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SARS-CoV-2 protease inhibiting phytocompounds from *Datura metel* L.: An *in silico* investigation for potential drugs unaffected by viral mutations against COVID-19

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Abstract

Viral mutations can become more common as a result of natural selection, random genetic drift or recent epidemiological trends. Even more difficult is to determine whether a single mutation will affect the fate of an illness or a pandemic. World Health Organization designated the latest strain of SARS-CoV-2, the Omicron, as a "variant of concern" as more countries are reporting cases, and it contains a unique mix of mutations that might help it spread faster. Mutations in the SARS-CoV-2 strains at the high rates lead to the in effectiveness of vaccines and developed drugs. As the mutations occur only on the spike proteins of the viral particles, targeting other vital enzymes, *i.e.*, proteases for drug discovery paves way for potential drug candidate irrespective of the mutations. So, the present study focuses on identifying the phytocompounds from *Datura metal* L. inhibiting the SARS-CoV-2 proteases. The druglikeness, PASS predictions and ADMET properties of the selected compounds were performed. 31 compounds were identified from the KNApSAck database and subjected to molecular docking studies. From the analysis, 7 compounds.Withametelin I, Withametelin J, Withametelin K, Withametelin L, Withametelin M, Withametelin N and Withametelin O showed significant binding energies and ADMET values. Therefore, these compounds can be further utilized for development of novel drugs for treatment of SARS-CoV-2 infections.

1. Introduction

SARS-CoV-2 is the seventh human coronavirus and belongs to the CoV genus of the coronavirinae subfamily of the Nidovirals order. According to the WHO (Nathan *et al*., 2020; Afroz Alam, 2021), SARS-CoV-2 was detected in Wuhan, Hubei Province, China, in the latter half of 2019 and has spread to 213 nations, regions, and territories. With 79.5 per cent sequence identity and the same mechanism for host cell entry, *via* the cell's angiotensin-converting enzyme-2 (ACE-2) surface protein, it most closely resembles the SARS-CoV-1, the coronavirus strain that caused the two most recent epidemics, in 2002-2003 and 2012, respectively. Although, the lung is the primary target of coronavirus infection, the widespread presence of ACE2 receptors in other organs (Wang *et al*., 2020).

Young people normally have modest symptoms, but it can lead to severe lower respiratory illness, which mostly affects the elderly and those with additional co-morbidities such cardiovascular disease, pre-existing respiratory disease, diabetes, hypertension, or cancer (Singhal, 2020). The most common symptoms of COVID-19 infection include fever, chills, a dry cough, muscular or bodily pains, shortness of breath, headache, fatigue, loss of taste or smell, sore throat, nausea or vomiting, congestion or runny nose and diarrhoea. These symptoms might appear anywhere between 2 and 14 days after you have been exposed to the virus (Huang *et al*., 2020). Symptoms include difficulty in breathing, chest discomfort or pressure, blue lips or face, abrupt bewilderment, and difficulties in staying awake (Li *et al*., 2020). Since then, the virus has spread around the world, infecting 265,730,859 individuals with a recorded death of 5,264,743 and recovery of 239,434,362 patients, as of December 5, 2021 (https://www.worldometers.info/coronavirus/). SARS-CoV-2, SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), all cause severe pneumonia, with death rates of 2.9 per cent, 9.6% and 36%, respectively. OC43, NL63, HKU1 and 229E are the other four human coronaviruses that induce self-limited sickness with modest symptoms.

However, a mutation tracker based on over 200000 genome isolates discovered over 5000 mutations in the spike (S) protein in SARS-Cov-2. Virus mutations can become more common as a result of natural selection, random genetic drift, or recent epidemiological trends. Because, these factors might interact, it is frequently difficult to tell whether a viral mutation spreads *via* fitness or by chance. Even more difficult is determining whether a single mutation will affect the fate of an illness or a pandemic (Chen *et al*., 2020). Early in the pandemic, an amino acid mutation in the virus's spike protein, D614G, appeared, and viruses containing G614 are currently prevalent in many parts of the world. The key concerns are whether this is due to natural selection and what this signifies for the COVID-19

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pandemic. Transmission is crucial for viruses like SARS-CoV-2 because if they do not get into another host, their lineage would die. E484K is a mutation that was originally discovered in the South African SARS-CoV-2 variant, has now been identified in the UK fast-spreading variant, prompting fears the virus is developing more and could become resistant to vaccines (Wang Dawei *et al*., 2020).

