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A Molecular Docking Study against COVID-19 Protease with a Pomegranate Phyto-Constituents 'Urolithin' and Other Repurposing Drugs: From a Supplement to Ailment

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Original Research Article

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ABSTRACT

Aim: We conducted an in silico study on Urolithin and different antimicrobial agents targeting virus protease and peptidase.
Methodology: The docking study was completed by using docking tools. Drug compounds and COVID-19 receptor molecules were prepared, docking was performed and interaction was visualized through Discovery Studio visualizer.
Results: Urolithin A has interacted against peptidase (PDB ID:2GTB) with binding energy -6.93 *kcal/mol* and against protease (PDB ID:6LU7) with the binding energy -5.46 *kcal/mol*, while Urolithin B has interacted to peptidase (PDB ID:2GTB) with binding energy -6.74 *kcal/mol* and with protease it interacted with a binding energy -4.67 *kcal/mol*. The antimicrobial agent Ofloxacin was found to interact against protease (PDB ID:6LU7) with a binding energy -6.84 kcal/mol and against protease (PDB:6LU7) with a binding energy -8.00 kcal/mol.
Conclusion: The most common interacting amino acids of target enzymes of the virus with studied drugs were His41, His164, Met165, Glu166, Gln189. From the docking studies, it is observed that

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Ofloxacin and Urolithin have the potential to inhibit the virus protease as well as peptidase significantly and these could prevent the entry of the virus to the inside of the host cell. Thus, further antiviral research on these antimicrobial agents and Urolithin could be helpful to control the COVID-19 disease.

Keywords: Antimicrobial agents; urolithin; antiviral; SARS-CoV-2; protease.

1. INTRODUCTION

The pathogenic human to human transmitted, respiratory illness caused by virus SARS-CoV-2. Initially, it was appeared at the end of December 2019 in Wuhan city of China and become pandemic worldwide. Till now there is no treatment is available and it is an urgent need to search a new effective therapeutic molecule against them. The COVID-19 respiratory infection in humans is due to virus multiplication and causes severe respiratory tract complications. It is a single-stranded RNA virus and recognized as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) virus and more commonly it is known as COVID-19 virus or 2019-nCoV [1-2]. Many male and female humans have been affected very rapidly of the many countries of the world and Thus, immediately, the World Health Organization declared this disease as pandemic. As of 29 May 2020, 5,704,736 confirmed cases of COVID-19 and 357,736 deaths have been reported by WHO [3]. It is believed that viruses are originated from the bat and it is closely related to the SARS-CoV virus [4]. The structural features of viruses have been explored including therapeutic targets protease, peptidase, spike protein ACE2 receptor s which has accelerated drug designing or discovery that can be used to manage the disease. Many natural compounds against these targets have been screened by computational biologist and it is suggested to conduct the further *in vitro* and *in vivo* evaluation against the virus targets [3-5].

One of the targets of SARS-CoV-2 (SARS-CoV-2S) is Spike belongs to class I fusion glycoprotein. The spike protein helps the virus for attachment via ACE2 (Angiotensin-converting enzyme 2) receptor and fuse them with the involvement of the S2 domain of protein after fusion, the pathogen gets enter into the host cell. The ACE2 receptor interacts with the S1 subunit of glycoprotein and facilitates the virus attachment. After the attachment protein goes under some conformational changes resulted into the fusion of membrane and entry of the virus into the host cell using the S2 domain of virus surface protein [6]. The union of S proteins, the virus pathogen seems as a trimeric form which provided a crown-like appearance, due to this it is commonly known as coronavirus [7-8]. The hydroxychloroquine, chloroquine, and antiviral drugs like favipiravir, remdesivir, ritonavir, lopinavir, oseltamivir have been studied by docking to screen out their potential against virus protease. Therefore, this study is conducted to find out the potentiality of some FDA approved drugs to manage the disease more significantly.

