Research Article

Elucidation of Stilbene-Derivatives as Potential Inhibitors of SARS-CoV-2 M^{pro} Binding Pocket: A Molecular Docking, and ADMET Prediction Studies

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ABSTRACT

Berries are well-known not only for their flavour and nutritional content but also for the potential health effects of their bioactive components. Stilbenes, a class of phenolic compounds found in berries, have essential pharmacological activities in many biological pathways. The COVID-19 pandemic had put many countries in the world in a state of chaos. Although the prevalence of COVID-19 seems to have subsided, the search for the remedy to overcome this pathogen is still ongoing. Plant-derived substances have well been recorded to display potent effects including antiviral activity. Hence, the aim of this study is to determine the potential of stilbene derivatives to act as antiviral agents against COVID-19. In silico molecular docking method was employed to elucidate the structural interaction of eleven stilbene derivatives to SARS-CoV-2 M^{pro} binding pocket using CB-Dock2 server, followed by drug-likeness and ADMET prediction analysis. Based on the docking score and ligand-receptor interactions, rhaponticin and polydatin had the best vina docking scores for the SARS-CoV-2 M^{pro} pocket with -8.1 kcal/mol and -8.0 kcal/mol respectively. These scores were found to be lower than controls, remdesivir (-7.8 kcal/mol) and inhibitor N3 (-7.9 kcal/mol), indicating its high affinity towards the binding target. In conclusion, the study identified that rhaponticin and polydatin might serve as potential lead compounds for developing new SARS-CoV-2 drugs. However, these results need to be validated by in vitro and in vivo experimental studies before these compounds can be considered for further development as antiviral agents.

Keywords: berries, COVID-19, molecular docking, SARS-CoV-2 M^{pro}, Stilbene

1. Introduction

Berries are a type of fruit that is recognized for their nutritional, preventive effect and health benefits (Folmer *et al.*, 2014; Golovinskaia and Wang, 2021). These functional fruits have significant vitamin, fiber, mineral, and antioxidant content, which contributes to their potential health effects. Berries also are rich in phenolic substances such as flavonoids (anthocyanins, flavonols, flavones, flavanols, flavanones, and isoflavonoids), tannins, and phenolic acids (Folmer *et al.*, 2014; Golovinskaia and Wang, 2021; Nile and Park, 2014; Puupponen-Pimiä *et al.*, 2005; Skrovankova *et al.*, 2015). Given the high concentration of polyphenols in berries, they have the potential to pharmacologically treat various diseases by reducing oxidative stress and inflammation, which are often underlying causes of conditions such as diabetes,

neurological disorders, cardiovascular disease, and cancer (Baby *et al.*, 2018; Folmer *et al.*, 2014; Golovinskaia and Wang, 2021; Kristo *et al.*, 2016; Lail *et al.*, 2021; Valdez and Bolling, 2019). One of the major bioactive commonly found is berries stilbenes, which is a class of phytochemicals that have an array of health advantages such as anti-inflammatory, antidiabetic, antioxidant, anti-dyslipidemia, and anti-cancer properties (Levenson, 2022; Reinisalo *et al.*, 2015; Rivera *et al.*, 2009; Tsai *et al.*, 2017; Varoni *et al.*, 2016; Zhao *et al.*, 2021).

Stilbenes are a type of polyphenolic compound that plants produce as a defensive strategy against external factors such fungal infections and UV radiation (Reinisalo *et al.*, 2015). Stilbenes are abundant in nature, with grapes, blueberries, raspberries, and cranberries being some of the most abundant sources (Shen *et al.*, 2009). Resveratrol, the most well-known stilbene, is found in grapes and red wine (Meng *et al.*, 2021; Salehi *et al.*, 2018; Thomas Wallerath Thomas Ternes, Henrik Anderson, Huige Li, Klaus Witte, Ulrich Forstermann, 2002). Stilbenes have attracted a lot of interest in recent years because of their potential health benefits. Stilbenes have been demonstrated to have neuroprotective, cardioprotective, anti-aging, anticancer, and anti-diabetic characteristics in addition to their anti-inflammatory and antioxidant properties (Baby *et al.*, 2018; Choi *et al.*, 2005; De Filippis *et al.*, 2017; Teka *et al.*, 2022; Xu *et al.*, 2020; Zhang *et al.*, 2019 Due to these potential health benefits, there is a growing trend of consuming stilbene-rich foods such as berries. Despite their potential health benefits, stilbenes' absorption and metabolism in humans remain unknown. Further research is required to better understand the processes by which stilbenes exert their health benefits and to find optimal dosages for these effects. Yet, emerging evidence of stilbenes' health advantages has sparked interest in the consumption of stilbene-rich foods, particularly berries, as a means of promoting health and preventing disease.

