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Targeting Omicron (B.1.1.529) SARS CoV-2 spike protein with selected phytochemicals: an in-silico approach for identification of potential drug

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KEYWORDS

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ABSTRACT

Severe acute respiratory syndrome coronavirus -2 (S ARS-CoV-2) emerging variants particularly those of concern contain numerous mutations that influence the behavior and transmissibility of the virus and could adversely affect the efficacies of existing coronavirus disease 2019 (COVID-19) vaccines and immunotherapies. The emerging SARS-CoV-2 variants have resulted in different waves of the pandemic within the ongoing COVID-19 pandemic. On 26 November 2021 World Health Organization designated omicron (B.1.1.529) as the fifth variant of concern which was first reported from South Africa on November 24, 2021, and thereafter rapidly spread across the globe owing to its very high transmission rates along with impeding efficacies of existing vaccines and immunotherapies. Omicron contains more than 50 mutations with many mutations (26-32) in spike protein that might be associated with high transmissibility. Natural compounds particularly phytochemicals have been used since ancient times for the treatment of different diseases, and owing to their potent anti-viral properties have also been explored recently against COVID-19. In the present study, molecular docking of nine phytochemicals (Oleocanthal, Tangeritin, Coumarin, Malvidin, Glycitein, Piceatannol, Pinosylnin, Daidzein, and Naringenin) with omicron spike protein (7QNW (electron microscopy, resolution 2.40 Å) was done. The docking study revealed that selected ligands interact with the receptor with binding energy

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in the range of -6.2 to-7.0 kcal/mol. Pinosylnin showed the highest binding energy of -7.0 kcal/mol which may be used as potential ligands against omicron spike protein. Based on the docking studies, it was suggested that these phytochemicals are potential molecules to be tested against omicron SARS-CoV-2 and can be used to develop effective antiviral drugs.

1 Introduction

The ongoing coronavirus disease 2019 (COVID-19) pandemic has posed a serious risk to the lives of humans across the world (Dhama et al. 2020; WHO 2022a). COVID-19 was first originated in December 2019 in China (Kim et al. 2020) and later spread globally as a deadly pandemic. The β-coronavirus (novel enveloped RNA) was found responsible for causing an infectious disease named COVID-19, which was phylogenetically similar to the severe acute respiratory syndrome coronavirus (SARS-CoV), and thus this pandemic virus was named SARS-CoV-2 (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses 2020; Owis et al. 2020). Since the SARS-CoV-2 pandemic virus has emerged it has undergone many mutations and evolved into various variants and mutants, and till date of April 2, 2022, five variants of concerns (VOC) of SARS-CoV-2 have emerged namely Alpha, Beta, Gamma, Delta, and Omicron (WHO 2022b). On 26 November 2021, World Health Organization (WHO) designated omicron (B.1.1.529) as the fifth variant of concern (VOC) that was reported from South Africa on 24 November 2021. As a most mutated SARS-CoV-2 variant, it is known to have more than 50 mutations in its genome, of which 26-32 mutations are present in spike proteins, which are related to humoral immune escape potential and high transmissibility rate (Shishir et al. 2022; Hanai 2022). Omicron has a doubling time of 2-3 days and has recently caused a very high surge in COVID-19 cases across the globe while posing high public health concerns owing to its adverse impacts on the effectiveness of existing COVID-19 vaccines and antibodies-based therapies resulting in breakthrough infections in vaccinated persons and reinfection in recovered patients, and presently different lineages of Omicron variant are being evolved that might increase the fears amid the pandemic (Khandia et al. 2022; Mohapatra et al. 2022; WHO 2022b). As of April 2, 2022, more than 486 million confirmed cases and over 6.1 million deaths have been reported worldwide due to COVID-19 (WHO 2022b).