2. MATERIALS AND METHODS

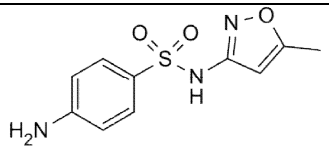
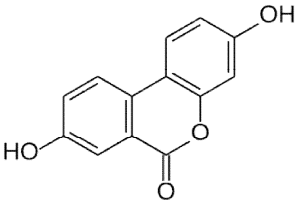
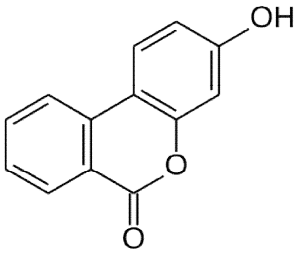
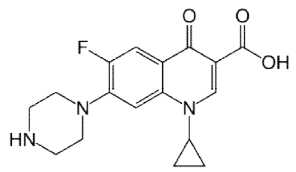
2.1 Drug Compounds Preparation

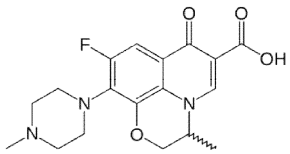
The 2 Dimensional (2D) structures of drugs molecules Sulfamethoxazole, Urolithin A, Urolithin B, Ciprofloxacin and Ofloxacin (Table 1) were downloaded from PubChem Database available on National Center for Biotechnology Information (NCBI) (https://pubchem.ncbi.nlm.nih.gov/), further converted to .pdb files and minimized using Chemistry at HARvard Molecular Mechanics (CHARMm) force field energy minimization steps as directed by Discovery Studio visualizer 2019 [9-10].

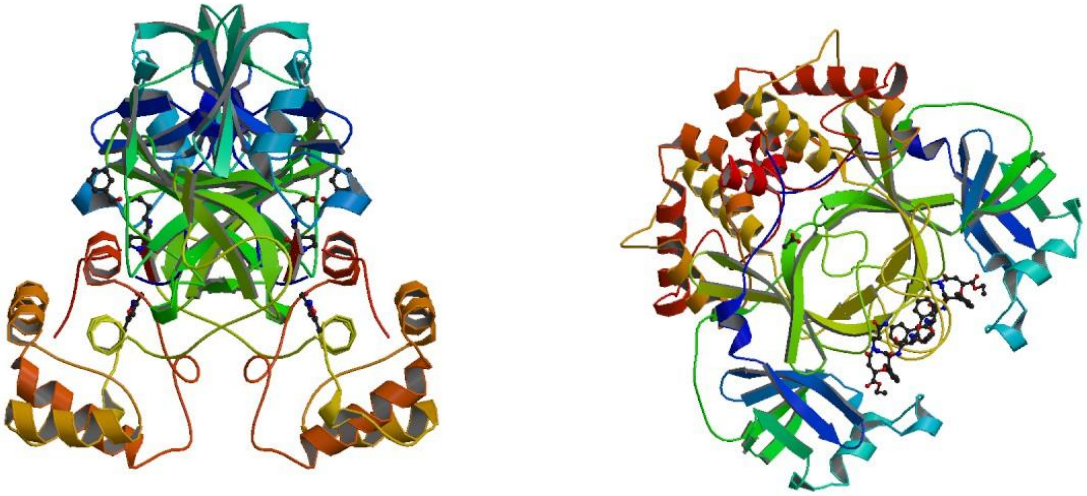
2.2 COVID-19 Receptor Molecules Preparation

The 3D structures of COVID-19 Protease (PDB ID: 6LU7) (Fig. 1a) bounded with N3 inhibitor and COVID-19 main peptidase (PDB ID: 2GTB) (Fig. 1b) bounded with Substrate-like Aza-peptide was downloaded from Protein Data Bank (PDB) (www.rcsb.org). To prepare the 3D crystal structure for docking studies, water molecules were removed and HETATM (hetero atom) from the published structures and also CHARMm force field was applied for energy minimization [11]. We also have analyzed the binding site of the pre-bonded ligand molecules in both structures and obtained the amino acid residues information those available in the active site to implement docking analysis on the same binding pocket. All editing of 3D structures has been done by Discovery Studio Visualizer 2019 [10-11].

Table 1. Showing detailed information related to selected drugs for the docking study against virus protease

S. no.	Drugs Name	Molecular Weight	Molecular Formula	Structure	SMILES ID	PubChem ID
1.	Sulfamethoxazole	253.28 g/mol	$C_{10}H_{11}N_3O_3S$		CC1=CC(=NO1)NS(=O)(=O)C2=CC=C(C=C2)N	https://pubchem.ncbi.nlm.nih.gov/compound/5329
2.	Urolithin A	228.2 g/mol	$C_{13}H_8O_4$		C1=CC2=C(C=C1O)C(=O)OC3=C2C=CC(=C3)O	https://pubchem.ncbi.nlm.nih.gov/compound/5488186
3.	Urolithin B	212.2 g/mol	$C_{13}H_8O_3$		C1=CC=C2C(=C1)C3=C(C=C(C=C3)O)OC2=O	https://pubchem.ncbi.nlm.nih.gov/compound/5380406
4.	Ciprofloxacin	331.34 g/mol	$C_{17}H_{18}FN_3O_3$		C1CC1N2C=C(C(=O)C3=CC(=C(C=C32)N4CCNCC4)F)C(=O)O	https://pubchem.ncbi.nlm.nih.gov/compound/2764