The Omicron variant of SARS-CoV-2 is the latest coronavirus strain to be labelled a "variant of concern" by the World Health Organization: more countries are reporting cases, and it contains a unique mix of mutations that might help it spread faster. Scientists are also attempting to establish if the currently available vaccinations are useful in combating it. The Omicron variation is the most divergent variety found in significant numbers during the pandemic, raising major concerns that it might be linked to a significant decrease in vaccination efficacy and an increased risk of reinfection.

Proteases are classified into distinct classes based on the catalytic amino acid. Whereas, the SARS-CoV-2 primary protease is a cysteine protease. Renin, a human pharmacological target, is also a member of this family. The HCV protease, as well as the human protease DPP-4, coagulation factor Xa, and thrombin, are all serine proteases, whereas the angiotensin-converting enzyme (ACE) is a metalloproteinase (Eleftheriou *et al*., 2020; Drag *et al*., 2020).

Similarities in the catalytic amino acids of the active site and the type of amino acids in the substrate may indicate that the proteases can be effectively inhibited by the same inhibitors. However, the type of the active site's surrounding amino acids, as well as the active centre's 3D shape, are critical. The primary protease (Mpro, 3CLpro, nsp5) garnered a lot of interest among the corona-viral targets that have been researched in the past, especially after the initial SARS-CoV outbreak in the early 2000s (Zhang *et al*., 2020). Mutation in the SARS-CoV-2 strains at the high rates leads to the ineffective vaccines and developed drugs. As the mutation occurs only on the spike proteins of the virus particle, targeting other vital enzymes, *i.e*., proteases for drug discovery paves way for potential drug candidate irrespective of the mutations.

D. metel, also known as Indian Thornapple, Hindu Datura, or Metel in Europe and Devil's Trumpet or Angel's Trumpet in the United States, is a shrub-like annual or short-lived, shrubby perennial, distributed throughout India (Khaton and Shaik, 2012; Kuntal Das *et al*., 2016). The tall shrub *D. metel* has spreading branches. A perennial herbaceous plant in the Solanaceae family. Datura is used in many Ayurvedic medicines after purification method. The leaves of the Datura plant have anticancer, anti-inflammatory and antirheumatic potentials, and the blooms have proven antiasthmatic properties. The leaves, root and seeds are anticatarrhal, antidiarrhoeal, febrifuge, antidermatosis in nature (Agharkar *et al*., 1991). Therefore, the present study concentrates on identification of phytocompounds inhibiting the main proteases of SARS-CoV-2. The druglikeness and ADMET properties of the selected compounds were performed.

2. Materials and Methods

2.1 Target proteins preparation

The protease of SARS-CoV-2 (PDB ID: 6LU7) was used as target protein and their 3D structures were collected from the protein Data Bank (http://www.rcsb.org/) for this current research. To visualize the target proteins, Pymol tool is used and then ligands, protein related water molecules, and co-crystal ligands are removed (Figure 1). To prepare the proteins, Auto Dock Tools were used. It is an open source free software by add up charges and for energy minimization. Swiss PDB viewer is used and next changed to pdbqt format.

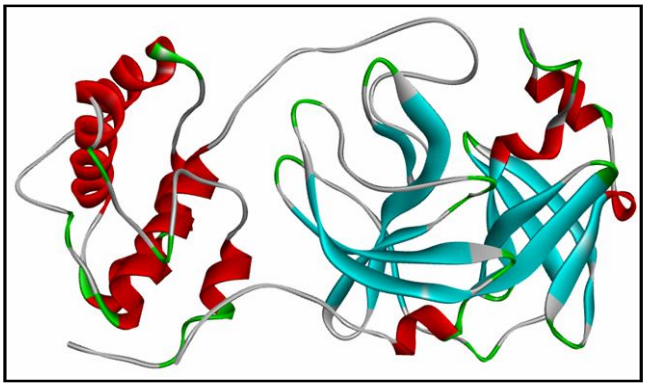

Figure 1: 3D structure of the SARS-Cov-2 Protease (PDB Id: 6LU7).

