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Identification of Potent Natural Inhibitor Against Papain-Like Protease of SARS-CoV-2 an in Silico Approach

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ABSTRACT

One of the most complicated tasks the healthcare system has faced in recent years has been the development of a curative treatment to stop the progression of the SARS CoV-2 virus. No consensus has been reached on a medical cure to slow the virus spread. From this point of view, investigating existing drugs such as SARS-CoV-2 inhibitors is an appropriate technique. With critical involvement in viral replication and host-immune suppression, Papain-like protease (PL-pro) is recognized as a key enzyme target for drug development among other SARS-CoV-2 druggable targets. Phytolignans have a wide range of physiological effects, making them an appealing drug for antiviral study. We used an *insilico* method to target SARS CoV-2 PL-pro with phytolignans in our investigation. The chemical structures of phytolignans were obtained from PubChem, whereas the protease structure 6WX4 was obtained from the Protein Data Bank website. The PyRx software was used for molecular docking.Of all the phytolignans examined, Sesamolin has the greatest binding affinity of -8.4 kcal/mol towards PL-pro.The docking results revealed that phytolignans are potent inhibitors of the SARS-CoV-2 papain-like protease and that they may be verified further *in vitro* and *in vivo*. Our findings suggest that Sesamolin might be used as a medication to block the action of SARS CoV-2 PL-pro.

Keywords: SARS-CoV-2; Coronavirus Papain-like proteases; Molecular docking; Sesamolin

NOMENCLATURE

SARS-CoV-2	:	Severe Acute Respiratory Syndrome Coronavirus 2
COVID-19	:	Coronavirus disease
PL-pro	:	Papain-like protease

1. INTRODUCTION

1.1 Background

The WHO declared a public health emergency of worldwide concern in January 2020 after a new viral pneumonic epidemic was initially found in Wuhan, Hubei Province, China, in December 2019. The causal virus was termed Severe Acute Respiratory Syndrome Coronavirus 2(SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV) and became known as Coronavirus disease(COVID-19).[1] Multiple signs of COVID-19 infection exist, ranging from asymptomatic and moderate symptoms to severe sickness and death. Cough, fever, and shortness of breath are common symptoms, as are weakness, malaise, respiratory discomfort, muscular pain, sore throat, and loss of taste and smell.[2] However, the SARS-CoV-2 virus was discovered to be capable of invading the central nervous system, causing multiple neurological indications such as acute cerebral vascular diseases, hypogeusia, encephalitis, acute polyneuropathy, and hyposmia, as well as non-specific symptoms such as migraine, muscle aches, drowsiness, and loss of balance3. Several vaccine development and drug discovery campaigns are currently in study. Understanding the damage caused by the virus and its mechanism of action is of paramount importance so that the treatment of patients suffering from COVID-19 can be constructive.

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1.2 Role of Viral Protease Papain-like Protease (PL-pro)

SARS-CoV-2 is a positive-stranded RNA virus of the Coronaviridae family. The infection cycle involves the translation of the viral polypeptides (pp1a, pp1ab) by protease cleavage, to generate viral proteins and gain functionality. The two viral proteases that were deemed essential for cleavage were main protease and PL-pro. Due to their role in viral replication, the two proteases have been reported to be attractive potential drug targets.[4] As a defensive mechanism against host antiviral immune responses, the PL-pro enzyme is also engaged in cleaving post-translational modifications on host proteins.[5] Hence, PL-pro's significance in viral replication, as well as host immune suppression, makes for a promising molecule target in the identification of

novel inhibitors for the treatment of COVID-19.

1.3 Antiviral Properties of Phytolignans

Recent literature have highlighted the significance and impact of medicinal plants and their phytochemicals against SARS-CoV-2.[6-8] Plant lignans, also known as phytolignans are essentially polyphenolic compounds that are known for their steroid-analogous chemical structure. These bioactive compounds are known for exhibiting various biological properties – anti-inflammatory, anti-oxidant, anti-tumor, and anti-viral activities. They are present in relatively small amounts in a variety of seeds, cruciferous vegetables, cereals and fruits but in high concentrations in sesame and flax seeds.[9] Plant-based antiviral molecules provide an effective and sustainable solution in the treatment of viral infections with minimized side effects.