S. no.	Drugs Name	Molecular Weight	Molecular Formula	Structure	SMILES ID	PubChem ID
5.	Ofloxacin	361.4 g/mol	$C_{18}H_{20}FN_3O_4$		CC1COC2=C3N1C=C(C(=O)C3=CC(=C2N4CCN(CC4)C)F)C(=O)O	https://pubchem.ncbi.nlm.nih.gov/compound/4583



(a) (b)

Fig. 1. (a) The 3D crystal structure of COVID-19 main protease (PDB ID:6LU7) and (b) main peptidase (PDB ID: 2GTB) in complex with an inhibitor N3 (PBD ID: 6LU7) and aza-peptide epoxide

3. RESULTS

Sulfamethoxazole has interacted with enzyme peptidase (PDB ID:2GTB) with binding energy -7.01 kcal/mol, inhibition constant 15.20 uM and among five hydrogen bonds two were A:GLY143:HN - :UNK1:O9, A:SER144:HG - :UNK1:O10 formed at a distance 2.5023 and 2.35075 Å respectively. The amino acid residues involved in hydrophobic interactions were His41, Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, His163, His164, Met165, Glu16 (Table 2). Sulfamethoxazole has interacted (PDB ID: 6LU7) with a binding energy -6.81 kcal/mol, inhibition constant 43.32 uM and among four hydrogen bonds two were:UNK1:H22 - A:CYS145:SG, :UNK1:H27 - A:GLN189:OE1 formed at a distance 2.40469 and 2.03178 Å respectively. The amino acid residues involved in hydrophobic interactions were His41, Met49, Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, His163, His164, Met165, Glu166, His172, Gln189. The above results have shown that Sulfamethoxazole binds significantly with the enzyme (PDB ID: 6LU7) as it has found to interact with more negative binding energy and involvement of hydrogen bonds. Although, hydrophobic interactions were found to be involved with both the enzyme (Table 3). Ciprofloxacin has interacted (PDB ID:2GTB) with binding energy -7.05 kcal/mol, inhibition constant 56.99 uM and favorable hydrogen bond was A:GLY143:HN - :UNK1:F21 form at a distance 2.04045 Å. The amino acid residues involved in hydrophobic interactions were His41, Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, His163, His164, Met165, Glu166, His172, Arg188, Gln189. Ciprofloxacin interacts (PDB ID:6LU7) with binding energy -7.66 kcal/mol, inhibition constant 20.63 uM and five hydrogen bond formed was: UNK1:H37 - A: PHE140: O form at a distance 2.48494 Å. The amino acid residues involved in hydrophobic interactions were His41, Met49, Tyr54, Phe140, Leu141, Gly143, Ser144, Cys145, His163, His164, Met165, Glu166, His172, Arg188, Gln189 (Table 2). Ciprofloxacin has found to interact more significantly with the target enzymes of the virus (--7.05 kcal/mol ; 7.66 kcal/mol). The binding interactions were found similar as the binding energies have very close values and the same number of hydrogen bonds. The involvement of hydrophobic interactions was also found to be observed with the distinct amino acids (Table 3). Ofloxacin was found to interact (PDB ID:6LU7) with a binding energy -6.84 kcal/mol, inhibition constant 46.19 uM and two hydrogen bonds formed were A:ALA191:CA - :UNK1:O26 , :UNK1:C17 - A:GLN189:OE1 form at a distance 2.90989 3.35633 Å respectively. The amino acid residues involved in hydrophobic interactions were His164, Met165, Glu166, Leu167, Pro168, Gln189, Thr190, Ala191, Gln192 (Table 2). Ofloxacin was also analyzed to interact against the virus target (PDB ID:6LU7) with a binding energy -8.00 kcal/mol, inhibition constant 17.02 uM and six involved hydrogen bonds were A:HIS41:HE2 - :UNK1:O11, A:GLY143:HN - :UNK1:O25, A:CYS145:HN - :UNK1:O26, A:GLU166:HN - :UNK1:O4, UNK1:H46 - A:LEU141:O, UNK1:C22 - A:THR190:O form at a distance 2.9611, 1.83274, 2.57688, 1.94514, 1.789, 2.9369, The amino acids residues involved in hydrophobic interactions were His41, Leu141, Asn142, Gly143, Ser144, Cys145, His163, His164, Met165, Glu166, Gln189, Thr190, Gln192. From the above results, it is clear that Ofloxacin interacts more significantly (PDB ID:6LU7) with high binding energy -6.84 kcal/mol, than the enzyme peptidase (PDB ID:2GTB) (Table 3).

