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In Silico Study of Mangrove Triterpenoids as SARS-CoV-2 Main Protease Inhibitors †

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Abstract: Aim: In the present study, we performed an in silico study on the triterpenoid compounds from the mangrove plant as potential COVID-19 main protease (Mpro) inhibitors, which can be used as a potential medicine target. Methods: In this study we performed molecular docking using AutoDock software. Results: The binding energies obtained through the docking of 6LU7 with beta-amyrin, betulin, germanicol, taraxerol, lupeol, lupane, simiarenol, tirucallol, ursolic acid, oleanolic acid, and alpha-amyrin were -8.37, −8.73, −8.06, −7.71, −8.32, −8.49, −8.16, −8.99, −9.24, −8.87, and −8.89 kcal/mol, respectively. Further, these results were also confirmed with drug-likeness properties by using Swiss ADME software. Conclusion: This study showed that triterpenoid compounds seemed to have the best potential to act as COVID-19 Mpro inhibitors, and that they contain a potential lead compound for the development of drugs, which can be used against SARS-CoV-2.

Keywords: SARS-CoV-2; molecular docking; 6LU7; mangrove; triterpenoids; drug likeness

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of COVID-19, a highly contagious illness that affects several sections of the respiratory system, and particularly the lungs [1,2]. There is not a specific treatment for COVID-19 at the moment [3]. Computationally aided drug design (CADD) methodologies have revealed significant implications for current research, and these procedures are quicker and more affordable [4]. In order to reduce the risk of wasting time and money, in silico approaches are used early on in the drug development process [5]. To manage SARS-CoV-2 infection, lead compounds derived from natural sources are thought to have fewer adverse effects and are considered to be inexpensive nutraceuticals [6]. The major subject of this investigation was mangrove-derived triterpenoid chemicals. Mangroves are either little trees or plants that thrive in rocky or muddy soils near brackish or salty coastal waters. Mangroves are facultative halophytes because they can tolerate salt and easily adapt to the harsh coastal environment [7]. Mangrove plants are abundant in new chemical compounds and natural products, which is becoming more common knowledge. Mangroves have received a great deal of scientific attention because of their strong ability to combat numerous ailments. Terpenoids make up more than 16% of the phytoconstituents in mangroves. Triterpenoids, which have 30 carbon atoms and are polymerized to create six isoprene units, are the most typical class of phytochemicals. In nature, triterpenoids are extensively dispersed. The variety of triterpenes and their extensive spectrum of pharmacological actions are closely connected. Triterpenes are conventionally used as anti-inflammatory, analgesic, hepatoprotective, cardiotonic, and sedative drugs in Asian countries [8]. Using molecular docking, we looked at triterpenoid chemicals that had been previously identified as being found in mangroves as potential inhibitors of the COVID-19 primary protease Mpro. The process of creating drugs to combat COVID-19 will benefit from these discoveries.

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2. Materials and Methods

2.1. Protein Preparation

The main protease of SARS COVID-19 is Mpro, and its 3D structure was obtained from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) in PDB format. The PDB is a library for the crystal structures of biological macromolecules [9] (PDB ID: 6LU7).

2.2. Ligand Preparation

The 3D structures of triterpenoid compounds from mangroves were obtained from the PubChem website in SDF format. Triterpenoid compounds like beta-amyrin (CID_73145), betulin (CID_72326), germanicol (CID_122857), taraxerol (CID_92097), lupeol (CID_259846), lupane (CID_9548715), simiarenol (CID_12442794), tirucallol (CID_101257), ursolic acid (CID_64945), oleanolic acid (CID_10494), and alpha-amyrin (CID_73170) were used in this study.

Drug-like properties were calculated using Lipinski's rule of five [10,11]. Adherence to Lipinski's rule of five was calculated using SWISSADME prediction.

2.3. Molecular Docking

The study was supported by tools like AutoDock, MGL, and Rasmol. The docking analyses were performed using AutoDock, Pymol, and Biovia Discovery Studio.

3. Results

3.1. Selection of Phytochemicals

A total of 12 compounds were selected based on adherence to Lipinski's rule of five. They can be used in molecular docking experiments with the target protein 6LU7. The drug scanning results (Table 1) showed that all tested compounds in this study were accepted by Lipinski's rule of five. The 2D diagrammatic representations (Table 1) of the selected triterpenoid compounds demonstrate interactions with the target protein Mpro. The 2D visualization of docking analysis results, including the H-bonds that interact with 6LU7 amino acids, is mentioned in Table 1.

Table 1. Properties of COVID-19 Mpro potential inhibitor candidates.