There is a growing body of evidence to suggest that the consumption of stilbene-rich foods, such as berries, may have potential benefits in the context of SARS-CoV-2, the virus responsible for the COVID-19 pandemic (Dong *et al.*, 2021; Yadav, 2021). SARS-CoV-2 is a highly infectious virus that primarily affects the respiratory system and can cause severe respiratory illness, particularly in individuals with pre-existing health conditions (Astuti and Ysrafil, 2020; Cascella *et al.*, 2020). One of the potential benefits of stilbenes in the context of SARS-CoV-2 is their anti-inflammatory properties (Wahedi *et al.*, 2021). SARS-CoV-2 infection is associated with a heightened inflammatory response in some individuals, particularly those with severe illness. This inflammatory response can contribute to the development of acute respiratory distress syndrome (ARDS), a potentially life-threatening condition characterized by severe lung inflammation (Astuti and Ysrafil, 2020; Badraoui *et al.*, 2021; Hachim *et al.*, 2021). Stilbenes have been shown to have anti-inflammatory properties in various experimental models, and some studies have suggested that they may help to reduce inflammation in the context of respiratory infections (Filardo *et al.*, 2020). In addition to their anti-inflammatory properties, stilbenes have also been shown to have antiviral properties (Filardo *et al.*, 2020; Gastaminza *et al.*, 2011; Mattio *et al.*, 2020; Segun *et al.*, 2021). Some studies have suggested that stilbenes may be effective at inhibiting the replication of various viruses, including influenza virus and herpes simplex virus (Bizzarri *et al.*, 2019; Filardo *et al.*, 2020; Li *et al.*, 2015; Ma *et al.*, 2016). While research on the effects of stilbenes on SARS-CoV-2 is limited, their demonstrated antiviral properties suggest potential as a complementary approach to preventing or treating COVID-19. This study aims to explore the molecular interaction of stilbene derivatives with SARS-CoV-2 M^{pro} in order to better understand their potential pharmacological effects.

2. Materials and Methods

2.1 Molecular Docking

In this study, eleven stilbene-based derivatives namely resveratroloside, rhaponticin, polydatin, oxyresveratrol, 3,4,5,4’-tetramethoxystilbene, resveratrol, piceatannol, pinosylvin, rhapontigenin, 4-hydroxystilbene and pterostilbene were chosen as ligands (Table 1). Remdesivir and inhibitor N3 were selected as the control ligands. The inhibitor N3 was redocked as standard inhibitor. 3D molecular structures

of all ligands were retrieved from PubChem and ChemSpider. The retrieved files were converted to Protein Data Bank format using BIOVIA Discover Studio Visualizer 4.0 software (Accelrys Software Inc., San Diego, CA).

Table 1 List of stilbenes.

No	Ligand	PubChem ID
1	Resveratroloside	5322089
2	Rhaponticin	637213
3	Polydatin	5281718
4	Oxyresveratrol	5281717
5	3,4,5,4'-Tetramethoxystilbene	163183610
6	Resveratrol	445154
7	Piceatannol	667639
8	Pinosylvin	5280457
9	Rhapontigenin	5320954
10	4-Hydroxystilbene	5284650
11	Pterostilbene	5281727

This study used SARS-Cov-2 M^{pro} (PDB ID: 6LU7) as a binding target. The 3D structure was retrieved from RCSB Protein Data Bank. Docking between ligands and protein was performed on CB-Dock 2 web server (https://cadd.labshare.cn/cb-dock2/) (Liu *et al.*, 2022). The CB-Dock (Cavity-detection guided Blind Docking) server predicts the binding sites of a given protein and calculates the centres and sizes with a novel curvature-based cavity detection approach. The server works in conjunction with AutoDock Vina and has been carefully optimized to achieve a success rate of over 70 % in the models developed. The analysis was conducted using protein files in .pdb format and ligands in .sdf format, and five possible coupling cavities were identified. Among these, the one with the lowest binding energy was selected based on the lowest Vina value obtained. The best binding conformation was selected and evaluated for molecular interaction with their receptors using BIOVIA Discovery Studio Visualizer v21.1.0.20298.

2.2 Drug-likeness prediction

The OSIRIS Property Explorer was used to investigate the drug-relevant properties of the compounds. Properties studied include Topology Polar Surface Area (TPSA), c log P calculation, log S calculation, molecular weight, and drug score.

2.3 ADMET prediction

Chemical absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of a substance are related to how that substance is absorbed, distributed, metabolized, excreted, and processed by the human body. ADMET predictions play important role in drug discovery and development. It is also critical for studying the pharmacokinetic profile of the drug molecule. We used the admetSAR 2.0 prediction tool for this work (http://lmmd.ecust.edu.cn:8000/). SwissADME (http://www.swissadme.ch/index.php) was also utilized to evaluate the ADME properties of the compounds. These web servers provide researchers the ability to lessen the laborious experimental work and enhance the success rate.