Urolithin A interacted (PDB ID:2GTB) with binding energy -6.93 *kcal/mol*, inhibition constant 22.80 uM and three hydrogen bonds were A:GLU166:HN - :UNK1:O9, : UNK1:H25 - A:THR190:O, : A:PRO168:CD - :UNK1:O17 form at a distance 2.03855, 2.20398 and 2.93912 Å respectively. The amino acids residues involved in hydrophobic interactions were His41, His164, Met165, Glu166, Pro168, Arg188, Gln189, Thr190, Ala191. Urolithin B interacted (PDB ID:2GTB) with binding energy -6.74 *kcal/mol*, inhibition constant 18.90 uM and a single hydrogen hydrogen bond was UNK1:H24 - A:GLN192:O form at a distance 2.42713 Å. The amino acids residues involved in hydrophobic interactions were Met165, Leu167, Pro168, Phe185,Thr190, Gln192, Ala193, Ala194 (Table 2; Fig. 2 A-B).

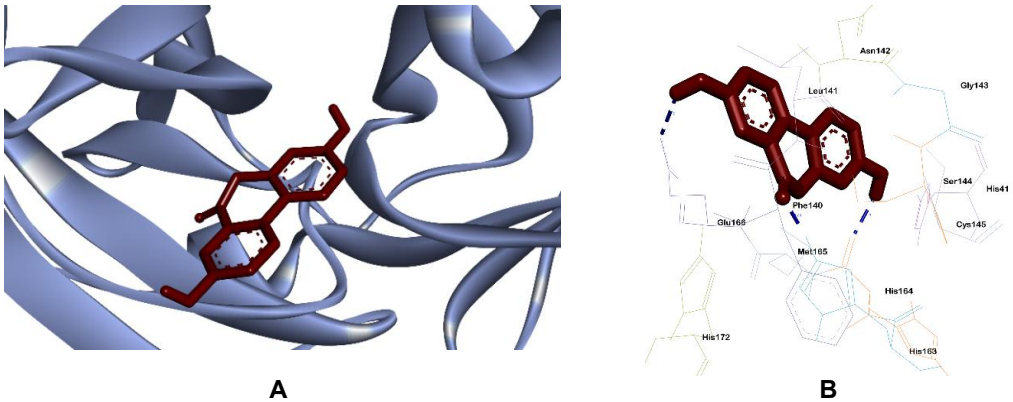
Urolithin A interacted (PDB ID:6LU7) with the binding energy -5.46 *kcal/mol*, inhibition constant 274.77 uM and 3 hydrogen bonds (:UNK1:H21 - A:ALA27:O, :UNK1:H25 - A:ILE68:O and A:HIS66:HN - :UNK1) form 2.41147, 1.96372, and 2.43154 Å, respectively, Ala27, Thr63, Trp64, Phe65, His66, Ala67 and ,Ile68 amino acids were involved in hydrophobic interaction(Table 2). Urolithin B interacted with the binding energy -4.67 *kcal/mol*, inhibition constant 133.58 uM and 2 hydrogen bonds (A:GLN218:HN - :UNK1:O16 and :UNK1:H24 - A:ASP215:OD2) formed with the lengths of

2.0037 and 2.01499 Å, respectively. Asn30, Phe32, Leu212, Asp215, Leu216, Pro217, Gln218 amino acids were involved in hydrophobic interaction (Table 2; Fig. 3:C-D). Both types of Urolithin have also found to be interacted with spike protein but interaction were less significant as compare to protease and peptidase. The observed binding energies of Urolithin A and Urolithin B with spike protein were found to be -5.16; -4.67 Kcal/mol. Urolithin molecules were also found to be interacted with spike protein but it was less significant.

