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

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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 3-chymotrypsin-like cysteine protease (3CLPRO), which is crucial for viral replication and polyprotein processing (6).

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 and 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

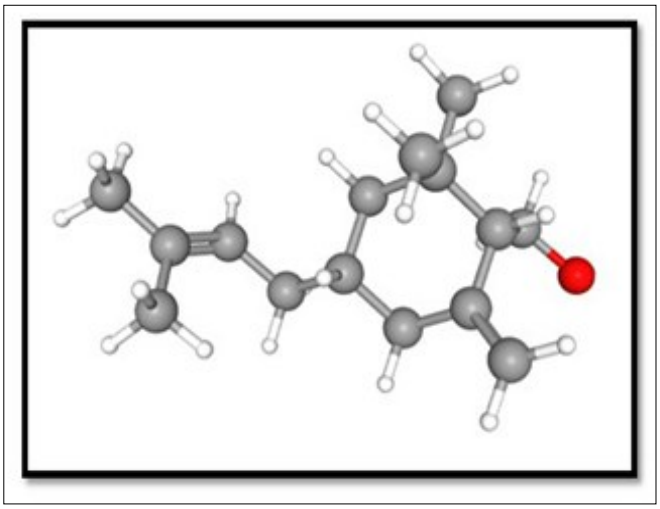

Fig. 1. 3D structure of 1-methylene-2b-hydroxymethyl-3,3-dimethyl-4b-(3-methylbut-2-enyl)-cyclohexane.

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).

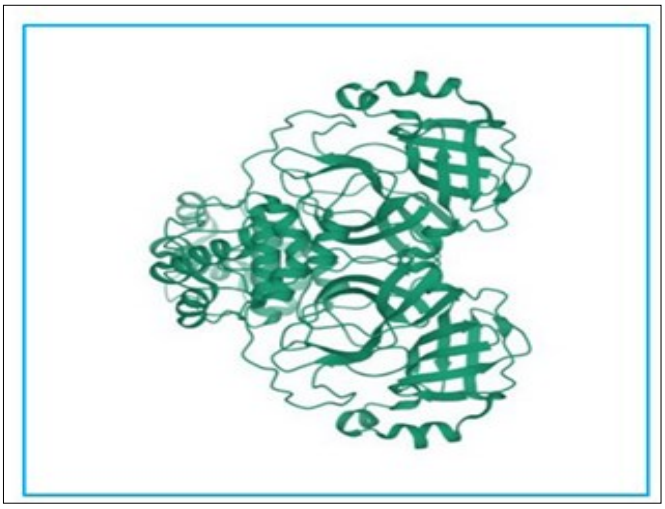

Fig. 2. SARS CoV-2 3CL protease (PDB ID: 7JVZ).

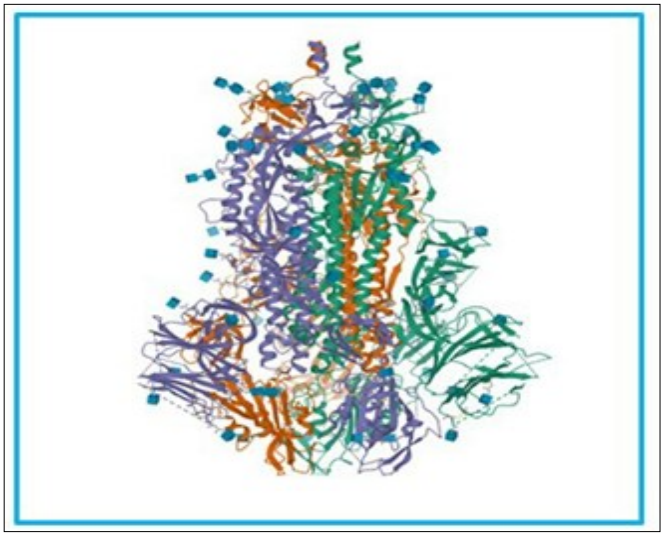

Fig. 3. SARS CoV-2 spike glycoprotein (6VXX).

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-2b-hydroxymethyl-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-2b-hydroxymethyl-3, 3-dimethyl-4b-(3-methylbut-2-enyl)-cyclohexane with 3CLPRO main 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

Table 1. Swiss ADME studies of phytochemicals of *Spinifex littoreus*

S. No.	Nam of the compound	Physicochemical properties						Pharmacokinetic properties			Bioavailability score
		MW	Log P	HBD	HBA	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.

