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Antiviral potential of withaferin A and titanium dioxide nanoparticle (TiO_2-np) complex against spike protein (S^{pro}) of omicron variant: An *in silico* approach

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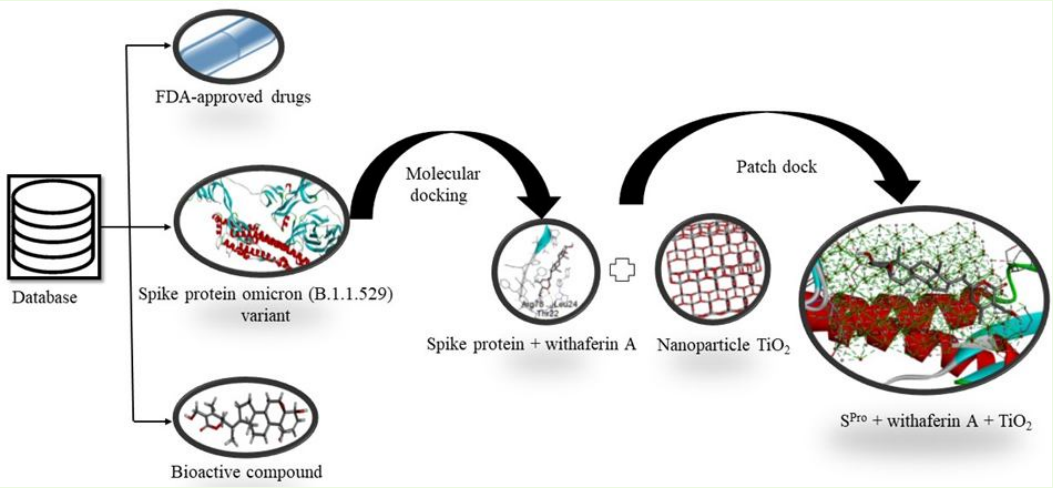
Abstract

Omicron variant (B.1.1.529) of SARS-CoV-2 cases increased rapidly across the world. It is crucial to determine how repurposing antiviral drugs work effective to neutralizing the pathogenicity and host invading mechanism induced by SARS-CoV-2. Therefore, it is necessary to identify the active site of the omicron variant protein and its molecular interaction with selected FDA-approved drugs as well as naturally occurring bioactive compounds. This research article focused on the comparative cum holistic *in silico* assessment for investigating the potential inhibitory effects of bioactive compounds and repurposing drugs like lopinavir, dexamethasone, favipiravir and chloroquine against spike protein (S^{pro}) of omicron variant in presence of titanium dioxide nanoparticle (TiO_2-np). The molecular docking and patch dock methods were used to explore the binding affinities of aforementioned drugs as well as compounds in presence of TiO_2-np. This *in silico* study revealed, that the bioactive compounds particularly withaferin A and withanolide A derived from *Withania somnifera* L. showed high binding affinity -8.6 and -7.9 kcal/mol, respectively, against the S^{pro} of omicron variant as compared to aforementioned four FDA-approved drugs. Interestingly, the docked complex of titanium dioxide withaferin A (TiO_2-np + withaferin A) also showed more high binding affinity against the S^{pro}. Subsequently, the docked complex (TiO_2-np + withaferin A) was showing as a potent inhibitor to S^{pro} and might perform significant inhibitory effect in the invasion process of omicron variant as an antiviral agent.



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1. Introduction

Globally, the COVID-19 pandemic triggered by the SARS-CoV-2 has culminated in about 300 million infections and 6.2 million fatalities. SARS-CoV-2 has established into numerous major variations that