Certain drugs having effectiveness against COVID19 had been reported in the literature including chloroquine, ritonavir, ribavirin, hydroxychloroquine, and oseltamivir, but these were not effective in immunocompromised patients (Narkhede et al. 2020; Ozdemir et al. 2022). Scientists have been working to find potential drugs for COVID-19. Recently, research has been carried out on natural plant-based compounds i.e., phytochemicals which include alkaloids, flavonoids, and other compounds that can be used in COVID-19 treatment (Vardhan and Shood 2020; Pandey et al. 2021; Tuli et al. 2022). Phytochemicals possess various beneficial health-promoting properties including antioxidant and immunomodulatory activities and are gaining interest as they have multiple beneficial effects on the health of human beings including serving as potent anti-viral agents, and have also been reported to act against SARS-CoV-2 (Dhama et al. 2018; Anand et al. 2021; Zrig 2022). Flavonoids are secondary metabolites (produced by plants), which play a wide role in plant physiology such as antiviral, antioxidant, antifungal, anti-inflammatory, antibacterial, and anti-cancer activities (Wang et al. 2018a). Naringenin is a flavanone found in some edible fruits, like *Citrus* species and tomatoes (Zobeirie et al. 2018), exhibited cardioprotective, antitumor, antibacterial, antiviral, antiadipogenic, anti-inflammatory, and antioxidant activity (Salehi et al. 2019). Diosmetinis found in *Acacia farnesiana* Wild legume and *Olea europaea* L. leaves are reported to show anti-inflammatory, anticancer, antioxidant, and antimicrobial activities (Wang et al. 2018b). Another phytochemical Pinosalvin possessed antifungal and antibacterial activity (Lee et al. 2005). Piceatannol, a polyphenolic stilbene that is found in various vegetables and fruits has been reported to exhibit anti-inflammatory and anticancer activity (Kershaw and Kim 2017). In-silico studies have revealed that many phytochemicals i.e., fisetin, quercetin, kamferol, curcumin, glycyrrhizic acid, maslinic acid, ursolic acid can act as potential drugs against targeted proteins of COVID-19 (Pandey et al. 2021). Therefore, the present work was planned to find out which natural compounds can inhibit SARS-CoV-2 viral spike protein, and thus docking studies of phytochemicals with the Omicron S-glycoprotein were carried out.

2 Materials and Methods

2.1 Retrieval of Receptor three-dimensional structure

The three-dimensional crystal structure of the Omicron spike glycoprotein with PDB ID: 7QNW with a resolution of 2.40 Å was downloaded from the online database Research Collaboratory Structural Bioinformatics-Protein Data Bank (RCSB-PDB) (Figure 1) (Dejnirattisai et al. 2021). The protein model was prepared by excluding heteroatoms and water molecules.

2.2 Ligand's preparation and analysis of ADME properties

Nine ligands were selected for virtual screening. The ligands library was prepared by downloading the 3-D structures of all the ligands from the PubChem database in sdf format and all structures were

converted into pdb format by OpenBabel (Figure 1). The online software tool was used to determine ADME (Unfavorable absorption, distribution, metabolism, and elimination) profiling of all the ligands (pH 7) (Jayaram et al. 2012). Lipinski's rule of five, including physicochemical properties of ligand viz. molar refractivity, molecular weight (<500 Da), H-bond acceptor (<10), H-bond donor (5), LogP (<5), and drug likeliness were considered (Lipinski 2004) (Table 1).

Table 1 Physio-chemical or ADME Properties of ligands

S. N.	Ligands	ADME Properties (Lipinski's Rule of Five)		Drug Likeliness
		Properties	Values	
1.	Oleocanthal	Molecular weight (<500 Da)	304	Yes
		LogP (<5)	2.2	
		H-bond donor (5)	1	
		H-bond acceptor (<10)	5	
		Molar Refractivity	81.3	
2.	Tangeritin	Molecular weight (<500 Da)	372	Yes
		LogP (<5)	3.3	
		H-bond donor (5)	0	
		H-bond acceptor (<10)	7	
		Molar Refractivity	98.5	
3.	Coumarin	Molecular weight (<500 Da)	146	Yes
		LogP (<5)	1.6	
		H-bond donor (5)	0	
		H-bond acceptor (<10)	2	
		Molar Refractivity	41.1	
4.	Malvidin	Molecular weight (<500 Da)	331	Yes
		LogP (<5)	3.03	
		H-bond donor (5)	4	
		H-bond acceptor (<10)	7	
		Molar Refractivity	85.1	
5.	Glycitein	Molecular weight (<500 Da)	284	Yes
		LogP (<5)	2.7	
		H-bond donor (5)	2	
		H-bond acceptor (<10)	5	
		Molar Refractivity	75.7	
6.	Piceatannol	Molecular weight (<500 Da)	244	Yes
		LogP (<5)	2.6	
		H-bond donor (5)	4	
		H-bond acceptor (<10)	4	
		Molar Refractivity	68.4	
7.	Pinosylnin	Molecular weight (<500 Da)	212	Yes
		LogP (<5)	3.2	
		H-bond donor (5)	2	
		H-bond acceptor (<10)	2	
		Molar Refractivity	6.1	
8.	Daidzein	Molecular weight (<500 Da)	254	Yes
		LogP (<5)	2.7	
		H-bond donor (5)	2	
		H-bond acceptor (<10)	4	
		Molar Refractivity	69.1	
9.	Naringenin	Molecular weight (<500 Da)	272	Yes
		LogP (<5)	2.5	
		H-bond donor (5)	3	
		H-bond acceptor (<10)	5	
		Molar Refractivity	70.19	