4. DISCUSSION

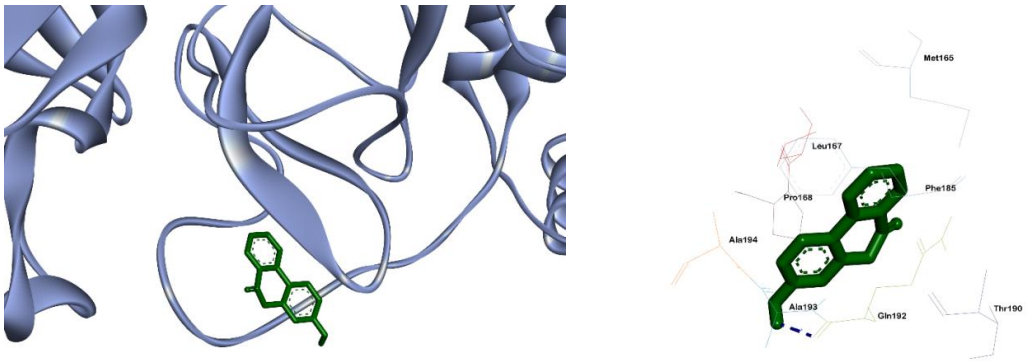
It is analyzed from the study that drugs interact with the formation of hydrogen bonds as well as the formation of hydrophobic bonds with the different amino acid residues of the virus protease and peptidase enzymes. All these drugs belong to the Fluoroquinolones class of antimicrobial agents, inhibit DNA gyrase, and interfere with the function of topoisomerase. This class of drugs has been used in bacterial infection including bacterial bronchitis. These drugs interact more strongly with the virus protease and could be a choice of drug to prevent the entry of viruses into the host cell [12].

Urolithin A and Urolithin B have also found to interact with spike protein but the interaction was less significant as compare to protease and peptidase. The interaction of Urolithins with virus target enzymes are shown in Fig. 2 and Fig. 3 and docking results in Table 2; Table 3. The observed binding energies of Urolithin A and Urolithin B with spike protein were found to be -5.16; -4.67 Kcal/mol. (Fig. 4 A-B). The most common interacting amino acids of enzymes target of the virus observed were His41, His164, Met165, Glu166, Gln189. Recently, docking studied have been conducted on Andrographolide and some other natural Phyto-constituents like g Rhein (-8.1 Kcal/mol), Withanolide D (-7.8 Kcal/mol), Withaferin A (-7.7 Kcal/mol), Enoxacin (-7.4 Kcal/mol), and Aloe-emodin (-7.4 Kcal/mol). Moreover, previously reported docking studies have also been described as the binding energy -7 to -9.0 Kcal/mole which are close to Urolithin and other drugs of this study [13-17]. From the docking studied parameters, it is stated that the Urolithin and antimicrobial agents of fluoroquinolones class could significantly inhibit the virus protease and peptidase. The antimicrobial agents have also been reported to reduce the inflammation, bronchitis, and inflammatory mediated fever. Thus, these antibiotics could be helpful to manage the COVID-19 disease. Moreover, the patient also required nutritional supplements along with the medications. The docking study revealed that Urolithin also has the potential to inhibit the virus protease and peptidase more significantly. Urolithin phyto-constituents of pomegranate and its anti-inflammatory, antioxidant and other pharmacological properties have been explored [15] and it is well-known as healing food and anciently used to cure, ulcers, aphthae, and diarrhea in folk medicine Thus, intake of pomegranate juice enriched with Urolithin could be helpful to potentiate the anti-inflammatory and antiviral effects of prescribed drugs.



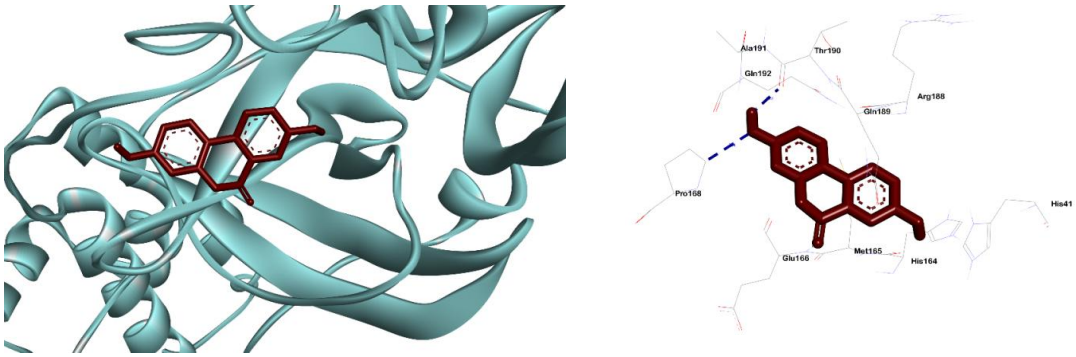
A B

Fig. 2. A and B light blue color ribbon pattern showing COVID-19 Peptidase (PDB ID: 2GTB) interaction with B (Urolithin A in maroon color) with the stick pattern in the center amino acid residues involved in hydrophobic interaction shown by wire pattern and in the surroundings formed hydrogen bonds are shown by blue dotted lines