bearing health hazards. Recently, variant omicron increased major concerns about how immunizations, neutralising antibodies, and widely used drugs will be significant inhibitor due to the efficacy of the prevalent mutation. The World Health Organization (WHO) declared the adverse effects of the omicron variant dated 26th November, 2021.The newly emerging omicron variant of SARS-CoV-2 was recorded as a single stranded (ssRNA) zoonotic virus infected from animal to human and re-infect to a normal healthy person. Taxonomically, this omicron variant belonging to the subfamily orthocoronavirina and family coronaviridae (Shereen *et al.,* 2020; Kumar *et al.,* 2023; Tabish *et.al.,* 2021). Apart from that the omicron variant is highly competent to the antigenic alteration and re-infectivity progression due to the high probability of mutation rate. SARS-CoV-2's four variants of concern (VOC) have been identified, namely alpha (B.1.17) in (S-RBD mutation (s) N501Y amino acid, this mutation increased transmission, beta (B.1.351) in S-RBD mutation(s) (K417N, E484K, N501Y amino acids) and gamma (P.1) in (S-RBD mutation (s) in L452R, T478K amino acids) by the Hu1 S^{pro}. While, in the case of fourth variant delta (B.1.161.7.2), the amino acids particularly K417N, L452R and T478K have been involved and might be playing a key role in rising infection and transmission rate. Consequently, the newly emerged omicron variant (B.1.1.529) showed the high mutation rate particularly in these amino acids sequences G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493K, G496S, Q498R, N501Y and Y505H) of the receptor-binding domain (RBD) region of S^{pro} chain (Kannan *et al*., 2021; Carter *et al*., 2022; Lupala *et al.,* 2022; Ortega *et al*., 2022). Therefore, this specific binding domain (RBD) region of receptor S^{pro} (virulent factor) is liable for viral attachment to the corresponding host cell. During the pandemic wave, certain repurposing drugs lopinavir, dexamethasone, favipiravir and chloroquine were widely used as a preliminary treatment for inhibition of SARS-CoV-2 infection. Apart from that, it was noticed that aforementioned drugs show unsatisfactory results with undesirable side effects due to the high mutation rate of S^{pro} of SARS-CoV-2 infected patient's health (Pandey *et al*., 2020; Srivastava *et al.,* 2021). There is a very long history of using natural bioactive compounds and bioactivity-guided fractionation of medicinal plants to treat a diverse range of viral and bacterial infections like the seeds powder of *Nigella sativa* L. immunomodulatory properties improved the cytokine gene expression leads to significantly inhibit the pathogenesis of H9N2 viruses (Sabina *et al.,* 2022). Numerous natural bioactive compounds have been studied and proved as a cell integration barrier or an inhibitor of viral replication mechanism. The latter is accomplished by interfering the interactions process of receptor-binding domain (RBD) of S^{pro} with human angiotensin-converting enzyme 2 (ACE-2) or by obstructing the transmembrane protease serine 2 activity (TMPRSS-2). It is documented that quite a few types of natural compounds have already been explored and recognized as an inhibitor of TMPRSS2, receptor binding domain-ACE2 and S^{pro} of SARS-CoV-2 (Vivek *et al.,* 2022; Hoffmann *et al.,* 2020; Chikhale 2021). However, the computational (Khan *et al*., 2021; Forrestall *et al*., 2022; Sayed *et al*., 2020) or a combination of computational and experimental *in silico* approaches have also been employed to identify the medicinal plant-based compounds as an inhibitors of SARS-CoV-2 major proteases. Such results have been reported in multiple reviews and publications (Wang *et al*., 2020; Verma *et al*., 2020). According to reports of herbal plants, different classes of naturally occurring bioactive compounds were excellent hit molecules in the search for new antiviral therapeutics that can control and minimize the infectivity rate of infectious diseases/ disorders. Therefore, there is an urgent requirement to identify and evaluate the specific bioactive compounds to fight viral diseases, particularly COVID-19. Subsequently, virtually screened bioactive compounds belong to different plant species such as *Tinospora cordifolia* (Giloy), *Azadirachta indica* (Neem), *Ocimum tenuiflorum* (Tulsi), *Curcuma longa* (Haldi), *Withania somnifera* (Ashwagandha) were considered for antiviral study (Pruthvish *et al*., 2018; Biswas *et al*., 2002; Kaur *et al*., 2018; Niranjan *et al.*, 2008; Sagar *et al*., 2020). Additionally, viruses are classified as a naturally existing nanoparticle due to their nanometric dimensions. Nanoparticles work as a diagnostic tool as well as drug delivery system in a specific drug target site in the treatment of several bacterial and viral diseases and considered as a biological, immunotherapeutic and chemotherapeutic agents. Site-specific and target-oriented drug discovery systems benefit from nanomedicine (Patra *et al*., 2018; Agback *et al*., 2021). Nanoparticle more abundant in ground water and water courses. While, titanium oxide nanoparticle (TiO_2-np) inhibited the SARS-CoV-2 infection (Nakano *et al*., 2022). and caused photocatalytic reaction which played bactericidal and virucidal activity (Mazurkova *et al*., 2010). Therefore, this study aimed to compare the inhibitory potential of screened bioactive compounds with FDA-approved drugs as an alternative antiviral therapeutic agent. In addition, to examine the antiviral efficiency of bioactive compounds in presence of titanium dioxide nanoparticle (TiO_2-np) against S^{pro} of omicron variant using patch dock.

2. Materials and Methods

The bioactive compounds and structural spike protein (S^{pro}) of SARS-CoV-2 were retrieved from authentic sources as an experimental data and followed by *in silico* study of bioactive compounds with target S^{pro} shown in the flow diagram Figure 1.

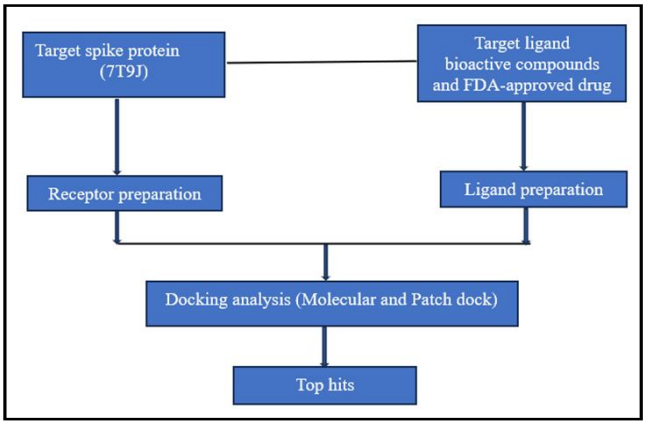

Figure 1: Flow chart of methodology steps, virtual screening, and plausible ligand hits with S^{pro} of omicron variant involved in *in silico* study.

2.1 Preparation of omicron variant S^{pro} as a receptor molecule

Three-dimension structure of S^{pro} of omicron variant of coronavirus PDB-ID (7T9J) was retrieved from RCSB protein data bank (http://www.rcsb.org/) and prepared as a receptor molecule by adding suitable charges, polar hydrogen atom using Autodock Vina tool and save it as in pdb.qt file format for molecular interactions with selected ligands molecules (Saxena *et al.,* 2018).

2.2 Preparation of the bioactive compounds as a ligand

The three-dimension (3D) structures of the screened compounds derived from various medicinal plants; namely, *T. cordifolia*, *A. indica*, *O. tenuiflorum*), *C. longa*, *W. somnifera*) and FDA-approved drugs [like lopinavir , dexamethasone, favipiravir and chloroquine] prepared as ligand molecules were retrieved from PDB and PubChem library (https://pubchem.ncbi.nlm.nih.gov/) in sdf. file format, respectively. Then the Lipinski rule of 5 (RO5) was applied (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp) to differentiate the drug likeness and non-drug likeness properties of all selected bioactive compounds (Lin *et al*., 2014; Jayaram *et al.,* 2012).

Consequently, the downloaded sdf. file format of both bioactive compounds and FDA-approved drugs convert to pdb file format using open babel tool for better results or output through AutoDock Vina. Subsequently, all ligands pdb files were open in AutoDock Vina, then chose torsions and saved all output files in pdb.qt file format. In the context of AutoDock Vina tool pdbqt. files of all selected bioactive compounds as well as drugs were prepared for molecular docking study.

2.3 *In silico* study of titanium dioxide nanoparticle (TiO_2-np) molecular interactions

Molecular interactions between titanium dioxide nanoparticle (TiO_2-np) with S^{pro}, further re-docked the complex of TiO_2-np + S^{pro} with best bioactive compound by the online sever Patch Dock, working on the critical assessment of prediction of interactions (CAPRI) platform. Moreover, the best docked score complex was selected for further *in silico* study (Vyshnava *et al*., 2016).