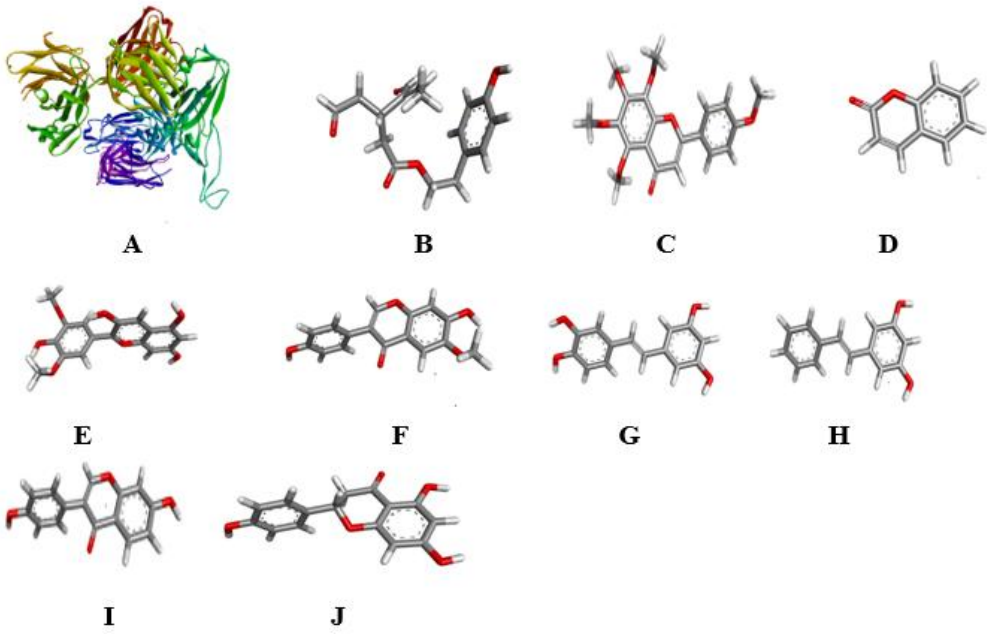

Fig 1 3D view of the receptor (A) Chemical structures of Oleocanthal (B), Tangeritin (C), Coumarin (D), Malvidin (E), Glycitein (F), Piceatannol (G), Pinosylnin (H), Daidzein (I) and Naringenin (J).

2.3 Molecular docking of ligands with Omicron Spike-glycoprotein

For virtual screening and binding studies, PyRx v0.8 was used. Universal Force Field (UFF) was applied for energy minimization of ligands and then OpenBabel convert ligands into.pdbqt (O'Boyle et al. 2011). Docked structures with high binding affinity were analyzed using PyMOL and Discovery Studio Visualizer.

3 Results and Discussion

A computational method is considered an important approach to search for potential drug candidature. *In-silico* virtual screening offers the advantages of rapid, convenient, and cost-effective testing. Computational studies suggested a mechanism for binding targets proteins to tested molecules (Skariyachan et al. 2020). In computer-aided molecular docking, the highest binding affinity score for the potential ligand in the active site of the receptor is calculated. Molecules binding with the highest binding affinity and least binding energy were the most stable binding with the target protein. Ligands with significant binding affinities were selected. Results revealed that Oleocanthal, Tangeritin, Coumarin, Malvidin, Glycitein, Piceatannol, Pinosylnin, Daidzein, and Naringenin showed the binding affinity in the range of -6.2 to-7.0 kcal/mol with receptor molecule (Table 2).