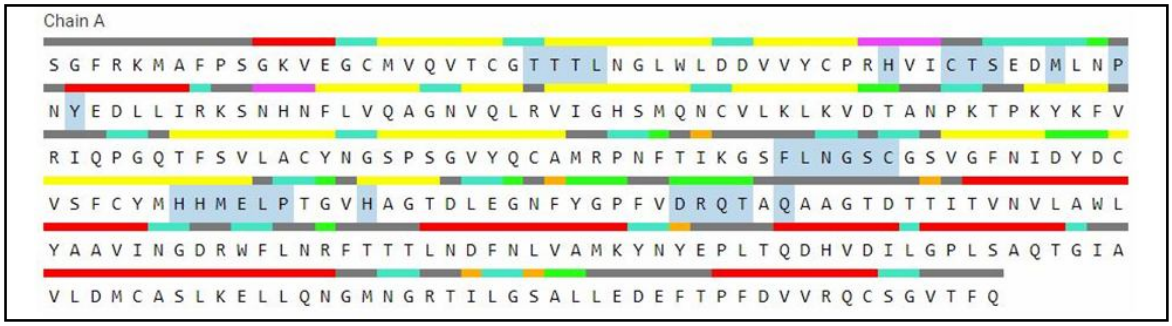

Figure 2: Binding site of the target protein. Binding sites were highlighted on grey.

2.2 Retrieval and preparation of ligands

By utilizing KNApSAck database (http://www.knapsackfamily.com/KNApSAcK/), the bioactive compounds present in the *D. metel* were recognized. Total of 31 phytocompounds were utilized in this present study (Table 1). The ligand preparation is carried out by identifying its assigning charges, optimising utilizing UFF (universal force field), torsion root, correcting torsion angle, and finally 3D atomic coordinates of the molecules formed by changed into pdbqt format.

Table 1: Compound showing druglikeness property

S. No	Compound name
1	Oleic acid
2	Putrescine
3	6beta-hydroxyhyoscyamine
4	Apohyoscine
5	Atropine
6	Hyoscine
7	Hyoscyamine
8	Littorine
9	Meteloidine
10	Norhyoscyamine
11	Pseudotropine
12	Tigloidine
13	Tropine
14	Obtusifoliol
15	3alpha-acetoxytropane
16	3beta-acetoxytropane
17	3beta-tigloyloxytropane
18	N-methylputrescine
19	N-methylpyrrolinium
20	Tropinone
21	Withametelin I
22	Withametelin J
23	Withametelin K
24	Withametelin L
25	Withametelin M
26	Withametelin N
27	Withametelin O
28	withametelin P
29	(-)-Hygrine
30	Phenyllactic acid
31	Phenylpyruvate

2.3 Screening of the of ligands for druglikeness

Swiss ADME (http://swissadme.ch/index.php) is used to determine druglikeness of the compounds. The druglikeness of a molecule is a critical criterion for validating it as a possible agonist for therapeutic targets. For screening the drug likeness property of compounds showing highest binding energy, Lipinski's rule of five (RO5) is used (Daina *et al.*, 2017).

2.4 Determination of functional sites of targets

For the significant docking analysis, precise estimation of the active (functional) site is needed. To identify amino acid residues in the active pocket site synthesis of target proteins, CASTp online server (Computed Atlas for Surface Topography) is used (Sanjay and Shanthi, 2020). By using CASTp which is a simple and handy tool is used to analyse protein topology and active site pockets. Active site evaluation is a censorious for setting the grid box prior to docking.

2.5 Molecular docking and protein-ligand interaction analysis

The PyRx tool *via* autodock wizard is used for all compounds which should be docked. Throughout the docking process, it was believed that the ligands were flexible and the protein was rigid. The grid parameter configuration file is formed in PyRxusing the grid box for 6LU7 (x = 17.27, y = 30.68, z = 48.04) (Dallakyan and Olson, 2015). The ligand with the highest binding energy (mostly negative) was identified as having the highest binding affinity after docking process. The ligands having lower binding energy were identified, and to analyse the interaction between ligand and the protein at the binding sites, Biovia drug discovery studio 2019 is used.

2.6 ADMET analysis of the selected ligands

ADMET analysis evaluation of absorption, metabolism, distribution, excretion and toxicity levels of the selected compounds using online based algorithms. There are many online database and offline software applications which helps in to predicting the drug candidates behaviour. We have used admet SAR (Cheng *et al.*, 2012) for ADMET predictions in this study. The potential phytochemicals showing higher binding energies were determined for their human intestinal absorption, blood-brain barrier penetration in *in vivo*, caco-2 cell permeability in *in vitro*, CYP4502C9 substrate and toxicity parameters including carcinogenicity on rats and mutagenicity by AMES test, *etc.*, were estimated.