3. Results

3.1 *In silico* study of selected bioactive compounds and FDA-approved drugs against omicron variant

Before performing *in silico* study, firstly we applied Lipinski's rule of 5(RO5) for filtering the bioactive molecules based on drug-likeness potential. After the preliminary screening, only five plant-derived bioactive compounds were selected and docked again in the presence of TiO_2-Np using the Patch dock tool. Subsequently, three-dimensional (3D) structure of S^{pro} (as a structural key component and highly susceptible for mutation) of omicron variant PDB-ID (7T9J) resolution: 2.79 Å was retrieved from latest version of RCSB PDB in (dot).pdb format Figure 2.

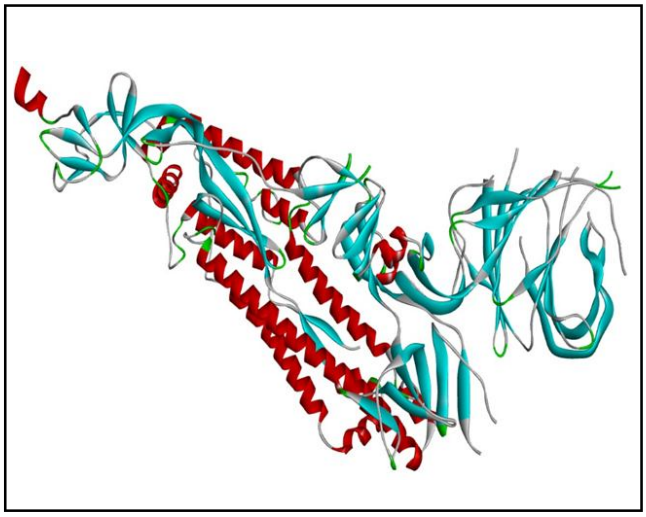

Figure 2: 3D image of S^{pro} of omicron variant PDB:ID (7T9J) resolution 2.79 Å.

In addition, chosen four FDA-approved drugs (D1 to D4) for docking analysis and exhibited the effective molecular interactions with S^{pro}. Molecular interaction of drug lopinavir (D1) with the S^{pro} exhibits two hydrogen and eleven hydrophobic bonds with their respective amino acid residues [Lys: 41, Val: 42, Ser: 221, Ala: 222, Lys: 206, Phe: 43, Thr: 284, Glu: 224, Pro: 225, Asn: 282 and Gly: 283 Try; 38] given in (Table 1) while binding free energy -7.6 kcal/mol shown in (Figure 3).

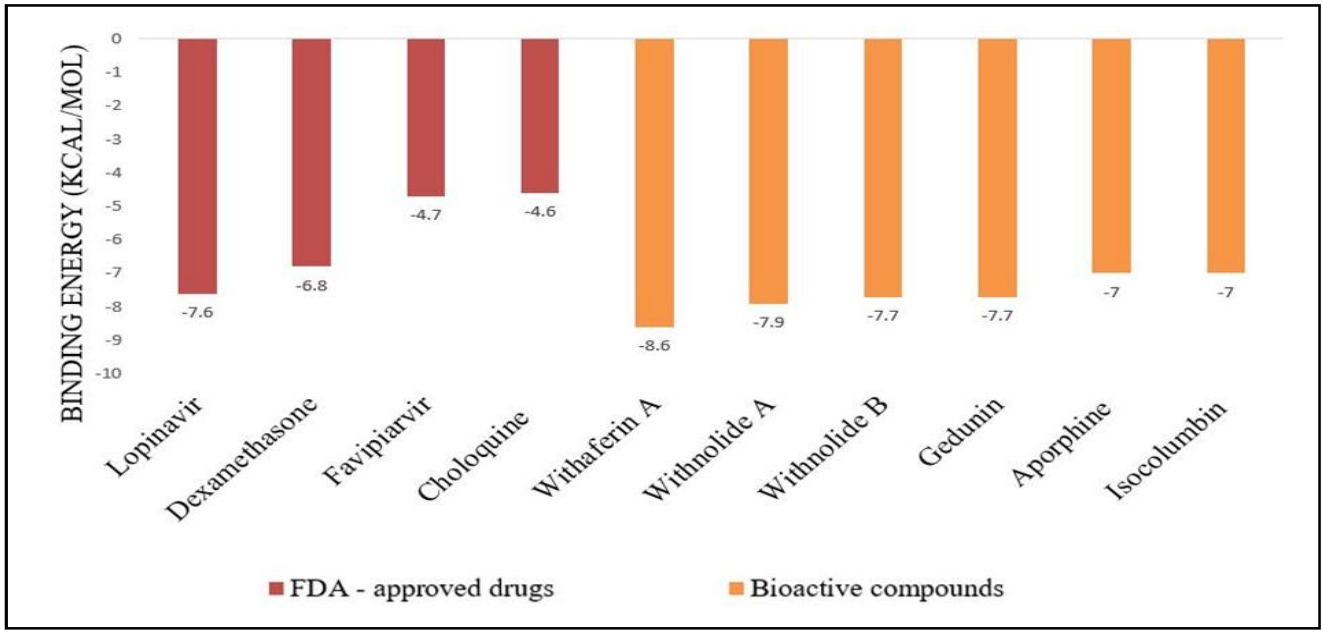

Figure 3: Comparative binding energies depiction of FDA-approved drugs and bioactive compounds with their binding energies.

While, the remaining three drugs D2, D3 and D4 showed a lesser binding energy -6.8, -4.7 and -6.8 kcal/mol, respectively (Table 1). The best docked images (3D and 2D) of selected drugs with target protein (S^{pro}) were given in (Figure 4).