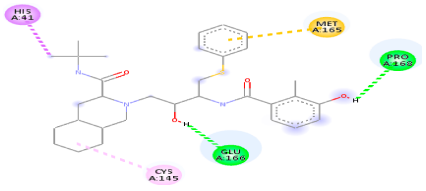
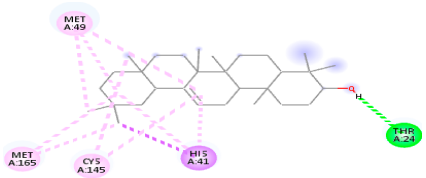
S. No.	Compound Name	Molecular Formula	Molecular Structure and Interaction with 6LU7	Lipinski's Rule of Five	
				Properties	**Value**
1.	Nelfinavir	$C_{32}H_{45}N_3O_4S$		Molecular weight (<500 Da)	567.78 g/mol
				LogP (<5)	4.33
				H-Bond donor (5)	4
				H-bond acceptor (<10)	5
				Violation	1
2.	beta-Amyrin	$C_{30}H_{50}O$		Molecular weight (<500 Da)	426.72 g/mol
				LogP (<5)	4.63
				H-Bond donor (5)	1
				H-bond acceptor (<10)	1
				Violation	1

Table 1. *Cont.*

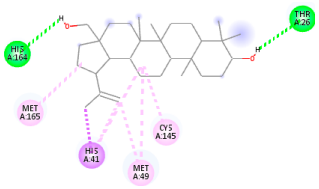
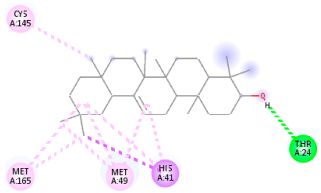
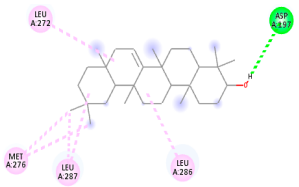
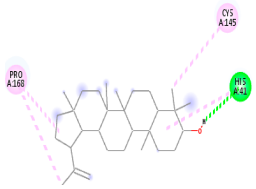
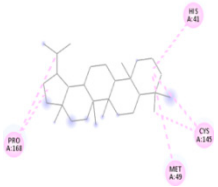
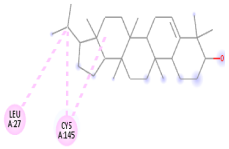
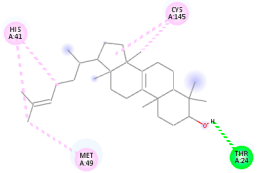
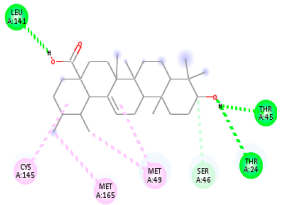
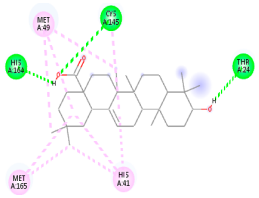
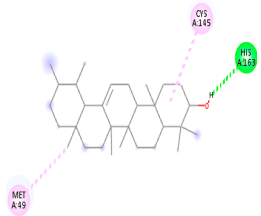
S. No.	Compound Name	Molecular Formula	Molecular Structure and Interaction with 6LU7	Lipinski's Rule of Five	
				Properties	**Value**
3.	Betulin	$C_{30}H_{50}O_2$		Molecular weight (<500 Da)	442.72 g/mol
				LogP (<5)	4.47
				H-Bond donor (5)	2
				H-bond acceptor (<10)	2
				Violation	1
4.	Germanicol	$C_{30}H_{50}O$		Molecular weight (<500 Da)	426.72 g/mol
				LogP (<5)	5.04
				H-Bond donor (5)	1
				H-bond acceptor (<10)	1
				Violation	1
5.	Taraxerol	$C_{30}H_{50}O$		Molecular weight (<500 Da)	426.72 g/mol
				LogP (<5)	4.73
				H-Bond donor (5)	1
				H-bond acceptor (<10)	1
				Violation	1
6.	Lupeol	$C_{30}H_{50}O$		Molecular weight (<500 Da)	426.72 g/mol
				LogP (<5)	4.63
				H-Bond donor (5)	1
				H-bond acceptor (<10)	1
				Violation	1
7.	Lupane	$C_{30}H_{52}$		Molecular weight (<500 Da)	426.72 g/mol
				LogP (<5)	4.63
				H-Bond donor (5)	1
				H-bond acceptor (<10)	1
				Violation	1
8.	Simiarenol	$C_{30}H_{50}O$		Molecular weight (<500 Da)	426.72 g/mol
				LogP (<5)	4.63
				H-Bond donor (5)	1
				H-bond acceptor (<10)	1
				Violation	1
9.	Tirucallol	$C_{30}H_{50}O$		Molecular weight (<500 Da)	426.72 g/mol
				LogP (<5)	5.14
				H-Bond donor (5)	1
				H-bond acceptor (<10)	1
				Violation	1