Docking studies revealed that among nine ligands Pinosylnin showed the best binding with a binding affinity of -7.0 kcal/mol. The ligands interact with Leu398, Ser446, 32,469, Tyr61,35,508, Pro103, Glu 471, Gln 506, Asn 49,437, Arg 4554, Lys 458 residues of omicron spike glycoprotein. The binding energy of studies ligands were depicted in Table 2. The docked pose of ligand and Glycoprotein (PDB ID: 7QNW) receptor has been shown in Figures 2, 3, 4, 5, 6, 7, 8, 9, and 10.

Table 2 Binding affinity of studied ligands with Omicron S-glycoprotein

S. N.	Ligands	Binding Affinity
1	Oleocanthal	-6.2
2	Tangeritin	-6.2
3	Coumarin	-6.3
4	Malvidin	-6.4
5	Glycitein	-6.8
6	Piceatannol	-6.9
7	Pinosylnin	-7.0
8	Daidzein	-6.9
9	Naringenin	-6.9

Docking studies presented in the present study revealed pinosylnin to have the highest binding affinity with the target protein and can be used as potential drugs against the Omicron spike protein. Spike glycoprotein plays a vital role in attachment of host cell surface with coronavirus via ACE-2 receptor. *In silico* binding studies of

natural compounds with Spike glycoprotein may interrupt attachment of ACE-2 receptor and S-glycoprotein and thus attachment of host's ACE-2 receptor and COVID -19 Spike glycoprotein will be lost. These ligands possessed potent effects in different therapeutic clinical conditions. Previous literature had some reports on docking studies of some phytochemicals i.e., quercetin, gingerol, luteolin-7-glucosidase, catechin, allicin, kaempferol, epicatechin-gallate that can be used as anti-COVID-19 agents (Khaerunnisa et al. 2020). Results of the current study are also in agreement with an earlier study by Koulgi et al. (2022) those who reported phytochemicals from AYUSH-64 (a poly herbal drug) viz. akummicine-N-oxide, akummiginone, echitamidine-n-oxide, and echitaminic acid may act as a potential drug against Omicron variant of SARS-CoV-2. Further, Nag et al. (2021) study also showed that curcumin and piperine are the most potent to bind with spike protein of omicron SARS-CoV-2 and restrict the viral entry. The computational docking studies of the phytochemicals glycyrrhizic acid and limonin resulted in binding with receptor binding domain of SARS-CoV-2 Omicron and supported traditional medicines can be useful in formulating adjuvant therapies to fight against the pandemic (Vardhan and Sahoo 2022).

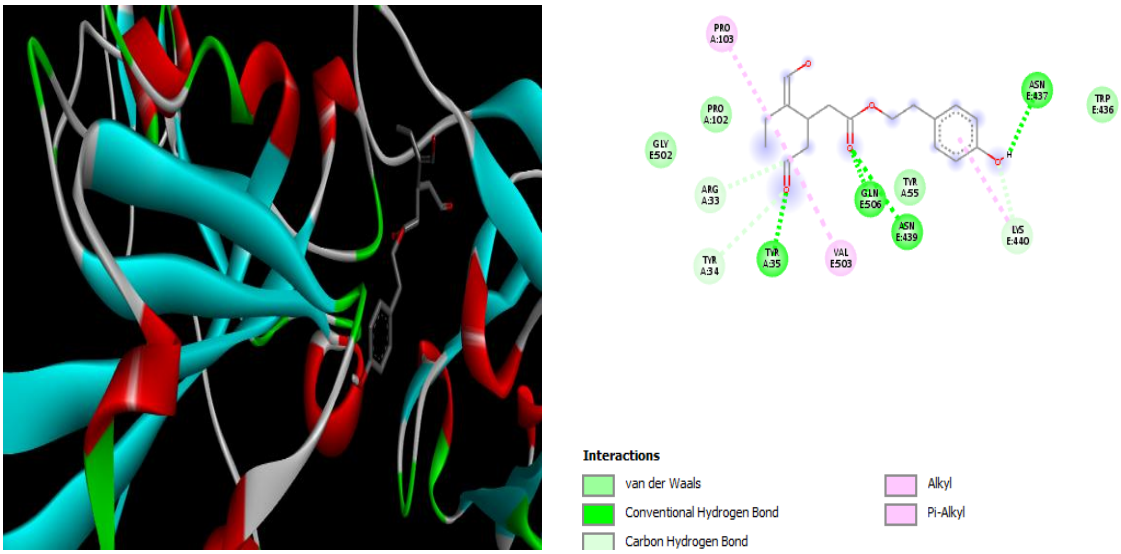

Figure 2 The molecular docking of Omicron spike protein and Oleocanthal (A) Best binding mode in the pocket of protein (B) The interacting amino acid of target with ligand

