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In-Silico Analysis of Phytochemicals as Potential Inhibitors of SARS-CoV-2 NSP-12

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ABSTRACT

Background: The coronavirus disease-19 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2), has a huge global impact.

Purpose: The only known preventive measures or therapies for COVID-19 at this time are physical segregation and aerial barriers between individuals. Researchers in the academic and industrial sectors are currently in urgent need of COVID-19 remedies, including vaccines to stop the virus's spread. Even if the widespread vaccination campaign has helped to limit the rate of death, the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues three and a half years after the pandemic began and the anticipated endemic transition. After the health emergency state was declared to be over, we are seeing a global loosening of preventive measures, a return to pre-pandemic mobility patterns, and an ever more coerced coexistence with the virus.

Methods: In the present study, the ability of SARS-CoV-2 proteins to bind natural substances, which is essential for host cell interaction and infection was examined. Using in silico tools and techniques, the docking analysis of Dibutyl phthalate, Betulin and Stigmasterol against SARS-CoV-2 non-structural protein-12 (NSP-12) was done.

Results: It was observed that stigmasterol had the highest binding affinity (-8.1 kcal/mol) for NSP-12 protein of SARS- CoV-2 followed by betulin (-6.9 kcal/mol) and DIBP (Dibutyl Phthalate) had the lowest affinity (-6.3 kcal/mol).

Conclusion: Based on current research, it was suggested that stigmasterol is a potential phytochemical to be tests against NSP-12 protein of SARS CoV-2 and can be used as antivirus drug.

1. Introduction

A cluster of pneumonia episodes in patients connected to a seafood market in Wuhan, China, in late 2019 led to the discovery of a novel coronavirus (SARS-CoV-2). Humans were infected by SARS-CoV-2, which led to the development of COVID-19. Over 542.18 million individuals had been infected as of June 29, 2022, and 6.32 million had died as a result of the infection. Notably, the biggest number of COVID-19 cases has been officially reported from the United States of America (USA), Russia, Brazil, France, Germany, and India. SARS-CoV-2 has a substantially lower projected death ratio (2.96%) than the previously reported SARS (Severe Acute Respiratory Syndrome), which was first identified in 2003. In case of SARS-CoV-2, the number of cases is growing quickly. The majority of infection in SARS- CoV-2 cases are asymptomatic raises substantial health concerns (Gautam *et al.,* 2020; Mehrotra & Sood, 2019). Researchers in the academic and industrial sectors are currently in urgent need of COVID-19 remedies, including vaccines to stop the virus's spread (Almadani & Alshammari, 2022). Even if the widespread vaccination campaign has helped to limit the rate of death, the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues three and a half years after the pandemic began and the anticipated endemic transition (Machado *et al.,* 2022). After the health emergency state was declared to be over, we are seeing a global loosening of preventive measures, a return to pre-pandemic mobility patterns, and an ever more coerced coexistence with the virus. Many lineages deriving from the Omicron BA.2 and BA.5 variants have emerged in recent months, including BQ.1, BQ.1.1, BA.4.6, BA.2.75.2, BF.7, and the recombinant XBB and its sub-variants, such as XBB1.5, which as of June

