26355/eurrev_202005_21377
- Bailey D, Brown D. High-throughput chemistry and structure-based design: Survival of the smartest. Drug Discov Today. 2001;6 (2):57–59. https://doi.org/10.1016/s1359-6446(00)01596-8
- Moitessier N, Englebienne P, Lee D, Lawandi J, Corbeil AC. Towards the development of universal, fast and highly accurate docking/scoring methods: A long way to go. Br J Pharmacol. 2008;153(S1):7–26. https://doi.org/10.1038/sj.bjp.0707515
- Chandran M, Vivek P, Kesavan D. Phytochemical screening and anti-bacterial studies in salt marsh plant extracts (Spinifex littoreus (Burm. f) Merr. and Heliotropium curassavicum L.).
 Int J Chemtech Res. 2014;6(9):4307–11. https://www.researchgate.net/publication/301655727
- El Fadili M, Er-Rajy M, Kara M, Assouguem A, Belhassan A, Alotaibi A, et al. QSAR, ADMET *In silico* pharmacokinetics, molecular docking and molecular dynamics studies of novel bicyclo (aryl methyl) benzamides as potent GlyT1 inhibitors for the treatment of schizophrenia. Pharmaceuticals. 2022;15(6):670. https://doi.org/10.3390/ph15060670
- Reyaz S, Tasneem A, Rai GP, Bairagya HR. Investigation of structural analogs of hydroxychloroquine for SARS-CoV-2 main protease (Mpro): A computational drug discovery study. J Mol Graph Model. 2021;109:108021. https://doi.org/10.1016/ j.jmgm.2021.108021
- Thurakkal L, Singh S, Roy R, Kar P, Sadhukhan S, Porel M. An insilico study on selected organosulfur compounds as potential drugs for SARS-CoV-2 infection via binding multiple drug targets. Chem Phys Lett. 2021;763:138193. https://doi.org/10.1016/j.cplett.2020.138193
- Lobo-Galo N, Terrazas-López M, Martinez-Martinez A, Diaz-Sanchez AG. FDA-approved thiol-reacting drugs that potentially bind into the SARS-CoV-2 main protease, essential for viral replication. J Biomol Struct Dyn. 2021;39(9):3419–27. https://doi.org/10.1080/07391102.2020.1764393
- Tran QH, Nguyen QT, Tran TT, Tran TD, Le MT, Trinh DT, et. al. Identification of small molecules as potential inhibitors of interleukin 6: A multi-computational investigation. Mol Divers. 2023;27(5):2315–30. https://doi.org/10.1007/s11030-022-10558-7