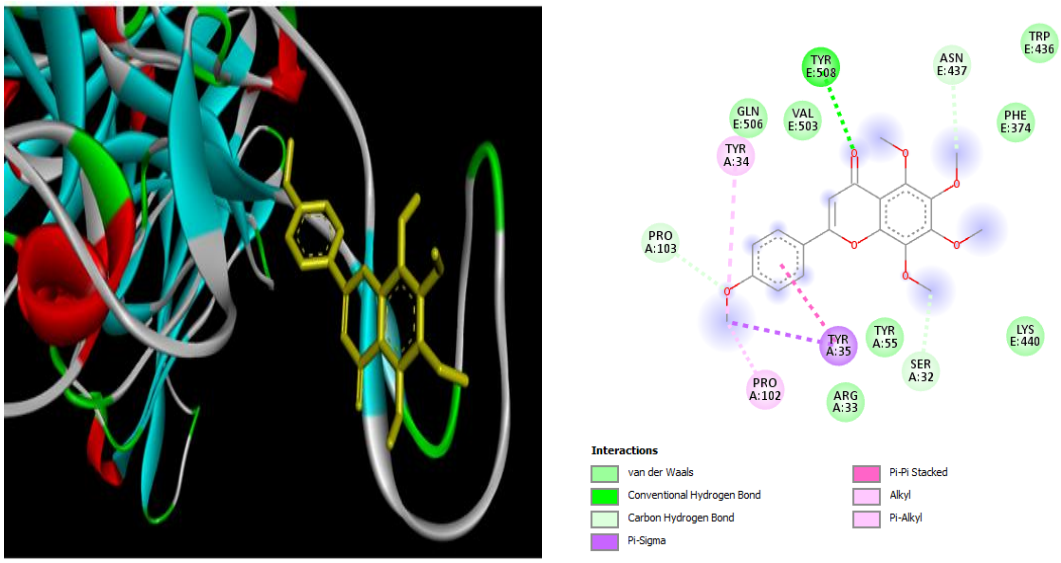

Figure 3 The molecular docking of Omicron spike protein and Tangeritin (A) Best binding mode in the pocket of protein (B) The interacting amino acid of target with ligand

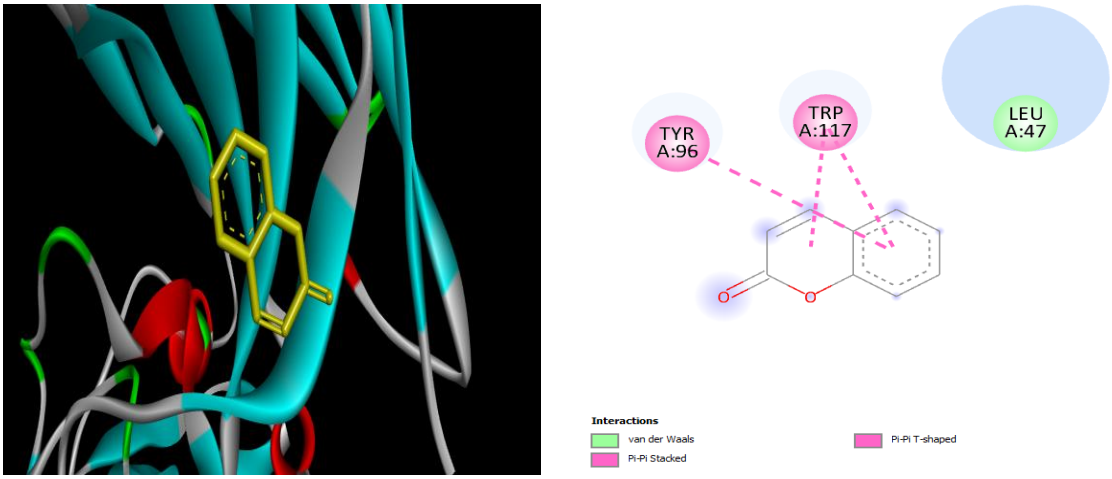

Figure 4 The molecular docking of Omicron spike protein and Coumarin (A) Best binding mode in the pocket of protein (B) The interacting amino acid of target with ligand