Table 1: Binding energy of FDA-approved drugs and their corresponding amino acids interactions with S^{pro} of omicron variant

S. No.	Compound name (PubChem ID)	Chemical formula	Binding energy (kcal/mol)	Hydrogen bond	Participating docked amino acids residues with S^{pro}
D1	Lopinavir (92727)	$C_{37}H_{48}N_4O_5$	-7.6	Lys:206, Asn:282	(2) Gly:283, Lys: 41, Val:42, Ser :221, Ala:222, Lys:206, Phe: 43, Thr:284, Glu :224, Pro: 225, Try: 38 (11)
D2	Dexamethasone (5743)	$C_{22}H_{29}FO_5$	-6.8	Asn:137, Arg:78	(2) Leu:18, Asp: 138, Asn:81, Pro:82, Asp: 80, Pro:26, Phe:65, Pro: 25, Leu:24, Gun:23 (10)
D3	Favipiravir (492405)	$C_5H_4FN_3O_2$	-4.7	Agr:1000, Try: 741, Met:740	(3) Gly:744, Ile:742, Cys:743, Val: 976, Ser:975, Lys:856, Leu:966 (7)
D4	Chloroquine (2719)	$C_{18}H_{26}C_lN_3$	-4.6	Arg:1009	(1) Leu:977, Val:976, Leu:966, Cys:743, Met:740, Lys:856, Ser:975, Ser:967, Asn: 978, Asp:745, Gly:744, Tyr: 741 (12)

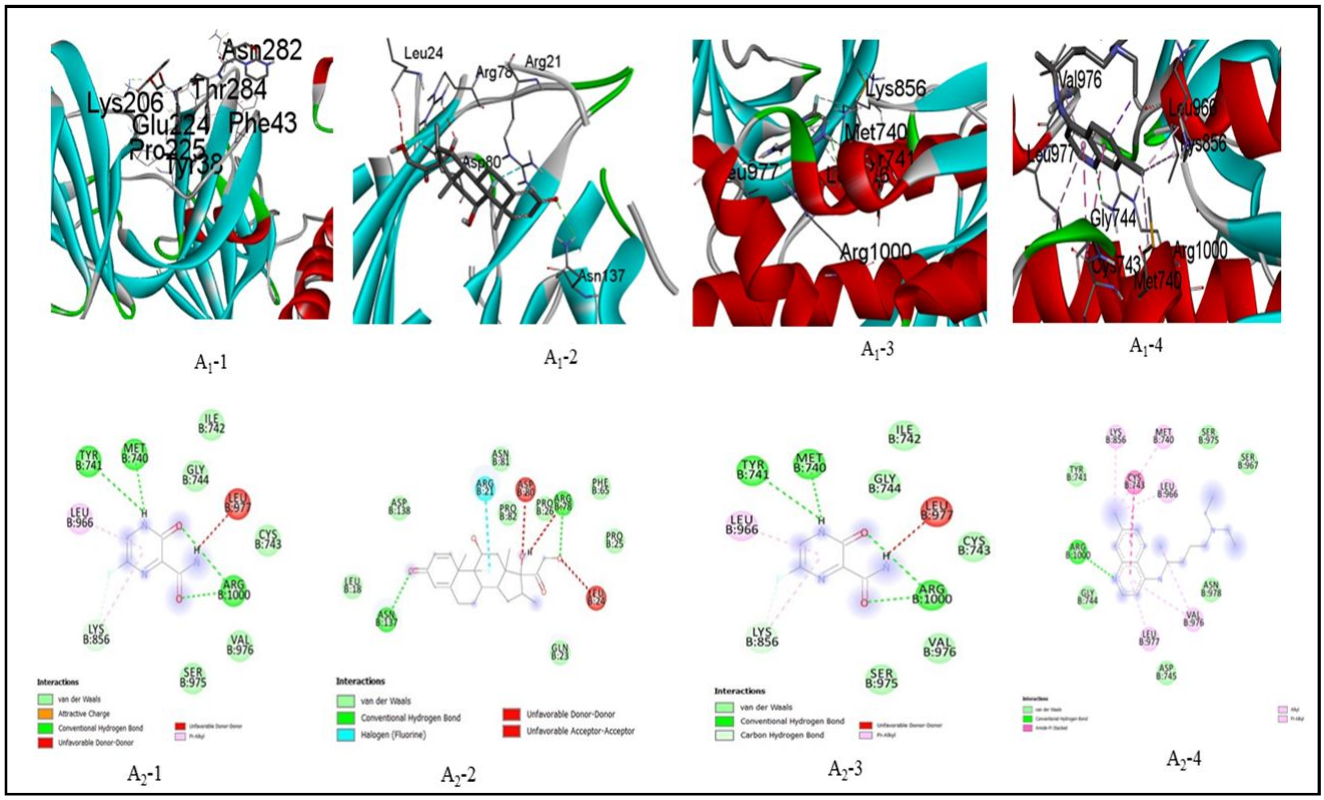

Figure 4: Molecular interactions docked images (3D and 2D) of FDA-approved drugs represent A_1-A_2:1 (lopinavir), A_1-A_2: 2 (dexamethasone), A_1-A_2: 3 (favipiravir) and A_1-A_2: 4 (chloroquine) against S^{pro} of omicron variant.

The potential active site of the receptor molecule S^{pro} was taken from whole B-chain for the random docking with different ligand molecules (C1 to C6). Then set an outline mark as a configuration of grid box [as a binding site coordinates x, y, and z 224.206, 209.56 and 211.076] for molecular interactions with S^{pro} of omicron variant. Apart from that, the docked bioactive compounds' binding energies were analyzed. Subsequently, the Lipinski rule of five (RO5) was applied to all docked bioactive compounds (C1 to C6) for predict stability and permeability. All screened bioactive compounds (C1 to C6) followed rule of five (RO5) and find fit for drug likeness properties shown in (Table 2) (Shivanika *et al*., 2020).

Table 2: Drug likeliness properties (RO5) of the selected bioactive compounds

S. No.	Bioactive compound with ID	Chemical formula	M.M< 500Da	HB donor<5	HB acceptor <10	LOGP <5	Molar refractivity
C1	Withaferin A(265237)	$C_{28}H_{38}O_6$	454.00	1	5	4.380499	123.0517
C2	Withanolide A(11294368)	$C_{28}H_{38}O_6$	470.00	2	6	3.495399	124.5115
C3	Withanolide B(14236711)	$C_{28}H_{38}O_5$	454.00	1	5	4.380499	123.0517
C4	Gedunin(12004512)	$C_{28}H_{34}O_7$	482.00	0	7	4.560699	123.7789
C5	Aporphine(114911)	$C_{17}H_{17}N$	235.00	0	1	3.438699	74.6569
C6	Isocolumbin(24721165)	$C_{20}H_{22}O_6$	235.00	0	1	3.438699	74.6569

M.M: Molecular Mass, Da: Dalton, HB: Hydrogen Bond

All screened plant-derived bioactive compounds (C1 to C6) were showing good molecular interaction with target S^{pro} with their corresponding binding efficiency/energies (BE) range from -7.0 to -8.6 kcal/mol given in (Table 3) in comparison to tested FDA-approved drugs.