In the current study, a molecular docking technique is used to find effective inhibitors of the viral SARS-CoV-2 enzyme PL-pro in the designing innovative natural therapeutics to combat COVID-19.

2. METHODOLOGY

2.1 Preparation and Validation of Receptor

The crystal structure of the SARS CoV-2 PL-pro in association with the peptide inhibitor VIR251 (PDB ID: 6WX4) was extracted in PDB file format from RCSB-PDB (https://www.rcsb.org/) with a resolution value of 1.66 Angstroms and R-Value Free, 0.170, and 0.196, respectively.[10] PROCHECK's Ramachandran plot[11] was utilised to validate the receptor. Before performing molecular docking analysis, ligand groups and water molecules were removed, and polar H was added, followed by geometry cleaning with Biovia Discovery Studio Visualizer 2020.[12] To obtain the structure for further study, the protein was energy minimised (E=-8782.053 KJ/mol) using GROMOS96 of Swiss-Pdb Viewer.[13]

2.2 Identification of Receptor Binding Sites

The PL-pro binding location was explored through the literature. The amino acid residues implicated in both catalytic triad and Substrate binding were chosen as Binding site residues for PL-pro[14]. CYS : 111, LEU : 162, MET : 208, TYR : 264, ASN : 267, TYR : 268, GLN : 269, CYS : 270, GLY : 271, HIS : 272, TYR : 273, ASP : 286, and THR : 301 are the active site amino acids that were considered for Molecular docking (Fig. 1).

2.3 Selection of Control Ligand

Metocurine is a non-depolarising competitive neuromuscular blocking drug that is utilized as both a muscle relaxant and an anesthetic agent. It is considered among the top 5 best drug candidates against SARS-CoV-2 PL-pro for management of COVID-19.[15] Apart from this, it has a high binding affinity towards

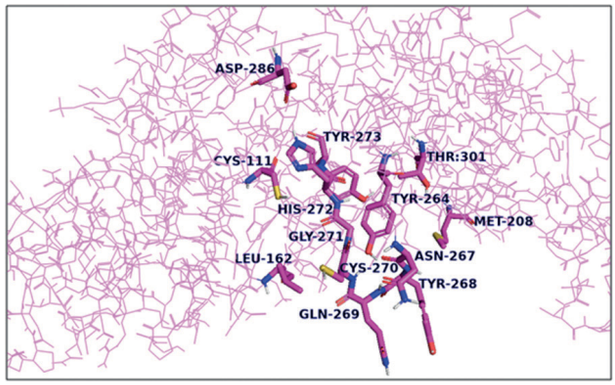

Figure 1. Binding site amino acid residues (in stick form) of PL-pro.

PL-pro with a large number of residues involved in hydrophobic interactions. As a result, in this investigation, we employed Metocurine as a control ligand to assess the ability of Phytolignans against PL-pro. Metocurine's chemical structures were retrieved in 3D-SDF file format from PubChem[16]. Marvin-JS-Online[17] web server was used to validate the structures.

2.4 Retrieval and Construction of Phyto- lignan's Library

The antiviral properties of Phytolignans that have been identified for over a decade now, have not been put to test their potency against the rapidly replicating viral PL- pro. The major Phyto- compounds from the class of Phyto-lignans were collected through a survey of the literature.[18-20] The library of Phytolignans was curated based on their conformity to Lipinski's rule and were eliminated on violation of any rule. The PubChem database was used to obtain the 3-Dimensional structures of phyto- lignans listed in Table 1 along with Control ligand Metocurine. They were geometrically optimised with the help of the Marvin-JS-online server. The ligand cluster, which included one control ligand, was produced using DSV in MDL/SD file format.

2.5 Virtual Screening and Molecular Docking Phytolignan's Against PL-pro

Docking was accomplished with the PyRx 0.8 utility.[21] All of the ligands were reduced with Universal Force Field and then saved in. pdbqt format. The receptor was similarly changed to.pdbqt format. The grid box was centered at x = 10.533, y = -25.328, and z = -41.699, with grid box dimensions in Angstroms of 23.000 X 30.587 X 28.256 and an exhaustiveness value of 8. The most stable receptor-ligand complex is chosen from among the nine output poses based on binding affinity (G) (Kcal-mol), zero RMSD value. Following the conclusion of docking, the ideal conformation of the ligands was recovered using the vina split algorithm.