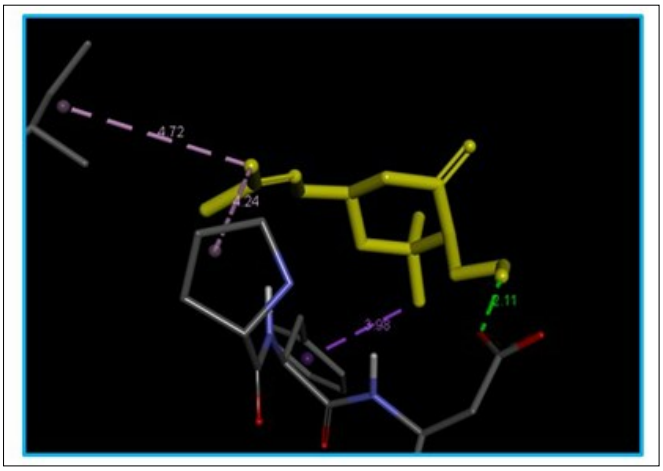

Fig. 4. 3D docking pose of the 1-methylene-2b-hydroxymethyl-3,3-dimethyl-4b-(3-methylbut-2-Enyl)-cyclohexane with SARS CoV-2 3CL protease.

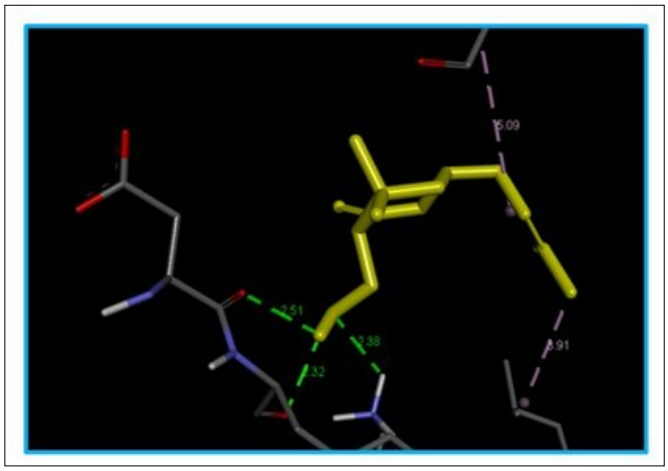

Fig. 5. 3D docking pose of the 1-methylene-2b-hydroxymethyl-3,3-dimethyl-4b-(3-methylbut-2-enyl)-cyclohexane with SARS CoV-2 spike glycoprotein.

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-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-2b-hydroxymethyl—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-(3-methylbut-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 H-bond 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