Table 3: Binding energy of top six bioactive compounds and their corresponding amino acids interactions with S^{pro} of omicron variant

S. No.	Bioactive compound with ID	Chemical formula	Binding energy (kcal/mol)	Hydrogen bond	Participating docked amino acids residues with S^{pro}
C1	Withaferin A (265237)	$C_{28}H_{38}O_6$	-8.6	Leu:24, Arg:78, Thr:22 (3)	Val:83, Pro82, Gln:23, Arg:21, Asn:81, Phe:79, Asp:80, Pro:26, Phe: 65, Leu: 84, Tyr:269, Thr: 63, Pro: 85 (13)
C2	Withanolide A(11294368)	$C_{28}H_{38}O_6$	-7.9	Met:153(1)	His:245, Ala:243, Leu:244, Glu:154, Asp:142, Arg:246, His:245, Arg:102,Asn:99, Asn:122, Ala:123 (11)
C3	Withanolide B (14236711)	$C_{28}H_{38}O_5$	-7.7	Asn:960(1)	Gln:957, Lys:304, Leu:303, Thr:302, Ala:956, Asn:953, Lys:304, Thr:961 (8)
C4	Gedunin (12004512)	$C_{28}H_{34}O_7$	-7.7	Gln:52, Arg,273(2)	Ala:292, Pro:272, Thr:274, Ser:316, Cys:291, Cys:301, Glu:298, Ser: 316, Pro: 272 (9)
C5	Aporphine(114911)	$C_{17}H_{17}N$	-7.0	NA	Pro:225, Lys:41, Asp: 40, Tyr: 38, Glu:224, Thr:284, Gly:283 Phe: 43 (9)
C6	Isocolumbin (24721165)	$C_{20}H_{22}O_6$	-7.0	Phe:175(1)	Leu:176, Ser:205, His:207, Lys:206, Leu:226, Glu:224, Pro:225 (7)

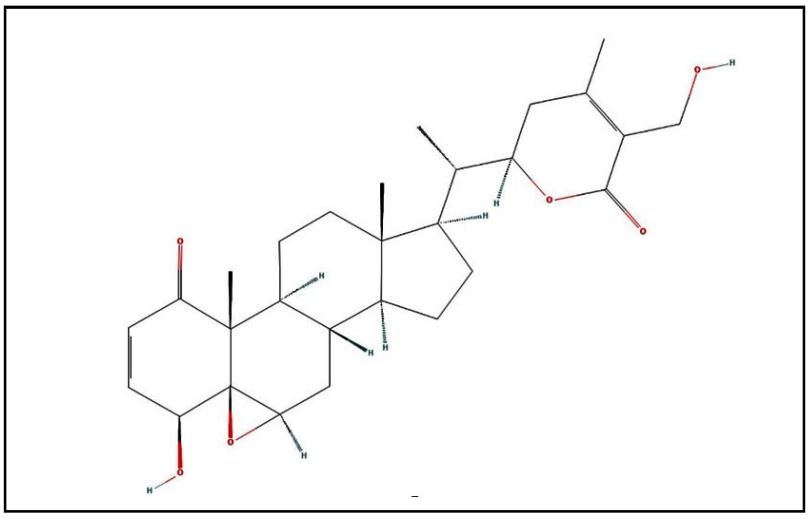

Figure 5: 2D structure of compound C1 (withaferin A).

The compound C1 (withaferin A) derived from ashwagandha a steroidal lactone, antineoplastic and apoptosis inducer agent two-dimensional structure shown in Figure 5. Showed high binding energy -8.6 kcal/mol (Table 3) out of the top five selected bioactive active compounds (C2 to C6) and revealed the involvement of three (3) hydrogen and thirteen (13) hydrophobic bonds with their corresponding residues amino acids residues mainly Leu:24, Arg:78, Thr:22 and Val:83, Pro82, Gln:23, Arg:21, Asn:81, Phe:79, Asp:80, Pro:26, Phe: 65, Leu: 84, Try:269, Thr: 63, Pro: 85, respectively. The molecular interactions docked images (3D and 2D) of bioactive compounds (C1 to C6) with S^{pro} shown in (Figure 6).