3. Results and Discussion

3.1 Interaction of the Ligands with SARS-CoV-2 M^{pro} Target

Docking analysis was carried out using CB-Dock 2 web server to identify the best-scoring stilbene-derivatives with the capability to inhibit SARS-CoV-2 M^{pro}. Remdesivir and inhibitor N3 were used as reference ligands. Inhibitor N3 is the co-crystal ligand found in the PDB structure of SARS-CoV M^{pro} (PDB ID:6LU7) while remdesivir is an antiviral medication that has been used widely to treat COVID-19 patients. Remdesivir displayed its protective effect in SARS-CoV-2 infected animals via inhibition of SARS-CoV-2 replication which eventually lowered the viral load (Beigel *et al.*, 2020; Frediansyah *et al.*, 2021). The original position and orientation of native-ligand inhibitor N3 in the protein structure and the re-docked pose are shown in Figure 1. Native-ligand inhibitor N3 formed 9 hydrogen bonds, 3 π-Alkyl interaction, and 3 Alkyl interaction with several amino acid residues of M^{pro} ligand-biding site (Table 2).

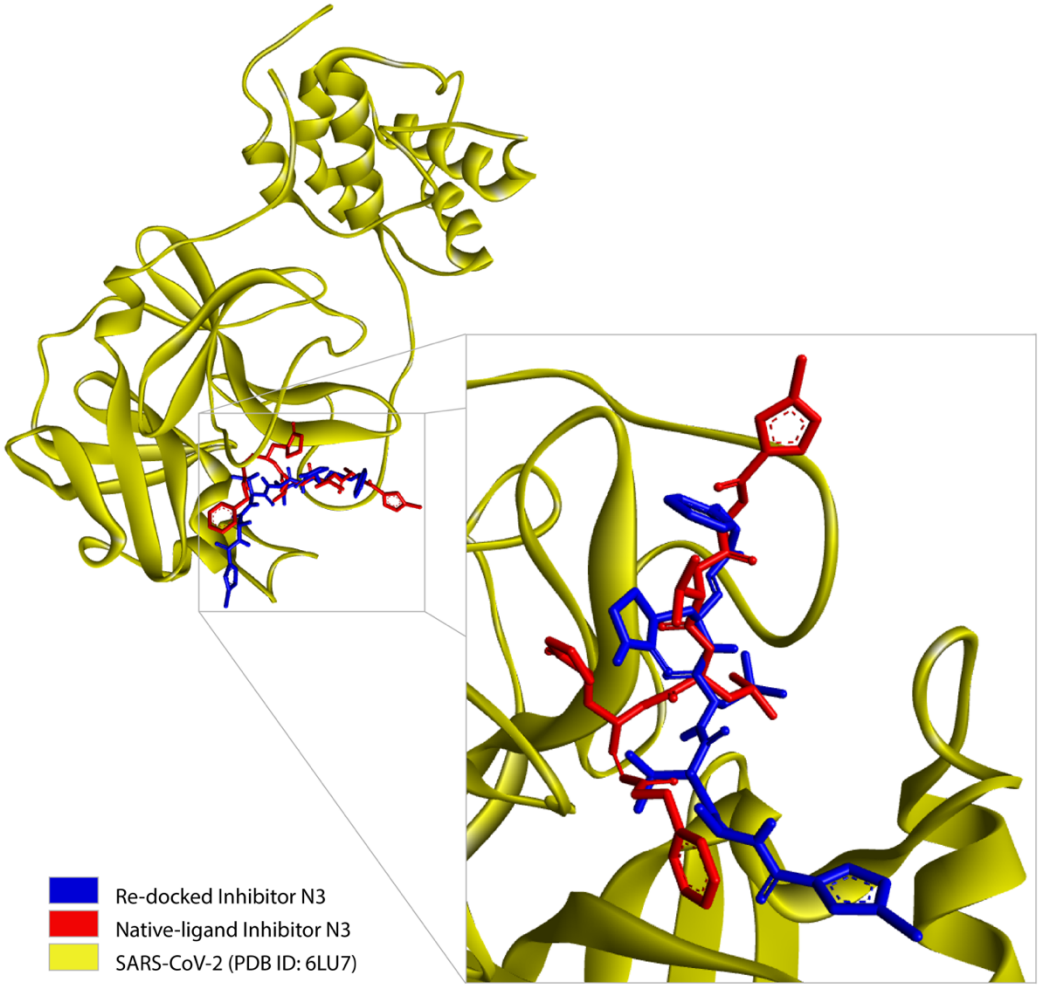

Figure 1 Illustration of binding interaction of the native-ligand inhibitor N3 and re-docked pose of inhibitor N3 using BIOVIA Discovery Studio Visualizer v21.1.0.20298.

Table 2 Interaction of Native-ligand Inhibitor N3 in the 6LU7.