2.6 Prediction of ADME Features of Plausible Ligands

The ADME qualities of a molecule should be examined

Table 1. List of selected phytolignans with their PubChem ID, molecular weight, hydrogen bond donor, acceptor, TSA and XLOGP3 values

S. No.	Phytolignan	PUBCHEM ID	Molecular Weight (G/MOL)	H Bond Donor	H Bond Acceptor	TSA (Å²)	XLOGP3
1.	Alpha-Peltatin	92129	400.4	2	8	104	2.6
2.	Arctigenin	64981	372.4	1	6	74.2	3.6
3.	Conidendrin	457194	356.4	2	6	85.2	2.8
4.	Cyclolariciresinol	4177125	360.4	4	6	99.4	2
5.	Dimethylmatairesinol	384877	386.4	0	6	63.2	3.9
6.	Diphyllin	100492	380.3	1	7	83.4	3.6
7.	Hinokinin	442879	354.4	0	6	63.2	3.7
8.	Honokiol	72303	266.3	2	2	40.5	5
9.	Isolariciresinol	160521	360.4	4	6	99.4	2
10.	Justicidin A	159982	394.4	0	7	72.4	4
11.	Lariciresinol	332427	360.4	3	6	88.4	2.4
12.	Matairesinol	119205	358.4	2	6	85.2	3.3
13.	Medioresinol	181681	388.4	2	7	86.6	2.3
14.	Niranthin	13989915	432.5	0	7	64.6	4.1
15.	Nortrachelogenin	394846	374.4	3	7	105	2.5
16.	Pinoresinol	73399	358.4	2	6	77.4	2.3
17.	Piperitol	10247670	356.4	1	6	66.4	2.5
18.	Podophyllotoxin	10607	414.4	1	8	92.7	2
19.	Secoisolariciresinol	65373	362.4	4	6	99.4	2.5
20.	Sesamin	72307	354.4	0	6	55.4	2.7
21.	Sesaminol	94672	370.4	1	7	75.6	2.3
22.	Sesamolin	101746	370.4	0	7	64.6	3
23.	Silymarin	5213	482.4	5	10	155	2.4
24.	Steganacin	299674	456.4	0	9	98.8	2.9
25.	Syringaresinol	100067	418.4	2	8	95.8	2.2
26.	Todolactol	102184257	376.4	4	7	109	1.9
C[a]	Metocurine	21233	652.8	0	6	55.4	6.7

Note: [a] Control inhibitor

as a critical criterion for developing a successful therapeutic candidate. As many medications are found to be unfit during clinical trials, prediction of the in silico molecule's ADME properties can lower the failure rate at an early stage. As a result, the observation of ADME tests is an essential aspect of the early-stage drug design process. The ADMET features such as Log S, GI absorption, Lipinski's violations, bioavailability score, and synthetic accessibility score were evaluated for the top 10 probable ligands using the free accessible server at Swiss-ADME[22] (http://www.swissadme.ch).

2.7 Analysis and Visualisation

The interactions between the five most potential ligands and PL-pro were illustrated using Discovery Studio Visualiser and PyMOL.[23]

3. RESULTS

3.1 Docking-based Virtual Screening Analysis

A total of 27 compounds (26 phytolignans, Control: Metocurine) were docked against the SARS-CoV-2 papain-like protease using Pyrx software. The molecular docking study revealed that the 27 docked compounds have binding affinities ranging from -8.4 kcal/mol

Table 2. PyRx docking results, denoting the binding affinity of Phytolignans against PL-pro