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2023 represents the most frequent sequence among those reported to the Global Initiative on Sharing All Influenza Data (GISAID). The well-known BA.2, BA.4, and BA.5 were de-escalated from the list of variations Of Concern (VOCs) on March 15, 2023, as a result of changes made by WHO to the monitoring and definition criteria in light of the ongoing evolution of the variations landscape (Islam *et al.,* 2023). The scientific community's efforts have resulted in an increased understanding of the virus's pathogenic and molecular mechanisms, as well as its evolution and symptoms. Additionally, new therapeutic approaches for treating the primary infection and its long-term effects, such as Long COVID, have been developed (Cascella, 2020), and next-generation mucosal vaccines that may serve as the foundation for combating other respiratory viruses have also been developed (Dotiwala & Upadhyay, 2023). A key strategy for finding anti-COVID drugs is to target several enzymes with treatments (Ng *et al.,* 2022). Nowadays, the in-silico approach to search for potential compounds against a variety of protein targets can be done quickly and easily (Zhang *et al.,* 2022). Like other coronaviruses, SARS-CoV-2 spreads throughout the host using an error-prone replicating mechanism. Using the cellular resources of the host, the nsp12 enzyme catalyzes the production of viral RNA (Cheng *et al.,* 2005). Because of its vital function, nsp12 is essential for the spread of viruses. Any interference with its function can prevent SARS-CoV-2 from replicating, lowering the viral load and delaying the course of the illness (Hillen *et al.,* 2020). According to computational research, these flavonoids might bind to nsp12, providing a fresh method of preventing viral replication with possibly fewer adverse effects (Tuli *et al.,* 2022).

An in silico approach was used to test FDA-approved Prestwick Chemical Library's 1520 compounds against MERS-CoV and SARS-CoV (Kumar *et al.,* 2021). Computationally molecular docking studies were reported to target spike protein of SARS-CoV-2 with three phytochemicals Quercetin, Kaempferol, and Apigenin and among them Quercetin was found to be used as a potential inhibitor against SARS-CoV-2 (Tuli *et al.,* 2022). The phytochemicals have previously been explored for pharmacological potentials whereas stigmasterol, betulin, and Dibutyl phthalate interacting with RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2 and NSP 12 proteins remain unexplored. Zhang *et al.* 2022 studied the antitumor effect of stigmasterol, triggering apoptosis by regulating the PI3K/Akt signaling pathway and found to inhibit malignancies and cell proliferation. Recent studies suggested that natural plant-based compounds such as flavonoids, alkaloids and others can be used to develop effective drug against SARS-CoV (He *et al.,* 2023; Majnooni *et al.,* 2021). Similarly, many computational analyses of phytochemicals have been used to inhibit the virulent protein i.e. spike and proteases protein of SARS CoV (Nag *et al.,* 2021). Non-structural proteins (NSP) present in SARS-CoV-2, are responsible for the virus's capacity to endure and are safeguarded in the host environment. Recently, two new synthesized active compounds (ZG-5 and ZG-7) showed inhibitory action against NSP-12 of SARS-CoV-2 (Gerçek *et al.,* 2021). In 2020, Lucas-G'omez conducted a study by using Betalains and Alfa-Bisabolol, natural compounds that were also reported as a potential inhibitor against NSP-12 (Lucas-Gómez *et al.,* 2020). Therefore, in the present study, an in-silico approach was used to test synthetic compounds against SARS-CoV-2 non- structural protein (NSP-12).

Compared to the current class of pharmaceuticals used for human health, natural products offer a rich source of innovative bioactive chemicals and various chemical scaffolds. Although such chemicals are quite abundant in other therapeutic situations, there are currently no licensed medications generated from plant sources. This represents a substantial and unexplored resource for the development of antibacterial and antiviral drugs (Chaachouay & Zidane, 2024). A large number of the medicinal drugs that are currently on the market were produced by compounds that were isolated from natural sources, mostly plants and microorganisms. The availability of highly standardized libraries of NPSM and extracts with guaranteed resourcing of lead extracts or compounds is the consequence of recent developments in the field of phytochemistry and the technologies related to extracting and pre-fractionating the extracts, as well as characterizing the lead compounds from complex mixtures of NP extracts. For instance, of 175 anti-cancer medications licensed between 1940 and 2014, 49% were either directly derived from NP or NP itself (Newman & Cragg, 2016; Newman & Cragg, 2020). NPSM and its structures have a noteworthy influence in other domains, like anti-infective agents. The fields of NP research have greatly increased since a large number of NP leads and medications are initially created by microorganisms or microbial interaction with host (Wang *et al.,* 2017). The majority of the current strategies used in NP antiviral drug development efforts have been based on small-scale random screening of NP compounds and extracts. For the development of new antiviral drug discovery paradigms, the current repository of NP from plant, marine, and microbial cultures collections offer an unrivalled supply of NP. Apart from extracts exhibiting strong antiviral properties, fractionation of extracts with moderate activity is necessary to guarantee that minor but crucial components in biological screening are not overlooked because of their low quantity. More hits are anticipated from the application of pre-fractionation utilizing sequential solvent extraction and fractionation with C18 cartridges and other high throughput technologies (Gomez *et al.,* 2021).