2.7 Prediction of activity spectra for substances (PASS) for antibacterial activity

The antiviral activity of the determined compounds was predicted using the prediction of activity spectra for substances (PASS) programme (Hasan *et al.*, 2019). To predict a variety of physiological effects for a high number of substances, PASS programme is used. The substance's activity is predicted and quantified as probable inactivity (Pi) and probable activity (Pa). The components that have a Pa greater than Pi are those that are viable for the particular biological activity.

3. Results

3.1 Binding site analysis

CASTp was used to determine the functional site pockets in proteases of SARS-CoV-2. CASTp is a web-based tool for determining the amino acid residues in a protein's active pocket. Figure 2 illustrates the CASTp results for SARS-CoV-2 proteases. From CASTp results, the amino acids in the active site and their positions are listed as Table 2. To cover the binding sites of target proteins, grid boxes were generated.

Table 2: Amino acid residues in the binding sites

S. No.	Target protein	Amino acid residues in binding sites
1	Protease	A: 24-THR, 25-THR, 26-THR, 27-LEU, 41-HIS, 44-CYS, 45-THR, 46-SER, 49-MET, 52-PRO, 54-TYR, 140-PHE, 141-LEU, 142-ASN, 143-GLY, 144-SER, 145-CYS, 163-HIS, 164-HIS, 165-MET, 166-GLU, 167-LEU, 168-PRO, 172-HIS, 187-ASP, 188-ARG, 189-GLN, 190-THR, 192-GLN

Table 3: Binding affinity of the phytocompounds

S. No	Compound name	Binding energy (Kcal/mol)
1	Oleic acid	-4
2	Putrescine	-3.5
3	6beta-hydroxyhyoscyamine	-6.1
4	Apohyoscine	-6.3
5	Atropine	-5.1
6	Hyoscine	-6.1
7	Hyoscyamine	-5.7
8	Littorine	-6.4
9	Meteloidine	-5.8
10	Norhyoscyamine	-6
11	Pseudotropine	-4.3
12	Tigloidine	-5.4
13	Tropine	-4.3
14	Obtusifoliol	-6.7
15	3alpha-acetoxytropane	-4.8
16	3beta-acetoxytropane	-4.8
17	3beta-tigloyloxytropane	-5.6
18	N-methylputrescine	-3.5
19	N-methylpyrrolinium	-3
20	Tropinone	-4.1
21	Withametelin I*	-7.9
22	Withametelin J*	-8.4
23	Withametelin K*	-8.2
24	Withametelin L*	-8
25	Withametelin M*	-8
26	Withametelin N*	-8
27	Withametelin O*	-8
28	(-)-Hygrine	-4
29	Phenyllactic acid	-5.1
30	Phenylpyruvate	-5

*Compounds showing lower binding energy (<-7Kcal/mol)

3.2 Druglikeness properties

The druglikeness properties of the phytocompounds were evaluated using Lipinski rule of five (RO5). The molecular weight, H-bond acceptors, H-bond donors and MlogP values were evaluated. From the analysis of 31 compounds, all the compounds except Withametelin P satisfied RO5.

3.3 Molecular docking analysis

PyRx was utilised to dock all 30 compounds to their target protein, SARS-CoV-2 protease. The binding energies of the compounds were determined, and those with a lower binding energy (-7.0 Kcal/mol) were identified. About 7 compounds demonstrated a substantial binding energy (-7.0 Kcal/mol) which are listed in Table 3.

Table 4: Protein-ligand interaction analysis

S. No.	Compounds	Protein-ligand interactions	
		H-bond	Amino acid resideues
1	Withametelin I*	2	A: 143-GLY, 166-GLU
2	Withametelin J*	3	A: 142-ASN, 143-GLY, 144-SER
3	Withametelin K*	2	A: 166-GLU, 189-GLN
4	Withametelin L*	3	A: 143-GLY, 144-SER, 145-CYS
5	Withametelin M*	1	A: 189-GLN
6	Withametelin N*	2	A: 24-THR, 166-GLU
7	Withametelin O*	1	A: 26-THR

Table 5: PASS predictions

S. No.	Compounds	Pa	Pi
21	Withametelin I*	0.244	0.134
22	Withametelin J*	0.286	0.284
23	Withametelin K*	0.311	0.230
24	Withametelin L*	0.326	0.201
25	Withametelin M*	0.325	0.203
26	Withametelin N*	0.431	0.037
27	Withametelin O*	0.238	0.146