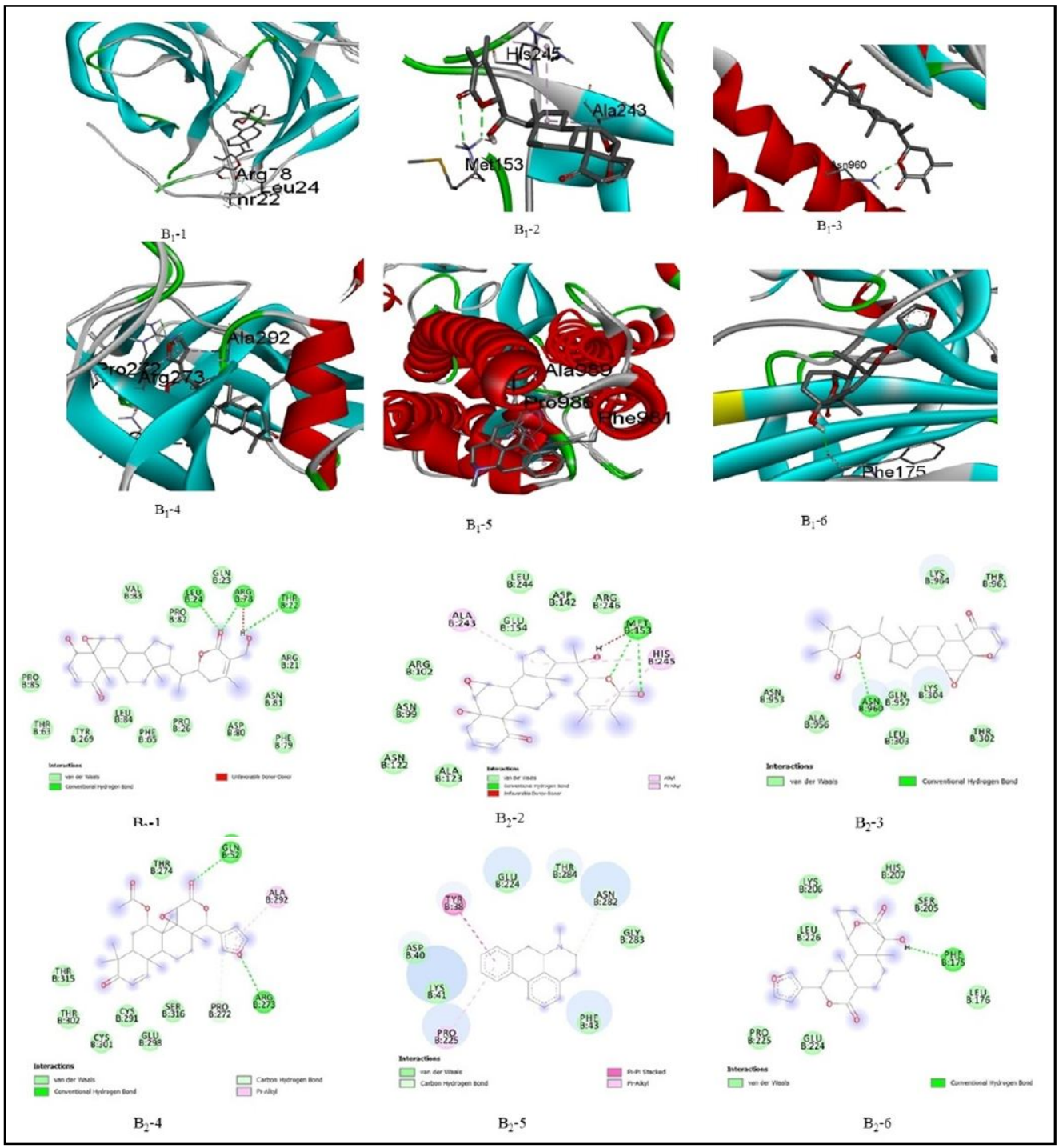

Figure 6: Molecular interactions docked images (3D and 2D) of bioactive compounds B_1-B_2:1 (withaferin), B_1-B_2:2 (withanolide A), B_1-B_2:3 (withanolide B), B_1-B_2:4 (gedunin), B_1-B_2:5 (aporphine) and B_1-B_2:6 (Isocolumbin) against S^{pro} of omicron variant of SARS-CoV-2.

3.2 *In silico* analysis of molecular interactions of bioactive compounds in presence of titanium dioxide nanoparticle (TiO_2-np)

SARS-CoV-2 omicron variant virus has positive-sense, single-stranded RNA and virions that are between 118 and 140 nm in size, which are required for viral reproduction (Deng *et al*., 2015). The receptor-binding region of spike glycoprotein helps membrane fusion in coronavirus infections, which promotes viral cell infiltration (Udugama *et al*., 2020). TiO_2 nanoparticles operate in two ways: first, it could breakdown biopolymeric compounds (such proteins and polysaccharides) that reside on the surface of an object, and second, it may modify an object's surface attributes so that it turns hydrophilic when TiO_2 is exposed to it (Dhasmana *et al*., 2014; Kaneko *et al.,* 2006). Nanoparticles have a significant potential to interact and easily bind with receptor-binding region of spike protein leading to inhibit the initiation of viral infection process (pathogenicity) due to their tiny dimensions and tunable surface charge. In order to effectively control COVID-19, it could be beneficial in developing nanomedicine-based approaches such as novel antigens for nanovaccines, antiviral drugs, and immunomodulatory therapeutics (Wrapp *et al*., 2020). Nano-antivirals might effectively cure COVID-19, if modified to certain antiviral ligands like copper, zinc, or silver (Ag) (Gupta *et al*., 2020). The nanoparticle particularly, titanium dioxide (TiO_2) is also showing the best molecular interaction with S^{pro} along with selected bioactive compound C1 (withaferin A). The geometry based molecular docking algorithm software PatchDock server, which is used extensively in the molecular interaction (Schneidman *et al.,* 2005). As per patch-docked results, the TiO_2-np+S^{pro} and Withaferin A + S^{pro} binding score 1278 and 5170 respectively Figure 7. (Naumenko *et al.,* 2016).