Ligand	Interacting Amino Acid	Types of Bonds	Distance (Å)
Inhibitor N3	His41	π-Alkyl	4.31
	Met49	Alkyl	4.66
	Phe140	H-Bond	3.13
	Gly143	H-Bond	2.80
	Cys145	Covalent Bond	3.07
	His164	H-Bond	3.07
	Met165	Alkyl	4.57
	Glu166	H-Bond	2.83
	Glu166	H-Bond	2.98
	Glu166	H-Bond	3.38
	Leu167	Alkyl	5.46
	Pro168	π-Alkyl	4.85
	His172	H-Bond	3.32
	Gln189	H-Bond	2.93

The re-docked inhibitor N3 produced Vina score of -7.9 kcal/mol, indicating its ability to interact with the M^{pro} with high affinity. A negative Vina score signifies the least energy required to form the interaction, demonstrating strong affinity. The re-docked pose formed interaction through the formation of 9 hydrogen bonds, 3 π-Alkyl interaction, and 1 Alkyl interaction (Figure 2).

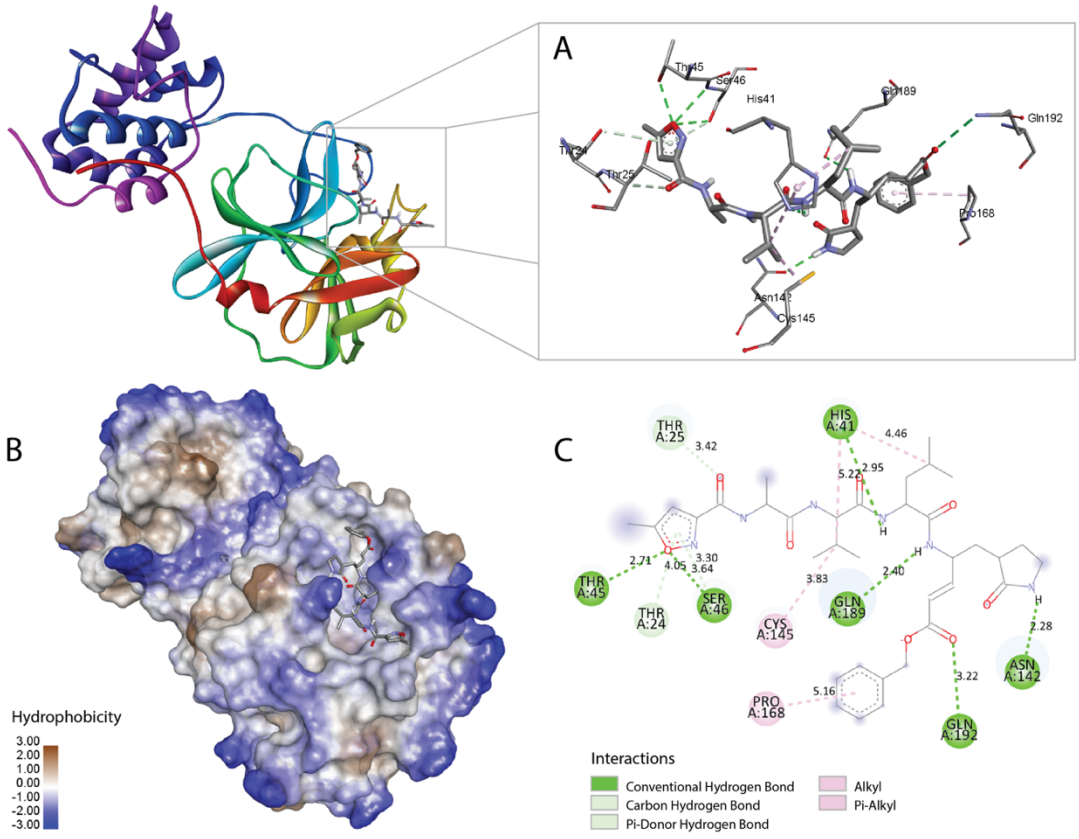

Figure 2 Visualization of docking interaction of inhibitor N3 with 6LU7. (A) 3D representation of the interaction between amino acid residues and inhibitor N3; (B) 3D visualization of hydrophobicity surface; (C) 2D representation of the interaction elucidating the bindings of inhibitor N3 with the active site of 6LU7.

Both native-ligand and re-docked inhibitor N3 formed interactions His41 with the former forming a π-Alkyl interaction with 4.3 Å bond distance while the latter interacted via 1 hydrogen bond (2.95 Å) and 2 π-Alkyl interactions (4.46 Å and 5.22 Å). Thus, the interaction with His41 is presumed to be vital in the inhibition of the protein. Patel *et al.* (2021) reported that the interaction with another amino acid residue, Cys145, possibly contributed to the inhibitory effect of the drug candidate (Patel *et al.*, 2021). Native-ligand inhibitor N3 formed a 1 π-Alkyl interaction with Cys145 with a 4.31 Å bond distance while the re-docked inhibitor N3 formed Alkyl hydrophobic interaction with a 3.8 Å bond distance. The other reference ligand, remdesivir, formed an interaction with Vina score comparable to inhibitor N3 which is -7.8 kcal/mol. This prodrug formed interactions with 7 amino acid residues including 5 with Cys145 and 1 with His41 (Table 3). The interaction illustration is shown in Figure 3.