S. No.	Ligand	Binding Affinity (kcal/mol)
1.	Sesamolin	-8.4
2.	Hinokinin	-8.1
3.	Silymarin	-8.1
4.	Sesaminol	-8.0
5.	Metocurine	-7.8
6.	Diphyllin	-7.7
7.	Sesamin	-7.7
8.	Justicidin A	-7.5
9.	Piperitol	-7.5
10.	Matairesinol	-7.2
11.	Medioresinol	-7.2
12.	Pinoresinol	-7.2
13.	Steganacin	-7.2
14.	Conidendrin	-7.2
15.	Arctigenin	-7.1
16.	Podophyllotoxin	-7.0
17.	Honokiol	-6.9
18.	Isolariciresinol	-6.9
19.	Lariciresinol	-6.9
20.	Alpha-peltatin	-6.9
21.	Cyclolariciresinol	-6.7
22.	Dimethylmatairesinol	-6.7
23.	Syringaresinol	-6.5
24.	Niranthin	-6.4
25.	Nortrachelogenin	-6.3
26.	Todolactol	-6.2
27.	Secoisolariciresinol	-6.1

Note: [a]Control inhibitor

Z to -6.1 kcal/mol (Table 2). Four phytolignans, namely, Sesamolin, Hinokinin, Silymarin, and Sesaminol, displayed significant binding affinity, as compared to the known inhibitor control, Metocurine (-7.8 kcal/mol). Therefore, these four phytolignans isolated from *Sesamum indicum* (sesame seeds), *Chamaecyparis obtuse* (Hinoki cypress), *Silybum marianum* (milk thistle), and sesame seed husk, respectively, were further analysed to study their potential as PL-pro inhibitors. Sesamolin, a lignan isolated from sesame oil, was found to exhibit the strongest binding affinity of -8.4 kcal/mol.

3.2 ADME Analysis

Pharmacokinetic ADME analysis of the potential PL-pro inhibitors, with respect to the control Metocurine, was carried out using the SwissADME server (Table 3). The results revealed that the four phytolignans were moderately soluble, with no violations of the Lipinski rule of five, the thumb rule in the identification of drug-like molecules. The bioavailability score of 0.55 confirms that all the investigated derivatives have good absorption.

3.3 Visualisation of Receptor-ligand Interactions

Based on Molecular docking and ADME predictions, Sesamolin, Hinokinin, Silymarin, and Sesaminol were identified as potential SARS-CoV-2 PL-proinhibitors. Sesamolin has the greatest binding affinity against PL-pro, with a value of -8.4 kcal/mol. Sesamolin formed two hydrogen bonds with residues ARG:166, THR:301 and also exhibits hydrophobic interaction with CYS: 111, TYR: 112, GLY: 163, MET: 208, SER: 245, ALA: 246, PRO: 248, GLN: 269, CYS: 270, GLY: 271, HIS: 272 (Table 4). Sesamolin docked into the PL-probinding pocket, with an illustration of all interactions displayed in (Fig. 2) The binding affinity of Hinokinin is -8.1 kcal/mol. It forms a hydrogen bond with VAL: 165, ARG: 166 residues and showed van der Waal's interaction with the following residues GLY: 163, MET: 208, SER: 245, ALA: 246, PRO: 248, TYR: 268, TYR: 273, ASP: 302 (Fig. 3).

Table 3. Swiss ADME results denoting essential chemical properties and Drug-likeness of the top 4 phytolignans, with respect to control drug Metocurine

S. No.	Phyto- lignan	LOG S (ESOL)	GI absorption	LIPINSKI violation (S)	Bio- availability Score
1.	Sesamolin	-4.14	High	0	0.55
2.	Hinokinin	-4.41	High	0	0.55
3.	Silymarin	-4.14	Low	0	0.55
4.	Sesaminol	-3.79	High	0	0.55
C[a]	Metocurine	-8.21	High	1 (MW>500)	0.55