2. Methodology

In the present study various online bioinformatics servers and tools were used to study dibutyl phthalate, betulin, and stigmasterol interactions with SARS-CoV-2 NSP-12, listed in Table 1.

Table 1: Enlists the Names and URL Addresses of the Online Resources, Databases and Servers

Online Tools	URL Links
RCSB Protein Data Bank	https://www.rcsb.org/
PubChem	https://pubchem.ncbi.nlm.nih.gov/
Open Babel	https://openbabel.org/
MGL Tools (Autodock Tools)	https://ccsb.scripps.edu/mgltools/
Biovia Discovery Studio	https://discover.3ds.com/

2.1. Preparation of 3-D Structure of Target

The three-dimensional structure of SARS-CoV-2 non-structural protein NSP-12 (PDB ID: 6NUR) was downloaded from RCSB PDB database in PDB format (Figure 1). The target protein was entered into the Autodock tools software. The protein was then prepared for docking by deleting water molecules, adding hydrogen and charges (Kollman charges) to target. The pdb file was converted to pdbqt file.

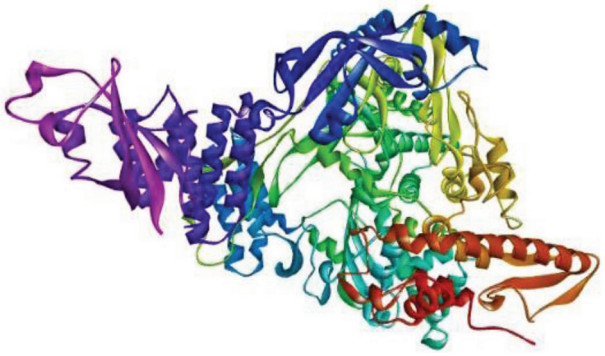

Figure 1: Crystal Structure of SARS-CoV-2 NSP-12

2.2. Preparation of Ligands

The natural compounds dibutyl phthalate, betulin, and stigmasterol were selected as ligand molecules. The 3D structure of ligand molecules was downloaded from the PubChem database in the form of SDF (structured data format) files and shown in Figure 2. Open Babel was used for converting SDF file into PDB file. Lipinski's rule of five of ligands were considered and summarized in Table 2. Ligands were prepared by Auto dock vina (Trott & Olson, 2009).