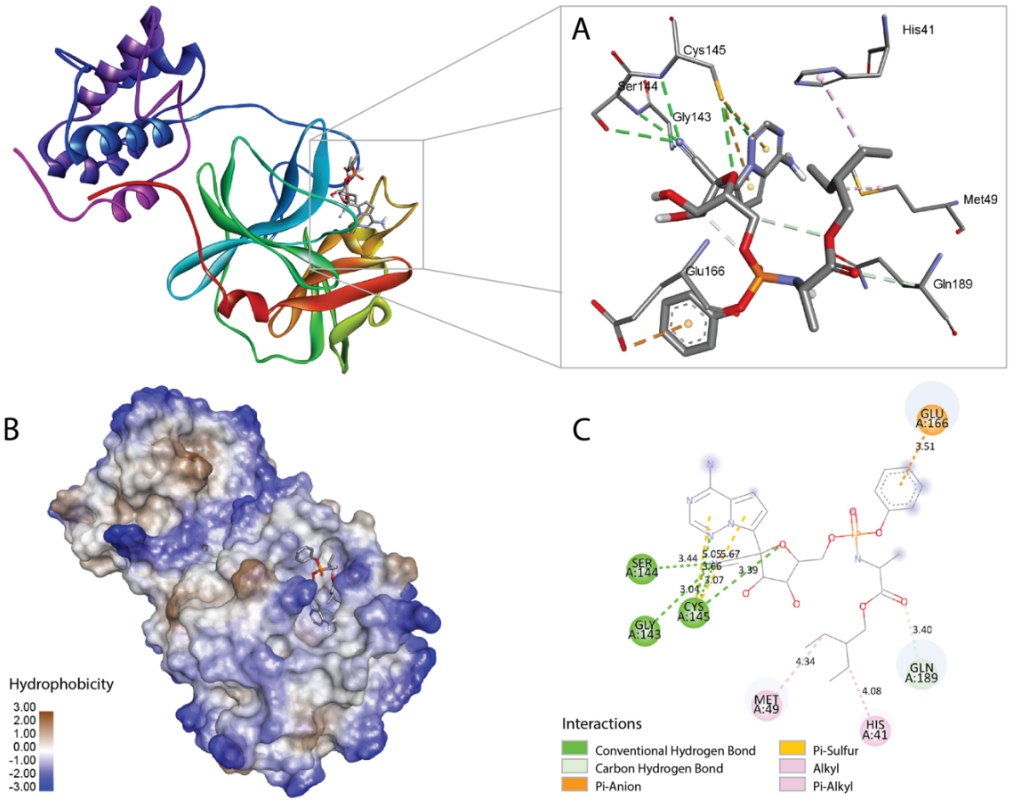

Figure 3 Visualization of docking interaction of remdesivir with 6LU7. (A) 3D representation of the interaction between amino acid residues and remdesivir; (B) 3D visualization of hydrophobicity surface; (C) 2D representation of the interaction elucidating the bindings of remdesivir with the active site of 6LU7.

As shown in Table 4, 11 stilbene-derivates demonstrated binding affinities ranging from -8.1 to -6.0 kcal/mol. For further analysis, two compounds with Vina score higher than inhibitor N3 and remdesivir were selected. Rhaponticin and Polydatin showed a binding affinity with Vina scores of -8.1 and -8.0 kcal/mol respectively. Rhapontincin interacted with His41 by forming 1 hydrogen bond with a 2.60 Å bond length and 1 hydrophobic π-π T-Shaped interaction with a 5.08 Å bond length (Figure 4). Polydatin, on the other hand, formed only 1 interaction with His41 through π-π T-Shaped interaction with a bond length of 5.15 Å. Polydatin also embodied a hydrogen bond with Cys145 with a bond length of 3.20 Å (Figure 5).

Table 3 Docking analysis of led ligands and controls with SARS-CoV-2-M^{pro}.

Ligand	Vina Score (kcal/mol)	Interacting Amino Acid	Types of Bonds	Distance (Å)
Remdesivir	-7.8	His41	π-Alkyl	4.08
		Met49	Alkyl	4.34
		Gln89	H-Bond	3.40
		Gly143	H-Bond	3.04
		Ser144	H-Bond	2.88
		His164	H-Bond	3.39
		Cys145	π-Sulfur	5.05
		Glu166	π-Sulfur	5.67
		Glu166	H-Bond	3.66
		Glu166	H-Bond	3.39
		Leu167	H-Bond	3.07
		Glu166	π-Anion	3.51
Inhibitor N3	-7.9	Thr25	H-Bond	3.42
		Thr24	H-Bond	4.05
		His41	H-Bond	2.95
		His41	π-Alkyl	4.46
		His41	π-Alkyl	5.22
		Thr45	H-Bond	2.71
		Ser46	H-Bond	3.64
		Ser46	H-Bond	3.30
		Asn142	H-Bond	2.28
		Cys145	Alkyl	3.83
		Pro168	π-Alkyl	5.16
		Gln189	H-Bond	2.40
		Gln192	H-Bond	3.22
Rhaponticin	-8.1	His41	π-π T-Shaped	5.08
		His41	H-Bond	2.60
		Gly143	H-Bond	2.89
		Gly143	H-Bond	3.05
		Ser144	H-Bond	2.59
		Ser144	H-Bond	2.87
		Ser144	H-Bond	2.97
		His163	H-Bond	2.41
		Met165	π-Sulfur	5.88
		Met165	π-Alkyl	4.76
		Pro168	π-Alkyl	5.00
		Pro168	Alkyl	4.38
		Ala191	Alkyl	4.36
		Gln192	H-Bond	2.95
Polydatin	-8.0	His41	π-π T-Shaped	5.15
		Leu141	H-Bond	2.23
		Ser144	H-Bond	2.54
		Cys145	H-Bond	3.20
		Pro165	π-Alkyl	4.77
		Pro168	π-Alkyl	5.11
		Ala191	H-Bond	3.62