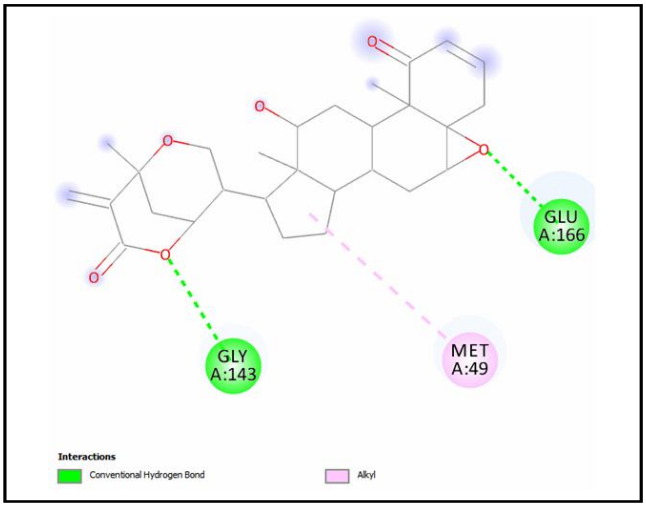

Figure 3: Interaction of withametelin I on SARS-CoV-2 protease.

Table 6: ADMET properties of the selected compounds

S. No.	Compound	ADMET analysis				
		In vivo blood-brain barrier penetration (C.brain/C.blood)	Human intestinal absorption	*In vitro* Caco-2 cell permeability (nm/sec)	Distribution	CYP4 502C9
1	Withametelin I*	0.86	0.94	0.56	0.74	0.82 (NS)
2	Withametelin J*	0.63	0.88	0.79	0.83	0.84 (NS)
3	Withametelin K*	0.87	0.94	0.57	0.83	0.87 (NS)
4	Withametelin L*	0.94	0.96	0.53	0.82	0.86 (NS)
5	Withametelin M*	0.94	0.96	0.53	0.82	0.86 (NS)
6	Withametelin N*	0.81	0.96	0.54	0.73	0.85 (NS)
7	Withametelin O*	0.63	0.88	0.79	0.83	0.89 (NS)

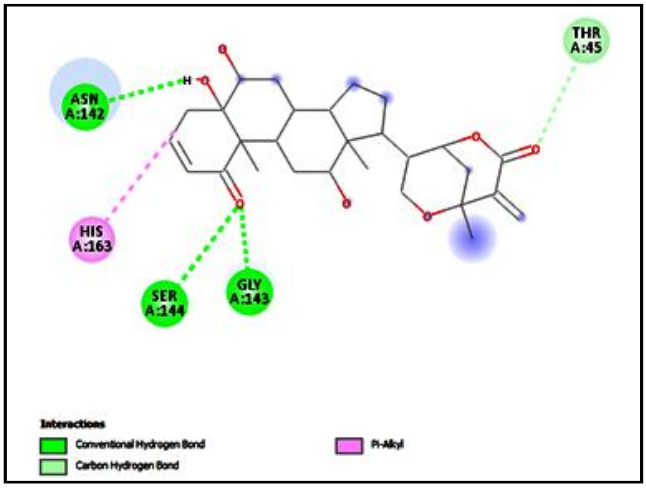

Figure 4: Interaction of Withametelin J on SARS-CoV-2 protease.

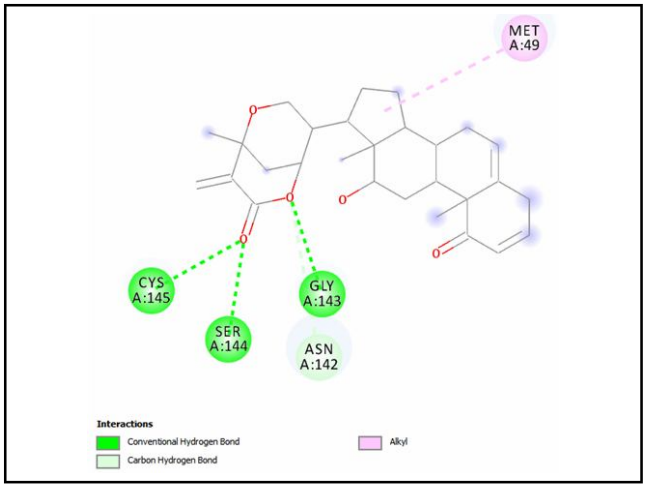

Figure 6: Interaction of Withametelin L on SARS-CoV-2 protease.