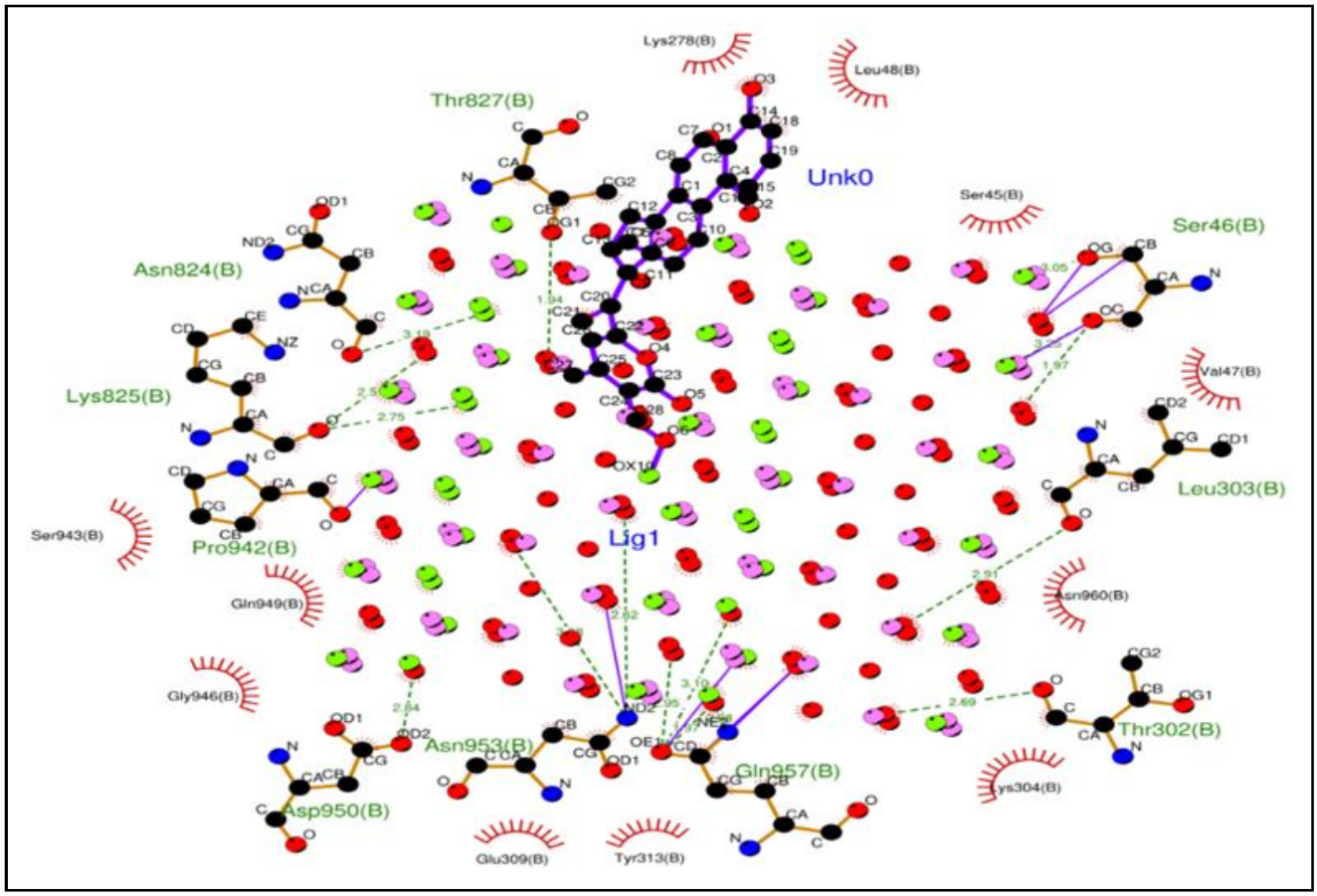

Figure 7: The '2 D-image' showing interacting amino acids residue of the S^{pro} with withaferin A in presence of TiO_2-np.

Interestingly, in the presence of TiO_2-np, the compound C1 (withaferin A) showed the best binding efficiency as well as effective molecular interaction with S^{pro} of the omicron variant with a high docked score 12198 (Table 4).

Table 4: Molecular interaction of withaferin A with S^{pro} in presence of titanium dioxide nanoparticle (TiO_2-nP)

S.No.	Dockedcomplex	Bindingscore	Correspondingamino acids
1.	TiO_2-nP + S^{pro}	1278	Glu281, Ser40, Ser45, Lys304, Thr302,
2.	Withaferin A + S^{pro}	5170	Leu304, Thr961, Asn 960, Glu957, Asn953,
3.	Withaferin A + S^{pro} + TiO_2-nP	12198	Asp950, Gly946, Lys845, Asn 824 and Pro942

4. Discussion

SARS-CoV-2 omicron variant is spreading worldwide with higher transmissibility than the previous strain. Notwithstanding the speedy development of effective and safe COVID-19 vaccinations, oral antiviral drugs have been approved to control the pandemic situation. It is essential to preferred preliminary treatment using naturally occurring bioactive compounds at the early stages of the illness, particularly in the context of kinetic pattern of SARS-CoV-2. An oral formulation of a protease inhibitor known as nirmatrelvir combination with ritonavir (NMV/r), which acts as a CYP3A inhibitor, has shown great potential in preventing the progression of the disease in high-risk patients without the necessity for supplemental oxygen supply. In this *in silico* study, the antiviral potential of FDA-approved drugs (D1 to D4) as well as bioactive compounds (C1 to C6) were compared and analysed. In SBDD, molecular docking is an efficient and widely used approach for screening large collections and forecasting receptor-ligand combinations (Sportelli *et al*., 2020). Apart from that, the solubility and capacity of a medicine/drug to pass intestinal membranes, which in turn relate to a compound's physicochemical characteristics like value of LogP, water solubility potential, the number of rotatable bonds nonpolar surface area play a significant role in a drug's bioavailability (Straughn *et al.,* 2020) also were analysed. Additionally, the molecular docking clustering poses of screened bioactive compounds (as ligands) with the RBD region of S^{pro} (as a receptor) were analysed including the involvement of hydrogen bonds with end-point free binding energy (Adnan *et al.,* 2022). The four FDA-approved drugs were preferred for knowing the binding efficacy against the active site of receptor molecule S^{pro} as an antiviral agent. Using AutoDock Vina, blind and restricted docking simulations at the interface were performed to provide the bioactive compounds with plausible binding modes (Narh *et al*., 2020). Subsequently, results obtained by molecular docking in the form of binding energies of receptor and ligands interactions, were analyzed as well as corresponding docked images were visualized by discovery studio. The best molecular docker as well as effective binder compounds C1 (withaferin A) as well as extract of C. *speciosus* L. (Al-Ahmadi, 2022) predicted as multi-therapeutic properties like antiviral, anti-inflammatory, antifibrotic, antiplatelet, antileishmanial, immunosuppressive, with healing potentials and anti-cancerous and reported to reduce the various secretion of proinflammatory cytokines such as TNF-Alpha IL-6, IL-8, and IL-18 in a metastatic model of ovarian cancer (Veber *et al*., 2002). This study compared the stability and inhibitory potential of the drug D1 (Lopinavir + S^{pro}) complex to the bioactive compound C1 (withaferin A + S^{pro}) complex for controlling the transmissibility of omicron variant. In addition, a number of characteristics, such as hydrogen bonds, Vander Waals contacts, buried surface areas, and binding free energies, were used to assess the molecular interactions. The analysis of the molecular interactions and binding energies of the drugs D1 (lopinavir) and bioactive chemical C1 (withaferin A) revealed that C1's binding energy was higher and that it was subsequently considered to be a more powerful inhibitor (antiviral) of the omicron variant. Interestingly, the molecular interaction of C1 with S^{pro} of the omicron version revealed a high binding score in the presence of titanium dioxide nanoparticles (TiO_2-np). It means nanoparticles may alter the structure of $S^{pro,}$ and inhibit its pathogenicity establishment process (Trott *et al*., 2002). ZnO-np and TiO_2-np, having particle sizes of 470.6 nm and a zeta potential of 5.92 mV, respectively, have been reported to exhibit half-maximal inhibitory concentrations (IC_{50}) of 526 and 568.6 ng/ml against the SARS-CoV-2. This *in silico* study revealed that the loss of the intended function of this target protein S^{pro}, which might be the reason of the interruptions of the attachment between the cell and the host interaction resulting in the occupied active site of S^{pro} by titanium dioxide (TiO_2) based complex compound C1 (withaferin A + S^{pro}). Furthermore, our study also suggests that complex C1 (withaferin A + S^{pro}) may be alters the adhesion mechanism of structural spike protein (S^{pro}) of omicron variant Figure 8.