Table 4 Docking analysis of led ligands and controls with SARS-CoV-2-M^{pro}.

Ligand	Vina Score (Kcal/mol)
Rhaponticin	-8.1
Polydatin	-8.0
Inhibitor N3 (positive control)	-7.9
Remdesivir (positive control)	-7.8
Resveratroloside	-7.2
Piceatannol	-7.0
Resveratrol	-6.9
Oxyresveratrol	-6.8
Rhapontigenin	-6.8
Pinosylvin	-6.5
Pterostilbene	-6.4
4-Hydroxystilbene	-6.2
3,4,5,4′-Tetramethoxystilbene	-6.0

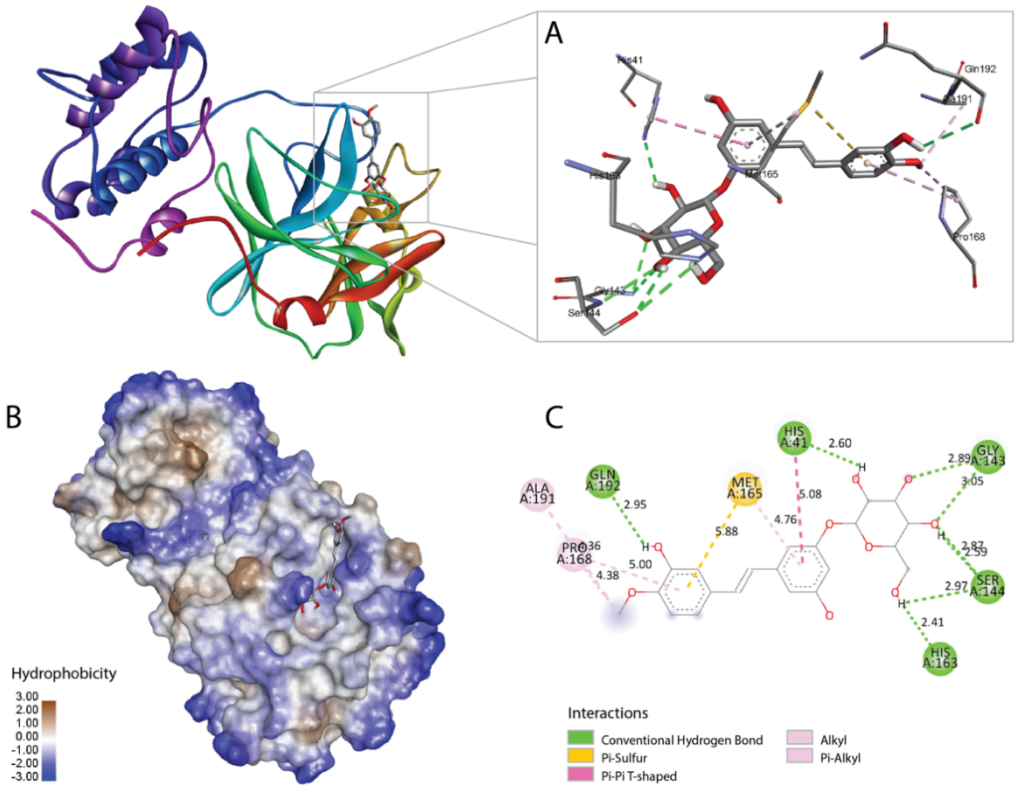

Figure 4 Visualization of docking interaction of rhaponticin with 6LU7. (A) 3D representation of the interaction between amino acid residues and rhaponticin; (B) 3D visualization of hydrophobicity surface; (C) 2D representation of the interaction elucidating the bindings of rhaponticin with the active site of 6LU7.