Table 1. *Cont.*

S. No.	Compound Name	Molecular Formula	Molecular Structure and Interaction with 6LU7	Lipinski's Rule of Five	
				Properties	**Value**
10.	Ursolic acid	$C_{30}H_{48}O_3$		Molecular weight (<500 Da)	456.70 g/mol
				LogP (<5)	5.82
				H-Bond donor (5)	1
				H-bond acceptor (<10)	1
				Violation	1
11.	Oleanolic acid	$C_{30}H_{48}O_3$		Molecular weight (<500 Da)	456.70 g/mol
				LogP (<5)	5.82
				H-Bond donor (5)	1
				H-bond acceptor (<10)	1
				Violation	1
12.	alpha-Amyrin	$C_{30}H_{50}O$		Molecular weight (<500 Da)	426.72 g/mol
				LogP (<5)	6.92
				H-Bond donor (5)	1
				H-bond acceptor (<10)	1
				Violation	1

3.2. Molecular Docking of Selected Compounds

Table 2 shows the molecular docking analysis results for the standard drug and 11 triterpenoid compounds against the main protease of SARS COVID-19 (6LU7). The binding energies obtained from the docking of 6LU7 with nelfinavir, beta-amyrin, betulin, germanicol, taraxerol, lupeol, lupane, simiarenol, tirucallol, ursolic acid, oleanolic acid, and alpha-amyrin were −6.21, −8.37, −8.73, −8.06, −7.71, −8.32, −8.49, −8.16, −8.99, −9.24, −8.87, and −8.89 kcal/mol, respectively. The visualization of 6LU7 binding with the selected triterpenoid compounds from the mangrove, including beta-amyrin, betulin, germanicol, taraxerol, lupeol, lupane, simiarenol, tirucallol, ursolic acid, oleanolic acid, and alpha-amyrin, as well as with nelfinavir (standard drug), is represented in Figure 1A to 1 L as potential inhibitors of the COVID-19 Mpro.

Table 2. Molecular docking analyses of triterpenoid compounds against 6LU7.

Protein	Ligand	Lowest Binding Energy (kcal/mol)	Ligand Efficiency	Inhibition Constant	Intermolecular Energy (kcal/mol)	VDW-H Bond Desolvation Energy (kcal/mol)
6lu7	**Nelfinavir**	−6.21	−9.709	27.83 uM	−9.79	−9.77
	beta-Amyrin	−8.08	−4.445	1.20 µM	−8.37	−8.33
	Betulin	−7.54	−6.161	2.96 µM	−8.73	−8.70
	Germanicol	−7.76	−4.229	2.04 µM	−8.06	−8.02
	Taraxerol	−7.41	−25.601	3.68 µM	−7.71	−7.43
	Lupeol	−7.73	−10.786	2.17 µM	−8.32	−8.31
	Lupane	−8.19	−9.698	996.23 nM	−8.49	−8.48
	Simiarenol	−7.56	−10.006	2.87 µM	−8.16	−8.15
	Tirucallol	−8.99	−4.998	255.21 nM	−10.49	−10.46
	Ursolic acid	−9.24	−3.784	168.90 nM	−10.13	−10.05
	Oleanolic acid	−8.87	−5.134	314.36 nM	−9.77	−9.69
	alpha-Amyrin	−8.89	−11.721	306.52 nM	−9.18	−9.14