Note: [a]Control inhibitor

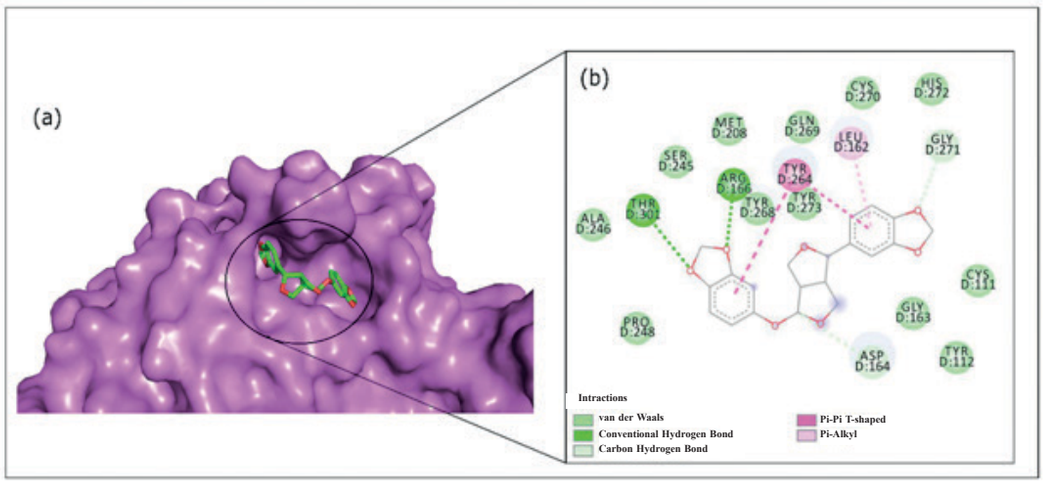

Figure 2. Binding interactions between PL-pro and Sesamolin: (a) Docked Sesamolin (green) inside binding pocket of PL-pro(violet) and (b) 2D interactions between Sesamolin and Binding site residues of PL-pro.

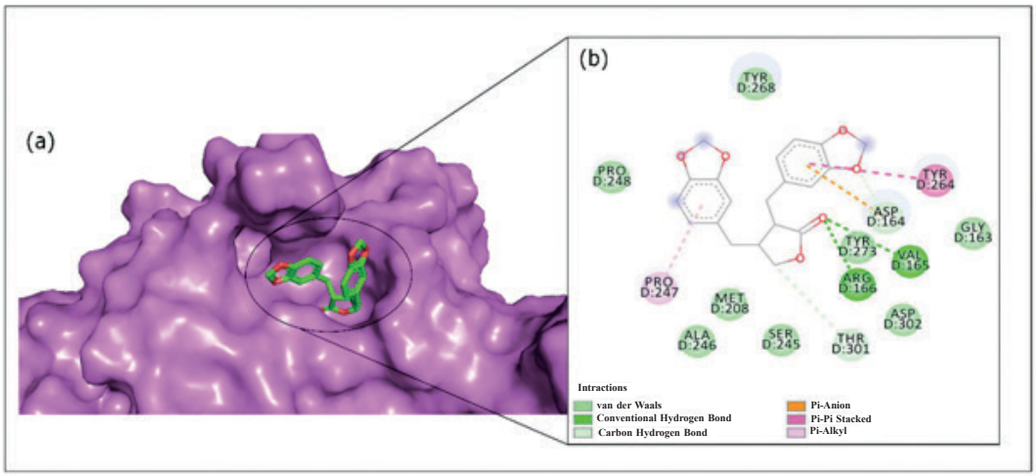

Figure 3. Binding interactions between PL-pro and Hinokini: (a) Docked Hinokinin(green) inside binding pocket of PL-pro(violet) and (b) 2D interactions between Hinokinin and Binding site residues of PL-pro.

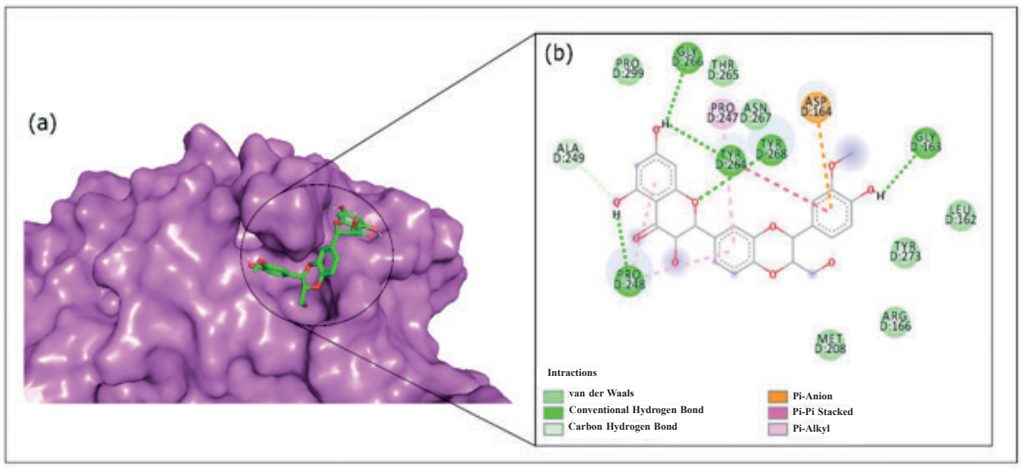

Figure 4. Binding interactions between PL-pro and Silymarin: (a) Docked Silymarin (green) inside binding pocket of PL-pro(violet) and (b) 2D interactions between Silymarin and binding site residues of PL-pro.