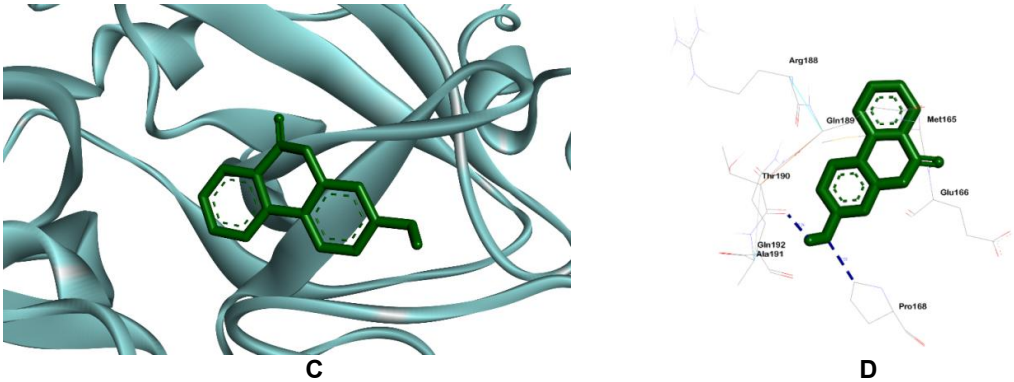
C D

Fig. 2. C and D light blue color ribbon pattern showing COVID-19 Peptidase (PDB ID: 2GTB) interaction with D (Urolithin B in green color) with the stick pattern in the center amino acid residues involved in hydrophobic interaction shown by wire pattern and in the surroundings formed hydrogen bonds are represented by blue dotted lines



A B

Fig. 3. A and B and E light turquois color ribbon pattern showing COVID-19 Protease (PDB ID: 6LU7) interaction with Fig 3 A (Urolithin A in maroon color) with the stick pattern in the center amino acid residues involved in hydrophobic interaction shown by wire pattern and in the surroundings formed hydrogen bonds are shown by blue dotted lines



C D

Fig. 3. C and D light turquois color ribbon pattern showing COVID-19 Protease (PDB ID: 6LU7) interaction with D (Urolithin B in green color) with the stick pattern in the center amino acid residues involved in hydrophobic interaction shown by wire pattern and in the surroundings formed hydrogen bonds shown by blue dotted lines

Table 2. Docking studies for Urolithin and selected drug candidates against covid-19 peptidase (PDB ID: 2GTB)

S. No.	Drugs Name	Final Intermolecular Energy (Kcal/mol)	vdW + Hbond + desolv Energy (Kcal/ mol)	Electrostatic Energy (Kcal/mol)	Inhibition Constant	Hbond name	Hbond length (Angstrom)	Residues involved in hydrophobic interaction
1.	Sulfamethoxazole	-7.01	-6.81	-0.20	15.20 uM	A:GLY143:HN - :UNK1:O9 A:SER144:HG - :UNK1:O10 A:CYS145:HN - :UNK1:O10 A:CYS145:HG - :UNK1:O9 A:HIS163:HE2 - :UNK1:O10 :UNK1:H22 - A:HIS164:O :UNK1:H28 - A:GLU166:OE1 A:GLU166:HN - :UNK1	2.35075 2.5023 2.72732 2.05675 2.7289 2.0756 1.91809 2.24257	His41,Phe140,Leu141,Asn142,Gly14,Ser144,Cys145,His163,His164,Met165,Glu166
2.	Urolithin A	-6.73	-6.47	-0.26	32.13 uM	A:HIS163:HE2 - :UNK1:O9 :UNK1:H21 - A:GLU166:OE1 :UNK1:H25 - A:HIS164:O	1.92685 2.40298 2.11331	His41,Phe140,Leu141,Asn142,Gly143,Ser144,Cys145,His163,His164,Met165,Glu166,His172
3.	Urolithin B	-6.74	-6.73	-0.01	18.90 uM	:UNK1:H24 - A:GLN192:O	2.42713	Met165,Leu167, Pro168,Phe185,Thr190,Gln192, Ala193,Ala194
4.	2,2-Dichloro-N-[1,3-dihydroxy-1-(4-nitrophenyl) propan-2-yl]acetamide Chloramphenicol	-6.71	-6.50	-0.21	96.50 uM	A:GLU166:HN - :UNK1:O13 :UNK1:H32 - A:ARG188:O A:PRO168:CD - :UNK1:O19 :UNK1:C8 - A:GLU166:O	2.04549 2.22512 3.73249 3.71591	His164,Met165,Glu166,Leu167,Pro168,Phe185,Arg188,Gln189,Thr190,Gln192,Ala193, Ala194
5.	Ciprofloxacin	-7.05	-5.91	-1.14	56.99 uM	A:GLY143:HN - :UNK1:F21 A:CYS145:HG - :UNK1:F21 :UNK1:H37 - A:PHE140:O	2.04045 2.43643 2.15751	His41,Phe140 ,Leu141,Asn142,Gly143,Ser144, Cys145,His163,His164,Met165,G