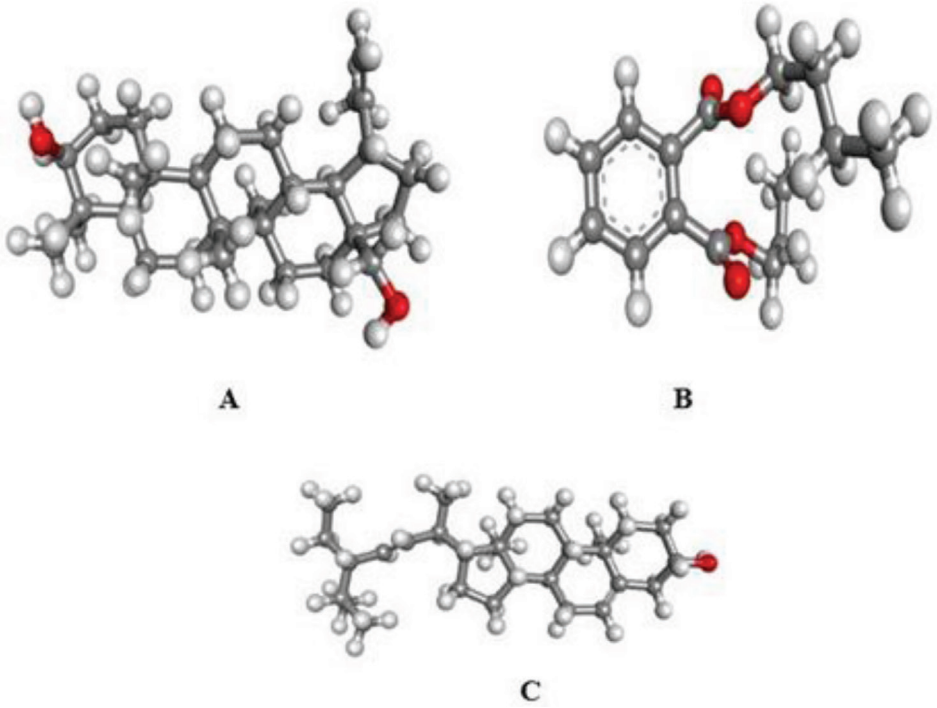

Figure 2: 3-D Structures of Ligands. Betulin (A), Dibutyl Phthalate (B), Stigmasterol (C)

Table 2: Physiochemical Properties of Ligands

S.No.	Ligands	PubCh em ID	ADME Properties (Lipinski's Rule of Five)		Drug Likeli ness
			Propert ies	Values	
1.	Betulin	72326	Molecular weight (<500Da)	442	Yes
			LogP (<5)	5.2	
			H-bond donor (5)	2	
			H-bond acceptor (<10)	2	
			Molar refractivity	132.06	
2.	Stigmasterol	5280794	Molecular weight (<500Da)	412	Yes
			LogP (<5)	7.8	
			H-bond donor (5)	1	
			H-bond acceptor (<10)	1	
			Molar refractivity	128.122	
3.	Dibutyl Phthalate	3026	Molecular weight (<500Da)	312	Yes
			LogP (<5)	0.05	
			H-bond donor (5)	5	
			H-bond acceptor (<10)	6	
			Molar refractivity	77.14	

2.3. Docking Analysis

The molecular docking analysis of all the selected phytocompounds were subjected to AutoDock tools (MGLTools 1.5.6.) AutoDock Vina 1.1.2, using the script standard method. AutoDock Vina 1.1.2, a popular docking program that is renowned for its speed and accuracy in predicting ligand-receptor interactions. Grid boxes with specific dimensions and a 0.3 spacing were to be created. The exhaustiveness value was 8 in docking. The interaction of docked protein-ligand structures was visualized by Discovery Studio Visualizer tool (Trott & Olson, 2009).

3. Results

Utilizing natural remedies and small antiviral compounds generated from plants is an excellent way to deal with severe viral infections. By using bioactive substances derived from plants and herbs, against SARS-CoV-2 proteins, molecular docking studies have been conducted to identify effective medications and bioactive phytochemicals to either prevent or treat COVID-19 [14]. The crystal structure of SARS CoV- 2 NSP 12 polymerase bound to nsp 5 and nsp 8 having three chains i.e. A, B and, among three chains only chain A was computationally docked

against three studied compounds. The best compound i.e., Stigmasterol scored -8.1 kcal/mol (Table 3) with SARS-CoV-2 non-structural protein NSP-12 complex forming alkyl interactions with Arg457, Pro675, Val677 residues present in the target protein (Figure 3). Swaminathan *et al.* 2021 investigated inhibitory efficiency of stigmasterol from Andrographis paniculata against SARS COV-2 proteins. The result revealed that stigmasterol also showed the highest docking scores against the membrane protein (-9.9 kcal/mol), NSP9 (-7.8 kcal/mol).