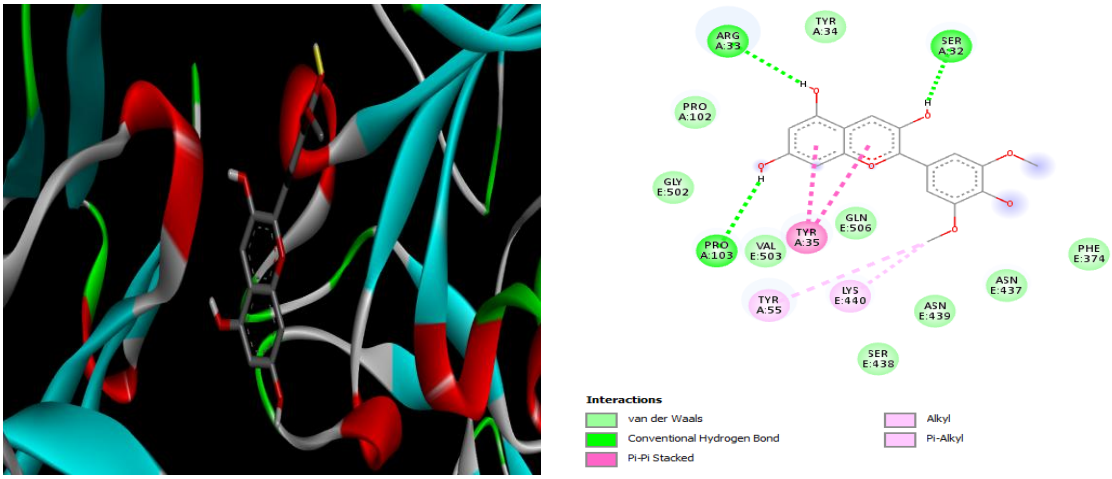

Figure 5 The molecular docking of Omicron spike protein and Malvidin (A) Best binding mode in the pocket of protein (B) The interacting amino acid of target with ligand

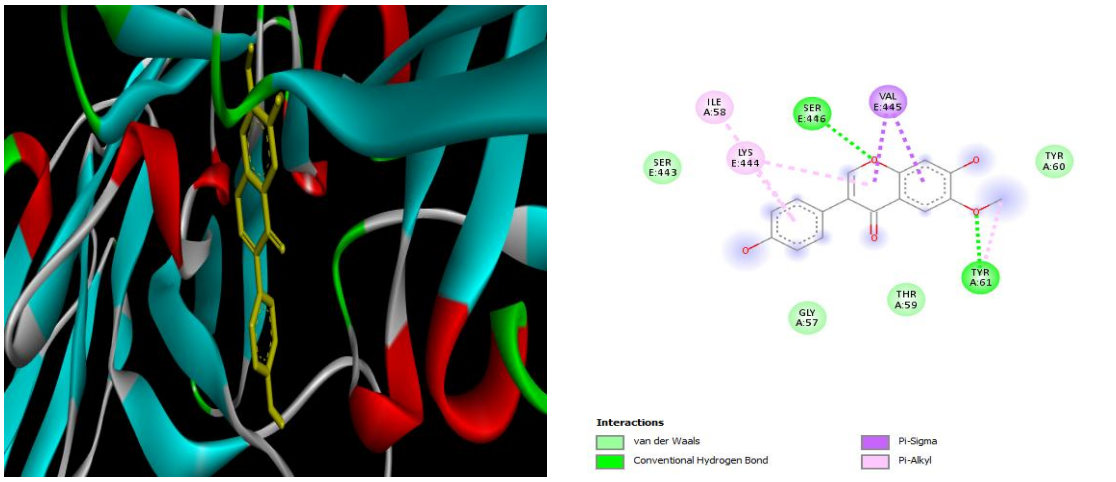

Figure 6 The molecular docking of Omicron spike protein and Glycitein (A) Best binding mode in the pocket of protein (B) The interacting amino acid of target with ligand