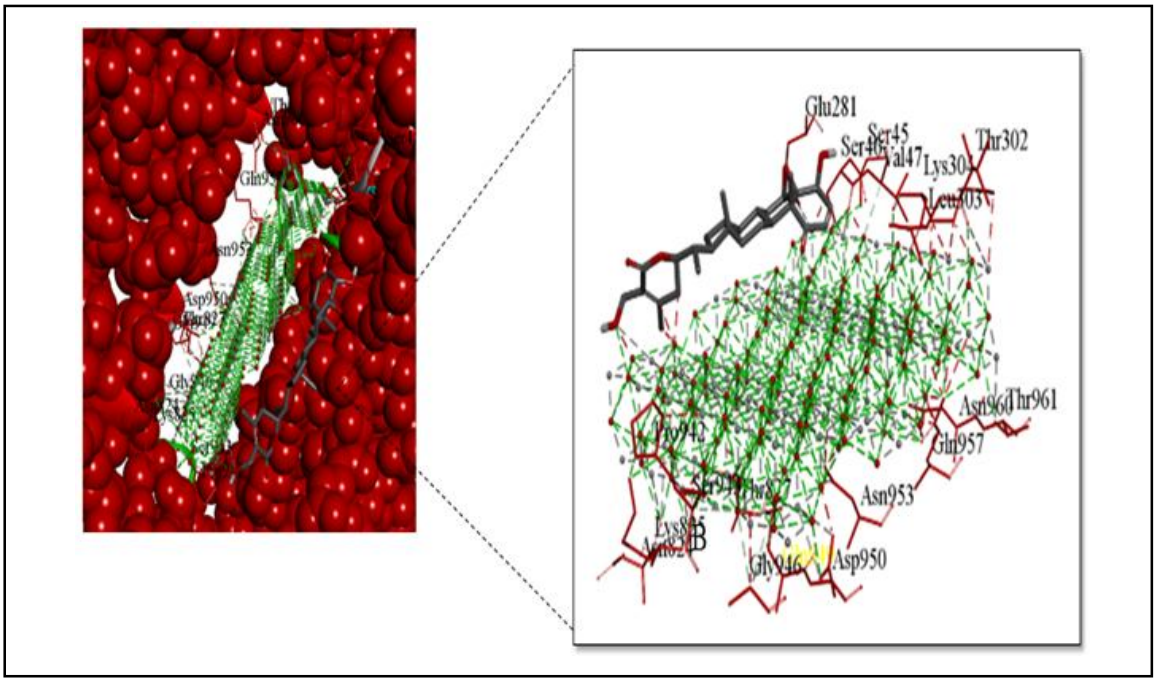

Figure 8: The 3D image showing interacting amino acids residue of the S^{pro} with withaferin A in presence of TiO_2-np.

The amino acids lysine and arginine have been associated to both infection and replication process of SARS-CoV-2 in previous studies (Sultana *et al*., 2021; Lin *et al*., 2014). An important amino acid named lysine has long been recommended as a treatment for herpes simplex virus (HSV) infection (Loutfy *et al*., 2020; Chen Nana *et al*., 2013; Troost *et al*., 2020). In evaluating the antiviral (inhibitory) potential of bioactive compounds, the computer-based structural study of biomacromolecules and their molecular interactions (ligand and protein) might become significant. The herbal medicines and some of the dietary comments have been widely used to treat a variety of viral infection (Sharma *et al.,* 2022). Interestingly, it is clearly indicated that the molecular interaction of all bioactive compounds, FDA-approved drugs and TiO_2-np with S^{pro} were showing that the Lysine as a common amino acid participated in the pathogenicity. Subsequently, an in-depth study is required to identify the modification of structural protein-protein interaction processes employing the most efficient approaches and tools. To verify the validity of the *in silico* results from this study, *in vivo* and *in vitro* validation is required. As a result, this insight regarding molecular interactions of bioactive compounds in presence of titanium dioxide leads to the diminishing the omicron variant's pathogenicity and infectivity rate.

5. Conclusion

At present, little data on the omicron variant and its threat were available. Oral direct antiviral treatments, such as routinely prescribed drugs, might have limited efficacy in preventing the transmission of SARS-CoV-2. The mechanism of action on targeting S^{pro} of the omicron Delta variant should not be impacted due to the high mutation rate. In this study, FDA-approved drugs (lopinavir, dexamethasone, favipiravir, chloroquine), and bioactive compounds exhibited effective molecular interactions against the S^{pro}. It was seen that when TiO_2 nanoparticle binding to S^{pro} Both TiO_2 and docked Withaferin A + TiO_2 exhibited the best molecular interaction. The docked form of Withaferin A + TiO_2 also expected as the most potent inhibitor of the protein due to occupying catalytical site. Consequently, in the presence of TiO_2 nanoparticle the compound C1 (withaferin A) might be a prime, natural, biocompatible antiviral agent for possibly inhibiting the pathogenicity, infectivity and re-infectivity of SARS-CoV-2.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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