S. No.	Drugs Name	Final Intermolecular Energy (Kcal/mol)	vdW + Hbond + desolv Energy (Kcal/ mol)	Electrostatic Energy (Kcal/mol)	Inhibition Constant	Hbond name	Hbond length (Angstrom)	Residues involved in hydrophobic interaction
						:UNK1:H37 - A:GLU166:OE2 :UNK1:C19 - A:LEU141:O	2.26076 3.37983	lu166,His172,Arg188,Gln189
6.	Ofloxacin	-6.84	-6.46	-0.38	46.19 uM	A:ALA191:CA - :UNK1:O26 :UNK1:C17 - A:GLN189:OE1	2.90989 3.35633	His164,Met165 ,Glu166,Leu167,Pro168,Gln189, Thr190,Ala191,Gln192

Table 3. Docking studies for Urolithin and selected drugs candidates for against covid-19 protease (PDB ID: 6LU7)

S. no.	Drugs Name	Final Intermolecular Energy (Kcal/mol)	vdW + Hbond + desolv Energy (Kcal/mol)	Electrostatic Energy (Kcal/mol)	Inhibition Constant	Hbond name	Hbond length (Angstrom)	Residues involved in hydrophobic interaction
1.	Sulfameth oxazole	-6.81	-6.62	-0.19	43.32 uM	:UNK1:H22 - A:CYS145:SG :UNK1:H27 - A:GLN189:OE1 A:ASN142:HA - :UNK1:O10 A:HIS163:HD2 - :UNK1:N5	2.40469 2.03178 1.82193 2.96616	His41,Met49 ,Phe140,Leu141,Asn142,Gly143,Ser14 4,Cys145,His163,His164,Met165,Glu16 6,His172,Gln189
2.	Urolithin A	-6.93	-6.92	-0.01	22.80 uM	A:GLU166:HN - :UNK1:O9 :UNK1:H25 - A:THR190:O A:PRO168:CD - :UNK1:O17	2.03855 2.20398 2.93912	His41,His164,Met165 ,Glu166,Pro168,Arg188,Gln189,Thr190, Ala191,Gln192
3.	Urolithin B	-6.91	-6.90	-0.01	14.34 uM	A:GLU166:HN - :UNK1:O16 :UNK1:H24 - A:THR190:O A:PRO168:CD - :UNK1:O13	2.10585 2.24132 2.89508	Met165,Glu166,Pro168,Arg188,Gln189, Thr190,Ala191,Gln192

S. no.	Drugs Name	Final Intermolecular Energy (Kcal/mol)	vdW + Hbond + desolv Energy (Kcal/mol)	Electrostatic Energy (Kcal/mol)	Inhibition Constant	Hbond name	Hbond length (Angstrom)	Residues involved in hydrophobic interaction
4.	2,2-Dichloro-N-[1,3-dihydroxy-1-(4-nitrophenyl)propan-2-yl]acetamide Chloramphenicol	-6.35	-6.01	-0.34	94.22 uM	A:GLY143:HN -:UNK1:O19 A:SER144:HN -:UNK1:O20 A:CYS145:HN -:UNK1:O20 :UNK1:H32 -A:GLU166:O	1.92205 2.93389 2.20462 2.39463	Asn142,Gly143,Ser144,Cys145,His164,Met165,Glu166,Arg188,Gln189,Thr190
5.	Ciprofloxacin	-7.66	-6.18	-1.48	20.63 uM	:UNK1:H37 -A:PHE140:O :UNK1:H37 -A:GLU166:OE2 :UNK1:C5 -A:GLN189:OE1 :UNK1:H42 -A:HIS41	2.48494 1.98064 3.51698 2.99067	His41,Met49,Tyr54,Phe140,Leu141,Gly143,Ser144,Cys145,His163,His164,Met165,Glu166,His172,Arg188,Gln189
6.	Ofloxacin	-8.00	-7.28	-0.72	17.02 uM	A:HIS41:HE2 -:UNK1:O11 A:GLY143:HN -:UNK1:O25 A:CYS145:HN -:UNK1:O26 A:GLU166:HN -:UNK1:O4 :UNK1:H46 -A:LEU141:O :UNK1:C22 -A:THR190:O	2.9611 1.83274 2.57688 1.94514 1.789 2.9369	His41,Leu141,Asn142,Gly143,Ser144,Cys145,His163,His164,Met165,Glu166,Gln189,Thr190,Gln192