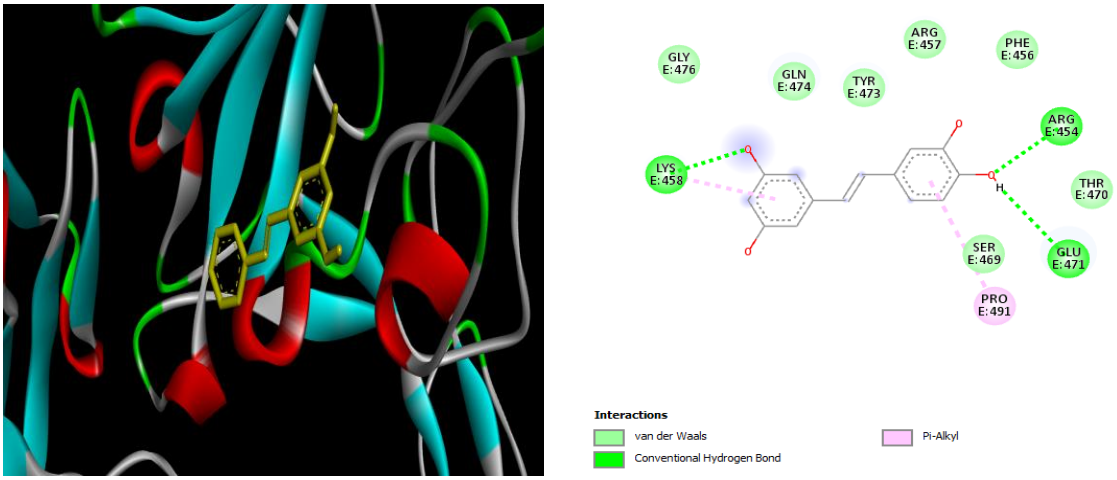

Figure 7 The molecular docking of Omicron spike protein and Piceatannol (A) Best binding mode in the pocket of protein, (B) The interacting amino acid of target with ligand

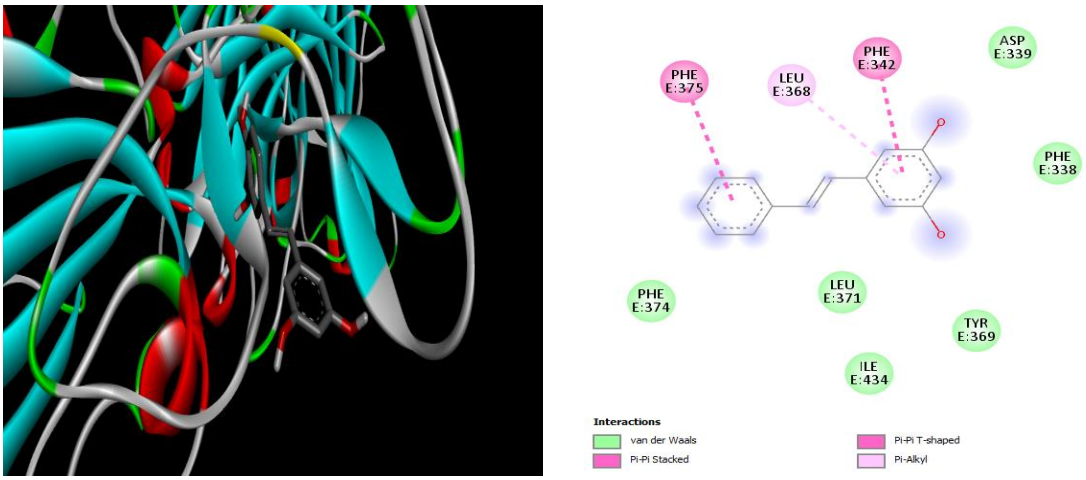

Figure 8 The molecular docking of Omicron spike protein and Pinosylnin (A) Best binding mode in the pocket of protein, (B) The interacting amino acid of target with ligand