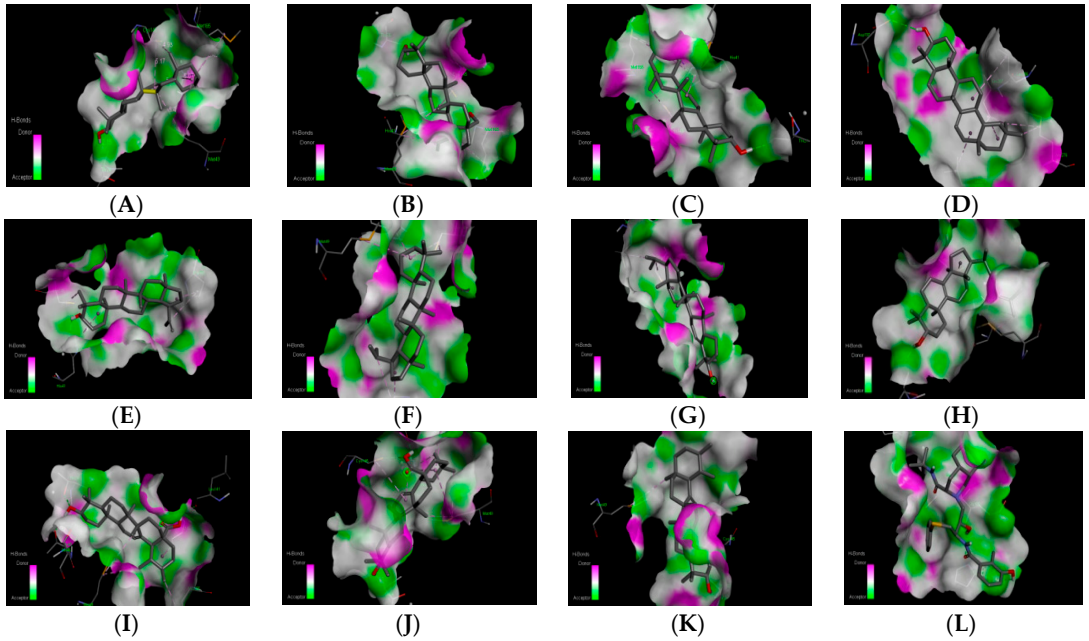


Figure 1. 3D visualization of 6LU7 binding with beta-amyrin (**A**), betulin (**B**), germanicol (**C**), taraxerol (**D**), lupeol (**E**), lupine (**F**), simiarenol (**G**), tirucallol (**H**), ursolic acid (**I**), oleanolic acid (**J**), alpha-amyrin (**K**), and nelfinavir (**L**) using Biovia Discover Studio. The green and pink colors represent H-bond acceptor and donor regions, respectively.

4. Discussion

With 6LU7, nelfinavir creates several chemical connections, such as hydrogen and hydrophobic bonds. These triterpenoid chemicals have been abandoned in mangroves, according to several studies (Table 3). Similar to nelfinavir, the triterpenoid molecules from this study also created many chemical connections. The results show that compared to other molecules, ursolic acid bonds have a stronger affinity. According to their affinity, ursolic acid, tirucallol, alpha-amyrin, oleanolic acid, lupane, beta-amyrin, germanicol, simiarenol, betulin, taraxerol, and nelfinavir were the compounds with the greatest potential for inhibition in the current study's docking analysis. The chemicals that are most suggested as potential COVID-19 Mpro inhibitors are mangrove triterpenoids, which should be investigated in further studies.

Table 3. Triterpenoids compounds from mangrove.

Compounds	Species Name	Parts	References
beta-Amyrin	*Rhizophora mucronata*	Bark	Rohini, R.M et al., 2009
Betulin	*Rhizophora mucronata*	Leaf	Ghosh A et al., 1985
Germanicol	*Rhizophora* sp.	Leaf	Koch, B.P et al., 2003
Taraxerol	*Avicennia marina*	Root	Mahera, S.A et al., 2011
Lupeol	*Rhizophora mucronata*	Bark	Rohini, R.M et al., 2009
Lupane	*Ceriops decandra*	Leaf	Ponglimanont, C. and Thongdeeying, P., 2005
Simiarenol	*Rhizophora mucronata*	Bark	Rohini, R.M et al., 2009
Tirucallol	*Excoecaria agallocha*	Leaf	Zou, J.H et al., 2006
Ursolic acid	*Brugurera gymnorhiza*	Leaf	Ghosh, A et al., 1985
Oleanolic acid	*Acanthus ilicifolius*	Leaf	Ghosh, A et al., 1985
alpha-Amyrin	*Ceriops decandra*	Leaf	Ghosh, A et al., 1985

5. Conclusions

This investigation looked at a number of mangrove-derived triterpenoid chemicals that might be used to block the COVID-19 infection pathway. The compounds with the

best binding energies and inhibition constants are beta-amyrin, betulin, germanicol, taraxerol, lupeol, lupane, simiarenol, tirucallol, ursolic acid, oleanolic acid, and alpha-amyrin. Compared to other molecules, ursolic acid bonds have a stronger affinity. Triterpenoids were therefore the substances found in mangroves that are most recommended as potential COVID-19 Mpro inhibitors. For the development of medicine from mangroves, additional clinical trials examining the potential of terpenoid chemicals against viral infection must be conducted, and should be followed by in vitro and in vivo research.

Author Contributions: R.P. and G.V. written the first draft of the complete manuscript and conceived the research idea T.R. commented on the previous versions of the manuscript. All authors contributed to the review and editing of 2nd and 3rd draft of the manuscript. All authors have read and agreed to the published version of the manuscript.

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