Table 3: Binding Affinities and RMSD Values of Stigmasterol Against SARS-Cov-2 NSP-12

Mode	Affinity (kcal/mol)	Distance from Best Mode	
		rmsd l.b	rmsd u.b
1	-8.1	0.000	0.000
2	-7.4	3.889	10.229
3	-7.3	3.416	9.862
4	-7.1	7.651	9.609
5	-6.9	9.618	12.308
6	-6.9	25.037	28.023
7	-6.8	30.876	32.967
8	-6.8	26.021	27.340
9	-6.8	17.631	21.566

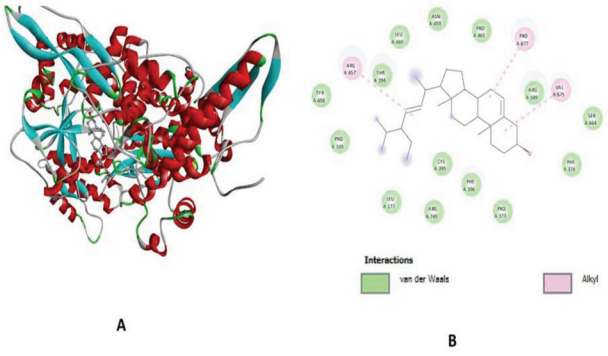

Figure 3: Binding Interactions of Stigmasterol with SARS-Cov-2 NSP 12. (A) 3-D View (B), 2-D View of Interactions

Compound betulin shows a significant binding affinity of - 6.9 kcal/mol (Table 4) by targeting Asn59 and Thr319 via conventional hydrogen bonding and carbon-hydrogen bonding interactions (Figure 4). Further, dibutyl phthalate exhibits a minimum binding affinity of -6.3 kcal/mol (Table 5) and shows a significant binding interaction through conventional hydrogen bonding, carbon-hydrogen bonding, amine π stacked, and π-sulfur (Figure 5).

Table 4: Binding Affinities and RMSD Values of Betulin against SARS-CoV-2 NSP-12

Mode	Affinity (kcal/mol)	Distance from Best Mode	
		rmsd lb	rmsd u.b
1	-6.9	0.000	0.000
2	-6.9	5.562	8.573
3	-6.8	29.580	33.020
4	-6.7	29.463	33.967
5	-6.6	5.262	8.651
6	-6.6	1.912	7.814
7	-6.6	2.080	8.322
8	-6.4	4.586	7.175
9	-6.4	6.855	9.827

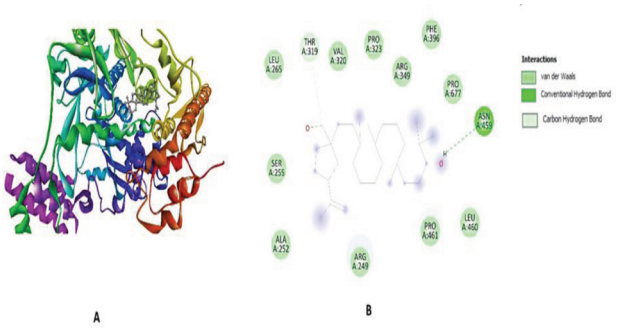

Figure4: Binding Interactions of Betulin with SARS- Cov-2 NSP 12. (A) 3-D View (B), 2-D View of Interactions

Table 5: Binding Affinities and RMSD Values of DIBP against SARS-Cov-2 NSP-12

Mode	Affinity (kcal/mol)	Distance from Best Mode	
		rmsd l.b	rmsd u.b
1	-6.3	0.000	0.000
2	-6.1	1.051	4.823
3	-5.8	2.220	3.561
4	-5.7	2.274	5.363
5	-5.7	1.916	2.471
6	-5.3	2.383	3.935
7	-5.3	32.105	33.972
8	-5.3	32.724	34.424
9	-5.2	1.890	2.770