Table 4. Receptor-ligand interacting residues

S. No.	Ligand	Interaction types (Chain D)							
		H- Bond	**VDW**	**Pi-Pi stacked**	**Pi-sigma**	**Pi-Pi T-shaped**	**Pi-Alkyl**	**Pi-Anion**	**C-H Bond**
1.	Sesamolin	ARG: 166 **THR: 301**	**CYS: 111** TYR: 112 GLY: 163 **MET: 208** SER 245 ALA: 246 PRO:248 **GLN: 269** **CYS: 270** **GLY: 271** **HIS: 272**	-	**LEU: 162**	**TYR: 264**	-	-	ASP: 164
2.	Hinokinin	VAL: 165 ARG: 166	GLY: 163 **MET:208** SER: 245 ALA: 246 PRO:248 **TYR: 268** **TYR: 273** ASP: 302	**TYR:264**	-	-	PRO: 247	ASP: 164	**THR: 301**
3.	Silymarin	PRO: 248 GLY: 263 **TYR: 264** GLY: 266 **TYR: 268**	**LEU: 162** ARG:166 **MET: 208** ALA: 249 THR: 265 **ASN: 267** **TYR: 273** PRO: 299	**TYR:264**	-	-	PRO: 247 PRO: 248	ASP: 164	-
4.	Sesaminol	GLU: 161 **LEU: 162**	LYS: 157 GLY: 163 ASP: 164 **GLN: 269** **TYR: 273** **THR:301**	**TYR: 264**	-	-	-	-	PRO: 248 **TYR: 268**
5.	Metocurine	-	GLY: 163 ARG: 166 **MET:208** SER: 245 PRO: 248 **GLN: 269** **TYR: 273** **THR: 301**	-	**TYR:264**	-	PRO: 247	ASP: 164	**TYR: 264** **TYR: 268**
6.	Diphyllin	-	LYS: 157 GLU: 167 **MET:208** PRO: 248 **TYR: 268** **TYR: 273** **THR: 301**	GLY:163 **TYR:264**	-	-	-	ASP: 164 ARG: 166	**LEU: 162**

7.	Sesamin	-	LYS: 157 ARG: 166 **MET: 208** SER: 245 ALA: 246 **TYR: 264** **TYR: 268** **GLN: 269** **TYR: 273** ASP: 302	-	-	-	**LEU: 162**	ASP: 164	GLY: 163 THR: 301
8.	Justicidin A	-	LYS: 157 GLU: 167 **MET: 208** **TYR: 268** **TYR: 273** **THR: 301**	GLY:163 **TYR:264**	-	-	-	ASP: 164 ARG: 166	**LEU: 162** PRO: 248
9.	Piperitol	-	GLU: 161 GLY: 163 ASP: 164 **MET: 208** ALA: 246 PRO: 248 **TYR: 268** **GLN: 269** **TYR: 273** **THR: 301**	-	-	**TYR:264**	**LEU: 162** PRO: 247	-	-
10.	Matairesinol	-	GLY: 163 VAL: 165 PRO: 248 **TYR: 268** GLN: 269 **CYS: 270** **GLY: 271** **THR: 301**	**TYR:264**	-	-	**CYS: 111** **LEU: 162** ARG: 166 **TYR: 273**	-	ASP: 164