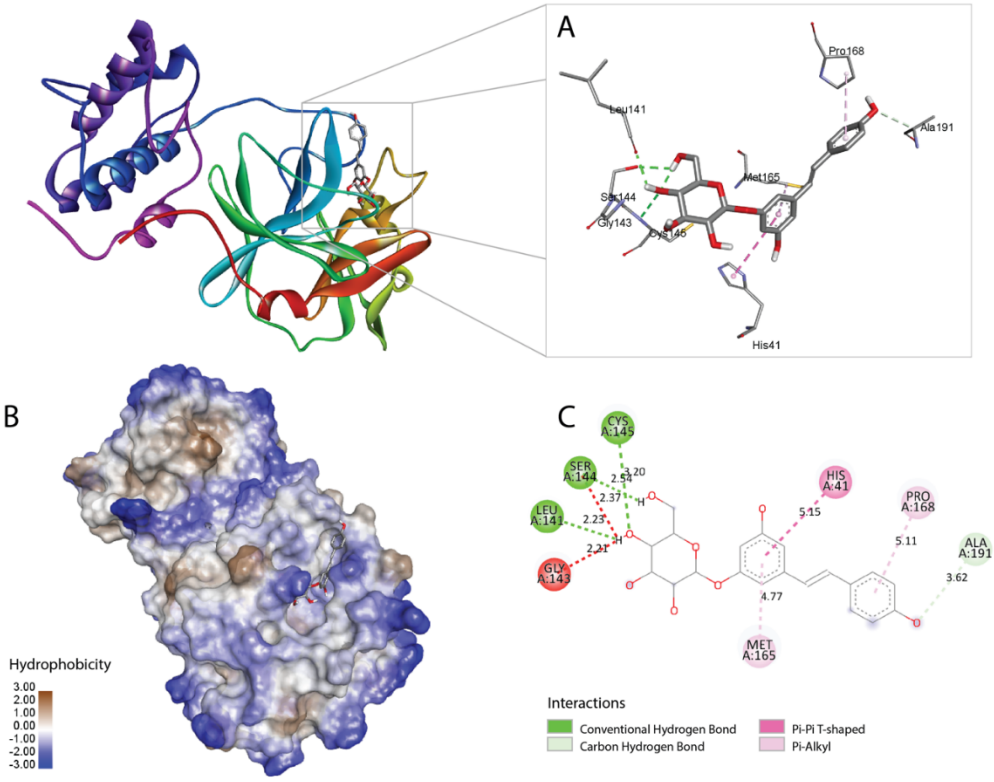

Figure 5 Visualization of docking interaction of polydatin with 6LU7. (A) 3D representation of the interaction between amino acid residues and polydatin; (B) 3D visualization of hydrophobicity surface; (C) 2D representation of the interaction elucidating the bindings of polydatin with the active site of 6LU7.

3.2 Drug-likeness Prediction

Drug-likeness computational methods are used to screen potential drug candidates from non-drug molecules. It evaluates a compound's potential as an oral medication. This prediction accelerates the drug discovery process and eliminates wastage of resources. In this study, OSIRIS Property Explorer was used to measure the drug-likeness of the lead ligands (polydatin and rhaponticin) and control ligands. Parameters like partition coefficients (cLog P), solubility (Log S), topological polar surface area (TPSA) and molecular weight are measured to evaluate the capability of the ligands as potent drugs. cLog P measures the lipophilicity of ligands, estimating the dispersal of drugs within the body. It also predicts the absorption of drugs across the intestinal epithelium. Hydrophobic drugs with high cLog P are mainly distributed to hydrophobic areas such as lipid bilayers of cells. Conversely, hydrophilic drugs with low cLog P are found primarily in aqueous regions such as blood serum (Lipinski *et al.*, 2001). Ideally, a good drug candidate should have cLog P equal to 0, indicating the drug has equal lipophilicity and hydrophilicity. cLog P for both rhaponticin and polydatin are 0.77 and 0.84 respectively (Table 5). These numbers are below the upper limit for drug penetration which is cLog P below 5. The cLog P for rhaponticin and polydatin is also near 0.

Solubility denoted by Log S is another important parameter which significantly affects drug absorption and distribution properties. A low aqueous solubility contributes to bad absorption. Approximately 80% of the drugs available today have Log S value bigger than -4. Our study found that rhaponticin and polydatin have solubility greater than -4 with -2.77 and -2.75 respectively while remdesivir and inhibitor N3 have solubility lower than -4 with -4.99 and -4.87 respectively (Table 5).

Drug capability to permeate cell membrane is a crucial factor in determining the success rate of drug delivery and absorption. The surfaces that the oxygen, nitrogen and hydrogen atoms occupy as well as the hydrogen atoms bonded to them are used to determine the TPSA. As a result, TPSA is related to the ability of a compound to form hydrogen bonding (Deconinck *et al.*, 2007). TPSA values of more than 140 Å2

indicate poor intestinal absorption of the drug while TPSA values lower than 90 Å2 is preferable for a molecule to easily penetrate the blood brain barrier which can eventually react with receptors in the central nervous system. The TPSA values for rhaponticin and polydatin are 149 and 139.8 respectively (Table 5). In contrast, the TPSA values for remdesivir and inhibitor N3 are 213.3 and 197.8 respectively.

Table 5 Drug-likeness prediction of the lead ligands and controls.