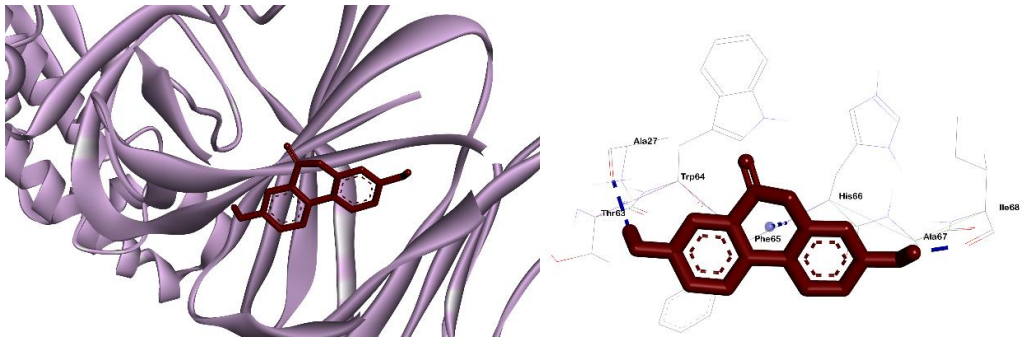


Fig. 4. A and B pink color ribbon pattern showing COVID-19 Spike protein (PDB ID: 6VYB) interaction with B (Uro A in maroon color) with the stick pattern in the center amino acid residues involved in hydrophobic interaction shown by wire pattern and in the surroundings. Formed hydrogen bonds shown by blue dotted lines

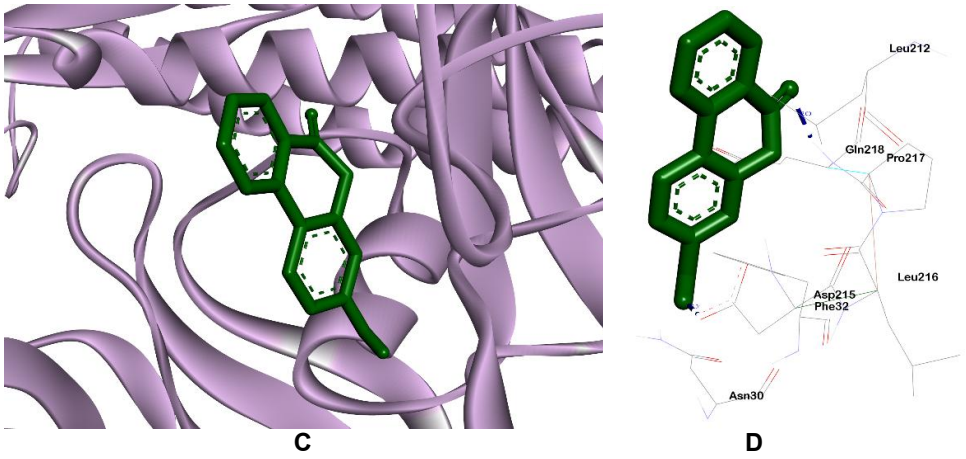


Fig. 4. C and D light pink color ribbon pattern showing COVID-19 Spike protein (PDB ID: 6VYB) interaction with C (Uro B in green color) with the stick pattern in the center amino acid residues involved in hydrophobic interaction shown by wire pattern and in the surroundings. Formed hydrogen bonds shown by blue dotted lines

5. CONCLUSION

The supplementation to ailment becomes popular since the last decades and the use of therapeutic agents with the supplement could synergies the curing effects. In the conclusion of this study, it is stated that Urolithin and antimicrobial agents have the potential to inhibit the virus protease as well as peptidase significantly and could prevent the entry of the virus to the host cell. However, the inventions to human use are limited for the Urolithin. Thus, further research on the antiviral potential of Urolithin and antimicrobial agents could be beneficial to control as well as manage COVID-19 disease. Thus, it concluded that prescribe medicines and nutritional supplements enriched with Urolithin, zinc, vitamins, and antioxidants could help to manage the COVID-19 disease.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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