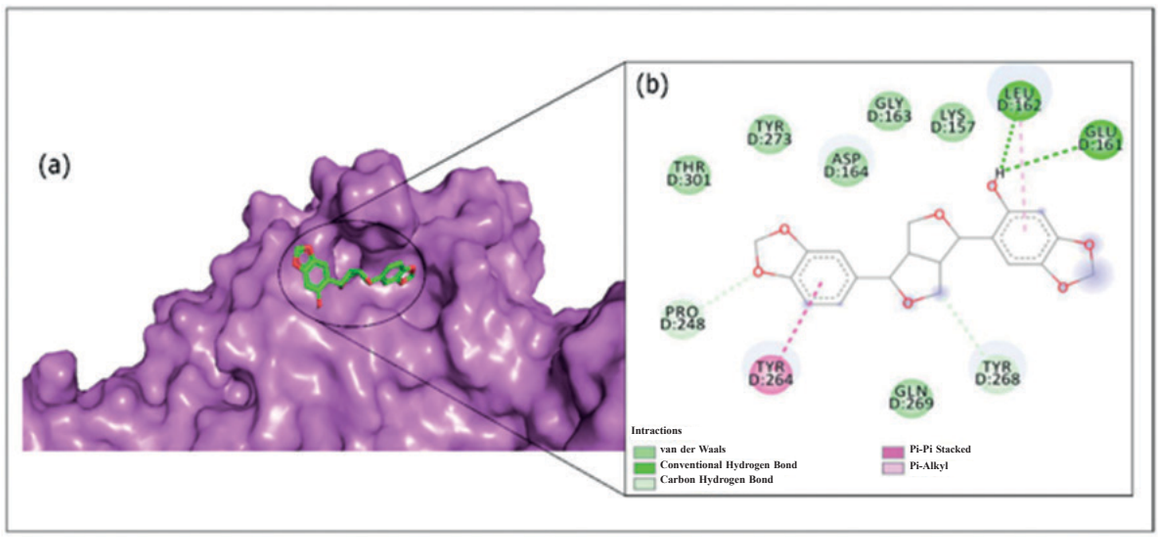

Figure 5. Binding interactions between PL-pro and Sesaminol : (a) Docked Sesaminol (green) inside binding pocket of PL-pro(violet) and (b) 2D interactions between Sesaminol and Binding site residues of PL-pro.

In comparison to other ligands, silymarin has a binding affinity of -8.1 kcal/mol for PL-pro. Silymarin formed five hydrogen bonds with PRO: 248, GLY: 263, TYR: 264, GLY: 266, TYR: 268 residues and also exhibits hydrophobic interaction with LEU: 162, ARG: 166, MET: 208, ALA: 249, THR: 265, ASN: 267, TYR: 273, PRO: 299 (Fig. 4).

Sesaminol has a binding affinity of -8.0 kcal/mol. It forms a hydrogen bond with GLU: 161, LEU: 162residues and showed van der Waal's interaction with the following residues LYS: 157, GLY: 163, ASP: 164, GLN: 269, TYR: 273, THR: 301 (Fig. 5).

As demonstrated in Table 4, the majority of the screened phytochemicals display comparable interactions and are involved in hydrogen bond and hydrophobic interactions with the same residues. The PL-pro binding pocket residues are highlighted in bold in Table 4.

The identified phytochemical compounds may be beneficial for improving therapeutics against COVID-19. On implementation of molecular modification techniques on the four compounds, further investigation can be carried out to validate the proposed theory in the pharmacological context.

4. CONCLUSION

Inhibiting SARS-CoV-2PL-pro effectively is a viable technique for controlling viral replication and identifying new therapeutic candidates.Our *in silico* study revealed the inhibition potential of phytolignans when docked in the active site of PL-pro. The study concludes four phytolignans – Sesamolin, Hinokinin, Silymarin, and Sesaminol as potential inhibitors against PL-pro, with sesame lignan Sesamolin displaying the strongest binding affinity of -8.4 kcal/mol. Furthermore, the putative inhibitors provided fulfilled the drug-likeness specifications on Lipinski's rule of five and ADME analysis. Receptor-ligand interactions revealed that Sesamolin interacted with two residues – CYS: 111 and HIS: 272 of the catalytic triad and can be considered as a suitable PL-pro inhibitor.

The application of natural phytolignans in this study will provide a sustainable treatment strategy with minimised side effects. Although this study is solely focused on *in silico* predictions, the present findings may positively contribute to the global search for effective inhibitors of the PL-pro.

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