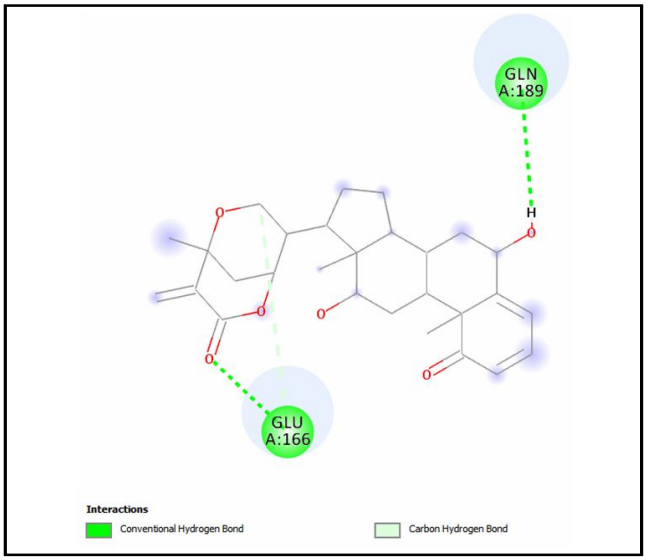

Figure 5: Interaction of Withametelin K on SARS-CoV-2 protease.

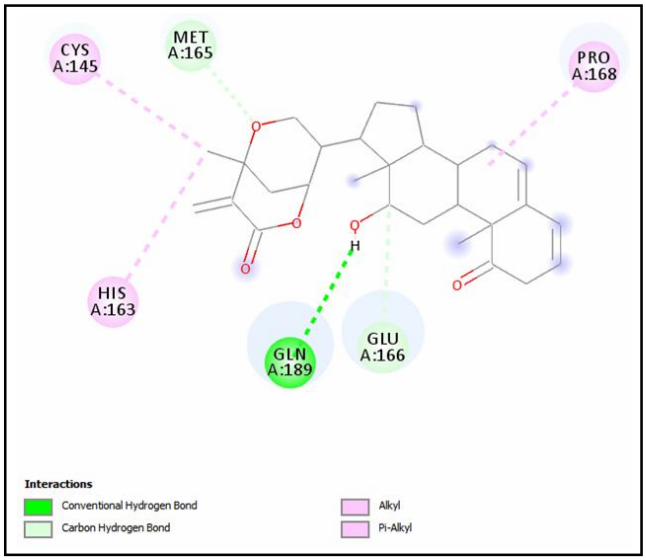

Figure 7: Interaction of Withametelin M on SARS-CoV-2 protease.

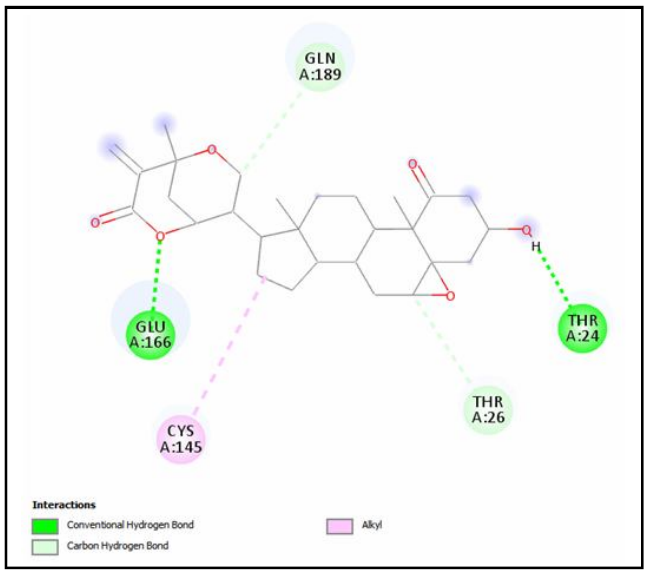

Figure 8: Interaction of Withametelin N on SARS-CoV-2 protease.