Ligand	*c* Log P	Solubility Log S	Molecular Weight	TPSA	Drug Score
Remdesivir	0.3	-4.99	602	213.3	0.05
Inhibitor N3	1.66	-4.87	680	197.8	0.21
Rhaponticin	0.77	-2.77	420	149	0.24
Polydatin	0.84	-2.75	390	139.8	0.25

Apart from cLog P lower than 5, Lipinski's rule-of-five states that any candidate drug should have molecular weight lower than 500, hydrogen bond donors lower than 5 and hydrogen bond acceptors lower than 10. Lipinski's filter is the pioneer rule-of-five which is used by pharmaceutical companies in optimizing their drug quality. As shown in Table 5, in comparison to remdesivir and inhibitor N3, which have molecular weights of 602 and 680, rhaponticin and polydatin have 420 and 390, respectively. Increasing the molecular weight of molecules is usually often associated with optimising them for high activity on biological targets. However, a molecule with higher molecular weight has a lower likelihood of being absorbed and reaching target site. Therefore, every drug forger should aim to keep molecular weights as low as possible.

3.3 ADMET Prediction

ADMET properties, as derived from admetSAR server indicate that rhaponticin and polydatin had lower human intestinal absorption (HIA) score than the control ligands. A higher human intestinal absorption indicates that the substance may be more effectively absorbed from the intestinal tract when taken orally. Furthermore, the penetration of rhanponticin and polydatin through the blood-brain barrier (BBB) is lower than the control ligands as indicated in Table 6. All control ligands and lead ligands show negative AMES toxicity and carcinogenicity (Table 6). In term of metabolism, all ligands were nonsubstrates and noninhibitors. Information on median lethal dose (LD50), a compound with lower dose is more lethal than the compound having higher LD50. Rhaponticin and polydatin had LD50 of 1.766 and 1.803 respectively indicating the toxicity of the compounds. Table 6 illustrates the various ADMET parameters obtained from admetSAR tool. Figure 6 depicts the comparative LD50 values of the lead ligands and the control ligands.

Table 6 ADMET prediction profiles of the lead ligands and controls.

Ligand	HIA	BBB	CYP Inhibition/substrate	Ames Toxicity	Carcinogenicity	LD50 in Rat
Remdesivir	0.8231	0.6500	Nonsubstrate/noninhibitor	Nontoxic	Noncarcinogenic	2.610
Inhibitor N3	0.9543	0.7750	Nonsubstrate/noninhibitor	Nontoxic	Noncarcinogenic	3.003
Rhaponticin	0.7123	0.5250	Nonsubstrate/noninhibitor	Nontoxic	Noncarcinogenic	1.766
Polydatin	0.7754	0.6500	Nonsubstrate/noninhibitor	Nontoxic	Noncarcinogenic	1.803

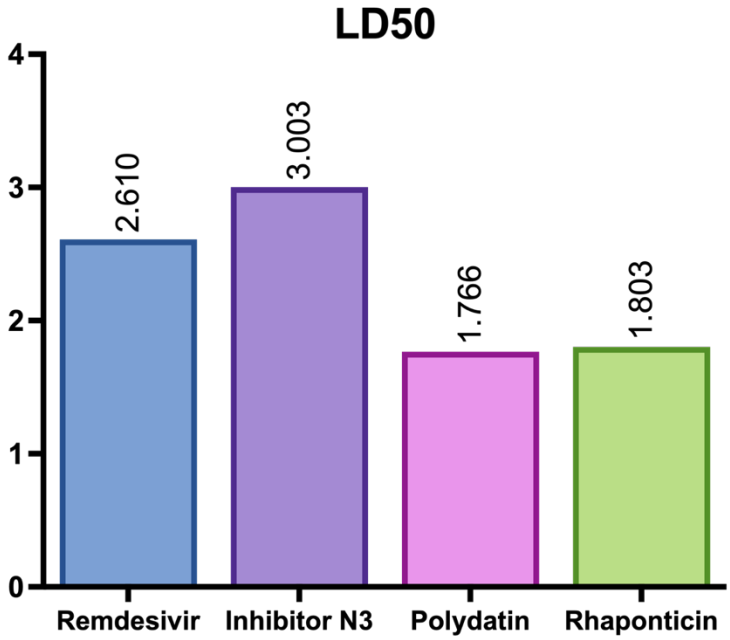

Figure 6 Comparative LD50 of the lead ligands and controls.

4. Conclusion

Molecular docking has been utilised in drug research and design in recent years. The investigation revealed that the compounds, polydatin and rhaponticin, have the potential to be exploited as inhibitors against SARS-CoV-2 M^{pro}. These compounds interact with amino acids in the hydrophobic cavity of the targets, producing hydrophobic interactions that significantly contribute to the stabilization of ligands at the binding interface. ADMET prediction analyses also showed that these compounds exhibit drug score with oral bioavailability comparable to the existing drugs. However, LD50 results verified that rhaponticin and polydatin exhibit less favourable characteristics that could be harnessed as prospective therapies for SARS-CoV-2 M^{pro}. In addition, this work also lacks biological experimental evidence that should be addressed in future research.

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