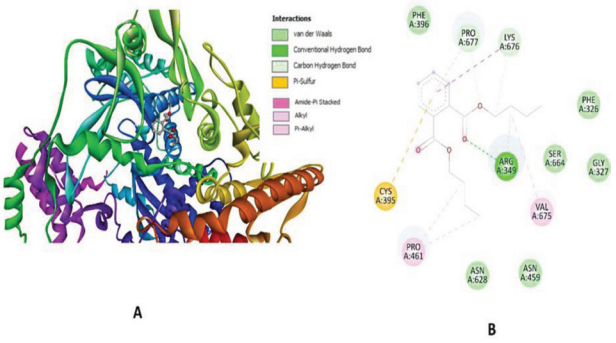

Figure 5: Binding Interactions of DIBP with SARS-Cov- 2 NSP 12. (A) 3-D View (B), 2-D View of Interactions

4. Discussion and Conclusion

Several antiviral and antimalarial medications were examined for their potential usage in treating COVID-19 for the specific anti-SARS-CoV-2 activity via the main viral protease. The interactions between ligands and receptors help in the development of new drugs or cures for chronic diseases (Sarhan *et al.,* 2021; Rahmah *et al.,* 2022). Recently, several studies have reported that in vitro and in silico screening of bioactive compounds from medicinal plants leads to identifying their therapeutic properties (Al-Mahrami *et al.,* 2024; Duraisamy *et al.,* 2024; Zafar *et al.,* 2024). In silico and in vitro analysis of bioactive compounds extracted from Ocimum basilicum against vancomycin-resistant enterococci. Previously, many in-silico analyses of various natural compounds against SARS- CoV-2 were reported in the literature, and the natural compounds can bind and inhibit the SARS- CoV-2 virulent protein. Our results agree with some previous reports. Stigmasterol was found in a wide range of natural sources and extracts of medicinal plants (Bakrim *et al.,* 2022). In silico analysis of Vigna radiata and Vigna mungo, stigmasterol was found to have high binding energy against SARS-CoV-2 proteins (Jannat *et al.,* 2020). Similarly, several phytosterols including stigmasterol docked against SARS-CoV-2 proteins. The phytosterols showed strong and highest binding affinity against Mpro SARS-CoV-2 protein (Rahmatullah, 2021). In another study, Stigmasterol found to have higher binding affinities against 3 chymotrypsin-like protease (3CLpro) inhibitors of novel coronavirus (Sharma *et al.,* 2023). Burkhanova *et al.* 2022 investigated betulin against SARS- CoV-2 protein. The result revealed strong binding interactions of botulin against targeted protein.

When it comes to natural compounds, new molecules are continually being discussed in the scientific literature, and their biological effectiveness against virulent protein is being evaluated by computational analysis. In the current study selected phytochemicals were docked computationally with SARS-CoV-2 NSP-12 protein and the binding affinity was found to be the range of -6.3 to -8.1 kcal/mol. The most effective phytochemical i.e., stigmasterol was chosen as a potential therapeutic candidate for further investigation. According to the results of the docking study, stigmasterol shows a strong affinity for nsp12, indicating that it may be used as an inhibitor of SARS-CoV-2. Its effectiveness and drug-like qualities will need to be confirmed by additional research, such as molecular dynamics simulations, in vitro enzymatic tests, and in vivo studies. Stigmasterol's potential as a therapeutic candidate against SARS-CoV-2 will be determined in part by these further investigations.

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Authorship Contribution

Shallu Saini: Conceptualization and data collection; Poonam Bansal: Conceptualization, data collection, writing, and editing; Gurpreet Kaur Bhatia: Conceptualization and data collection; and Hardeep Singh Tuli: Conceptualization, write-up, and editing etc.

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Conflict of Interest

Authors declare that there is no conflict of interest.

Ethical Approvals

No ethical approvals were required for this study.

Declaration

It is an original article and has been neither sent elsewhere nor published anywhere.

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