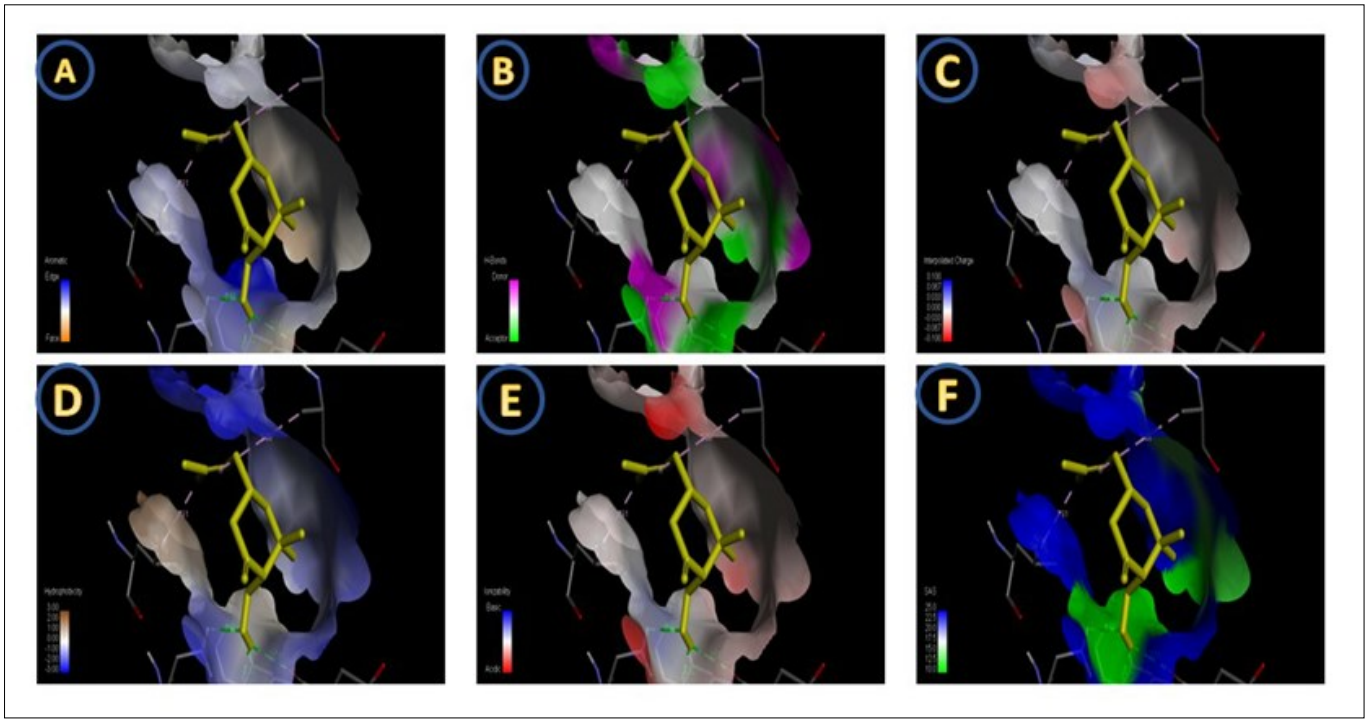

Fig. 6. Surface **i**nteractions of spike glycoprotein and 1- methylene -2b- hydroxymethyl -3,3- dimethyl -4b- (3-methylbut-2-enyl) -cyclohexane: A – Aromatic ring of target protein with ligand; B - H-bond donor and acceptor region around target protein and ligand; C - Interpolated charge region around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