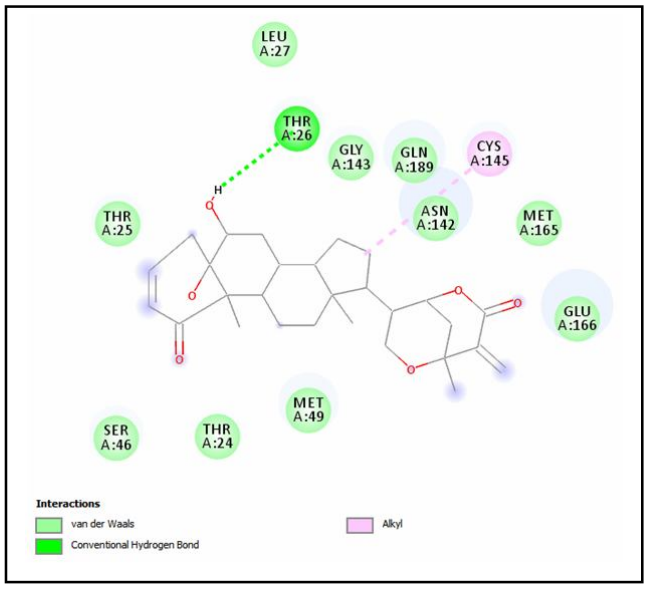

Figure 9: Interaction of Withametelin O on SARS-CoV-2 protease.

3.4 Protein-ligand interactions

The best-docked compounds were further examined for binding interactions on active sites with amino acid residues using Biovia Accelrys Discovery Studio Visualizer software. Bonding type, number of hydrogen bonds and hydrophobic interactions are a very important determinant of protein-ligand interactions as equal as binding affinity. The number of hydrogen bonds formed and amino acids involved in the interactions are tabulated in Table 4. The hydrogen bonds and other hydrophobic interactions of the ligands on the binding sites of the target proteins were shown in the Figures 3 to 9. All the 7 compounds showed H-bond formation on binding sites of the target protein.

3.5 PASS predictions

PASS prediction is evaluated to predict the antiviral action of the phytocompounds. The probable activity (Pa) should be higher than the probable inactivity (Pi). All the compounds showed higher Pa than the Pi. This is an indication of antiviral actions of the identified compounds (Table 5).

3.6 ADMET properties

The selected phytocompunds were subjected to distribution, absorption, metabolism, excretion and toxicity analysis using admet SAR program. *In vivo* blood-brain barrier penetration, human intestinal absorption, *in vitro* caco-2 cell permeability, mitochondrial distribution, non-substrate for CYP4502C9 were examined. Table 6 shows the ADMET properties of the compounds and the compounds were found to be AMES non-toxic and non-carcinogen.

4. Discussion

Increasing mutations in the spike protein of SARS-CoV-2 results in higher mortality and inability to develop new drugs for treatment. Protease enzyme is required for viral replication and has no near human homologues, making it a promising therapeutic target. Each of the active sites, like other cysteine proteases, has a Cys-His catalytic dyad that is responsible for the hydrolysis of the peptide bond at specified places along a polypeptide chain. The free protease (PDB codes 6Y2E (2) and 6Y84 (6) and inhibitor-bound proteases (PDB codes 6LU7, (6) 6Y2F, (7) and 6LZE (8)) have both had their structures determined by x-ray crystallography and have been placed in the protein data bank (PDB) (Shiryaev *et al*., 2012).

The structure of the SARS-CoV-2 major protease is nearly identical to that of the SARS-CoVortholog (96 per cent identity). Furthermore, all of the key residues involved in catalysis, binding, and dimerization are entirely conserved. As a result, the substrate choices of these two ortholog enzymes are very similar (Lankas *et al*., 2012). Therefore, the present study examined the inhibiting potential of *D. metel* compounds against SARS-CoV-2 proteases.

D. metel, that can grow to be 1.5 metres tall. Simple, alternate, dark green, widely ovate, shallowly lobed, and globous leaves are simple, alternate, dark green, roughly ovate, shallowly lobed, and globous. Flowers are enormous, solitary, trumpet-shaped, and have a delicious smell that is best experienced in the mornings and nights (Bristol *et al*.,1969). They come in a variety of colours, from white to yellow and light to dark purple. Insects pollinate the hermaphrodite blooms, which are hermaphrodite. The fruit is shaped like a capsule with small spines on it. Datura can grow in regular soil, but it loves rich, wet soil, or even highly alkaline soil, and it does not grow well in the shadow. It is distributed in warmer regions across the world as it prefers a such a climate (Drake *et al*., 1996).

D. metel is now seen all over the Southeast Asia even though, it is thought to have originated in north part of India. It also spreads to Africa and Central and South America, as well as the Caribbean through human migration. In modern days, in tropical regions around the globe, it is farmed as a source of the alkaloid-scopolamine, (Ratsch 1998). In India, *D. metel* is common in tropical areas and in the temperate parts of Himalayan mountain range. Apart from the

neighbouring Bangladesh where it grows widely in fallow lands and being used as a herbal medicine, they also seen in parts of Kenya, Uganda and Tanzania. Fertile calcareous soil nourishes its growth and different species of Datura are largely cultivated in subtropical and tropical areas for their beautiful flowers (Glotter *et al*., 1973).