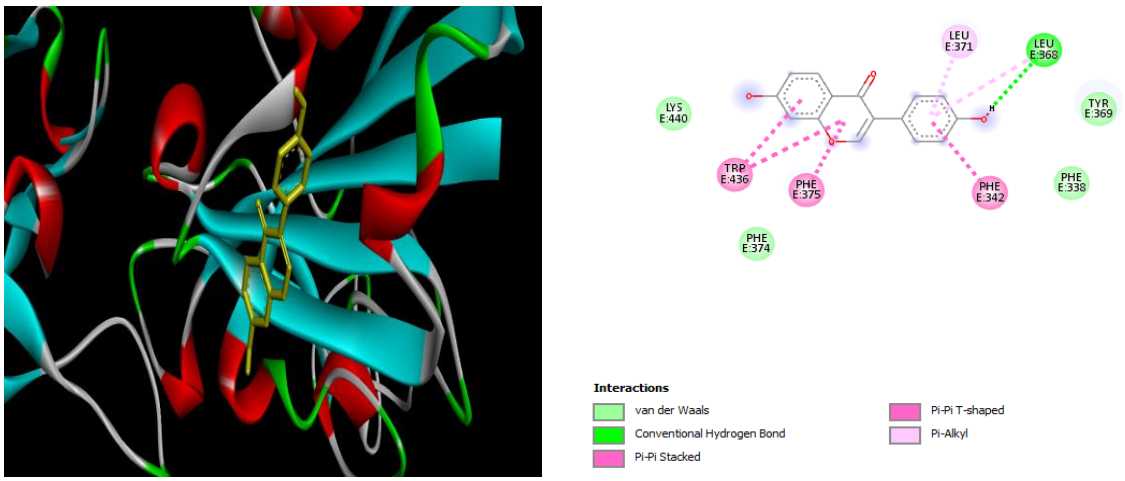

Figure 9 The molecular docking of Omicron spike protein and Daidzein (A) Best binding mode in the pocket of protein, (B) The interacting amino acid of target with ligand

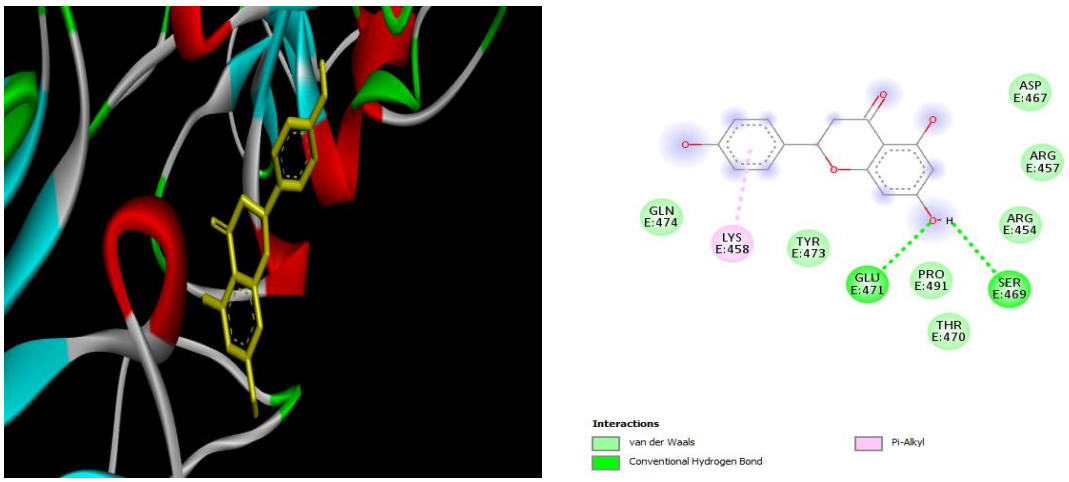

Figure 10 The molecular docking of Omicron spike protein and Naringenin (A) Best binding mode in the pocket of protein, (B) The interacting amino acid of target with ligand

Conclusion

Scientists are studying a new variant of concern' of SARS-CoV-2 named Omicron, the most mutated variant having 26-32 mutations in the spike protein. In the present study, natural products were molecularly docked with Omicron spike protein. Computational-based drug designing is time saving and cost-effective method to select compounds as a potential drugs for further studies. Pinosylnin showed the highest binding energy. Moreover, the compound used in this study satisfies Lipinsik's rule of five and can be used as anti-COVID-19 therapeutics. Besides, *in-vivo* and *in-vitro* studies are suggested before using these ligands as a potential drug to combat Omicron infection.

Conflict of interest

The authors declare no conflict of interest.

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