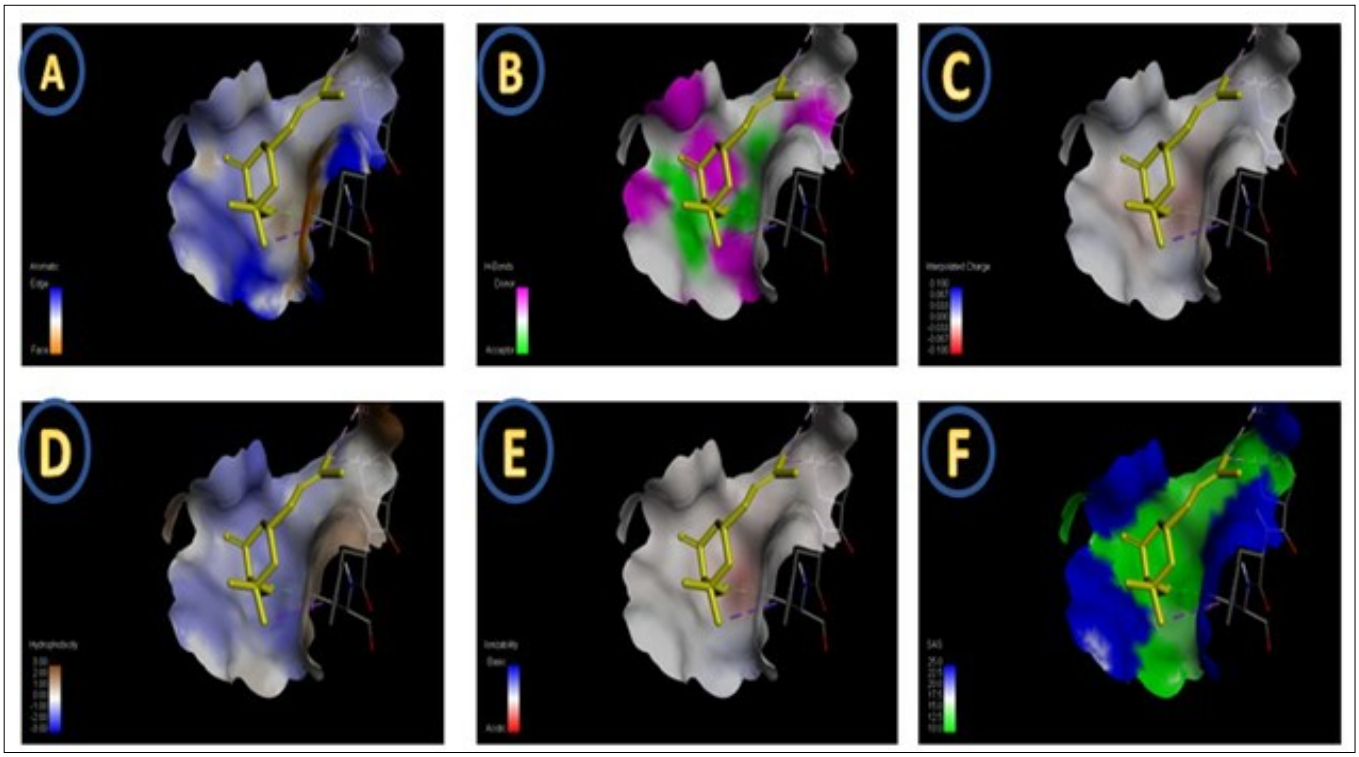

Fig. 7. Surface interactions of 3CL main protease and 1- methylene -2b- hydroxymethyl -3,3- dimethyl -4b- (3-methylbut-2-enyl) -cyclohexane: A - Aromatic ring of target protein with ligand; B - H-bond donor and acceptor region around target protein and ligand; C-Interpolated charge region around target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

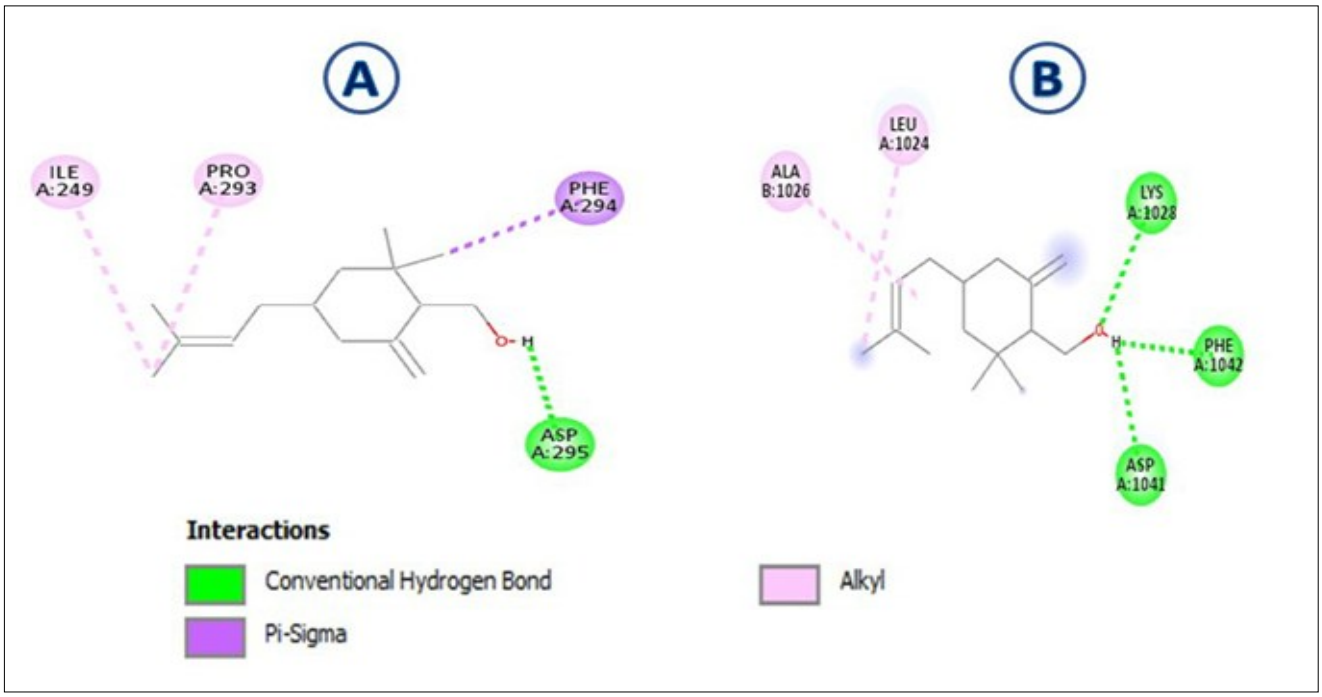

Fig. 8. 2D representation describing the amino acid interactions of 1- methylene -2b- hydroxymethyl -3,3- dimethyl -4b- (3-methylbut-2-enyl) -cyclohexane with the active site of (A) 3CL main protease and (B) spike glycoprotein.

(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

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 anti-coronaviral 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 their 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 and physicochemical properties, it was docked against 3CLPRO and the spike glycoprotein of SARS-CoV-2. The *in-silico* docking of the screened compound with 3CLPROmain 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, 3-dimethyl-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.

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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

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