D. metel seeds have been documented as having been utilised in ancient Indian medicine, current Indian folk medicine, and Ayurvedic medicine. Skin diseases, mental disorders, and respiratory ailments, among a slew of other maladies, are among the most prominent medical applications for Datura in these systems. The seeds are also occasionally used as an opiate replacement (Ratsch, 1998).

Datura has a long history of use, including the treatment of epilepsy, hysteria, insanity, heart illness, fever with catarrh, diarrhoea, and skin problems, among other things. Pain is relieved by crushing leaves. The herb is utilised in the treatment of asthma in China. The dried flowers and leaves are chopped into little bits and used in anti-asthmatic cigarettes in Vietnam. The flower extract can be used as an anaesthetic by ingesting 3 to 5 grams, which produces general anaesthesia in 5 minutes and lasts for 5 to 6 hours. Pain, chronic bronchitis, and asthma are all treated with the *D. metel* flower (Ko, 1999; Kam and Liew, 2002).

Leaves are used to treat scabies, eczema, and allergies in Bangladesh (Chowdhury *et al*., 1996). Dried entire plant powder is smoked to treat excessive or irregular breathing, and it is also used to increase pupils surrounding the eyes. Leaf juice can be applied to the skin or consumed to reduce pain and edoema. To minimise swelling of the gums or the base of the ears, leaf juice is combined with a little opium and administered to the afflicted region. On relieve, breast discomfort, combine leaf juice with lime and turmeric and apply it to the breasts (Rahmatullah *et al*., 2010). *D. metel* flowers have been used in traditional Bangladeshi medicine for millennia to cure asthma, convulsions, pain and rheumatism.

The flowers of *D. metel* are known as baimantuoluo in traditional Chinese medicine and are used to treat skin irritation and psoriasis (Wang *et al*., 2008). *D. metel* seeds are used to treat skin rashes, ulcers, bronchitis, jaundice and diabetes in Ayurvedic medicine. Seeds are used to make tea, which is a sedative, and blooms are dried and smoked as cigarettes in Brazil (Agra *et al*., 2007). Datura species are currently cultivated for the synthesis of secondary metabolites in a variety of ways.

Many distinct alkaloids may be discovered throughout the Datura plant, with the number of alkaloids increasing with the plant's age (Afsharypuor *et al*., 1995). A large variety of tropane alkaloids (hyoscyamine, hyoscine, littorine, acetoxytropine, valtropine, fastusine, fastusinine), a number of with anolides, and different trigloyl esters of tropine and pseudotropine are the main ingredients of the Datura plant. It has also been reported that the alkaloids like calystegines, nortropane, *etc.*, which block glycosidase, were also purified from various species of Datura (Ghani, 2003). The root has a larger concentration of atropine than the other sections. When compared to the root of the plant, the aerial sections frequently collected larger concentrations of scopolamine and lesser amounts of atropine (Afsharypuor *et al*., 1995).

The compounds present in the *D. metel* were subjected to molecular docking and compounds with higher binding energies were identified. The selected compounds were further subjected to druglikeness, PASS predictions for antiviral activity and ADMET properties. All the compounds were found to be AMES non-toxic and non-carcinogen. Similarly, Firdaus *et al*. (2020) investigated that Soxhlet and cold extracts of *D. metel* fruit and seed extract for antiviral activity against the rabies virus. *In vitro* cytotoxicity assay was done using 3-(4, 5-dimethyl-thiazolyl-2)-2, 5-diphenyltetrazolium bromide assay. The Datura seed extract showed potential *in vitro* antirabies activity. The study suggests further screening for *in vivo* activity against rabies virus in a murine model.

Roy *et al*. (2016) investigated that the Datura extracts were not cytotoxic below 5 mg/ml (CC_{50}). Titre of 10"4 rabies virus challenge virus standard (RV CVS) (50% tissue culture infective dose [1 $TCID_{50}$] was obtained by RFFT method and the challenge dose of 10 $TCID_{50}$ was used for antirabies assay. Datura fruit and seed (Soxhlet and cold) extracts showed 50% inhibition of RV CVS at 2.5 mg/ml and 1.25 mg/ml (inhibitory concentration 50% [IC_{50}], respectively. The tested extracts showed selectivity index (CC_{50}/ IC_{50}) ranging from 2 to 4. After the extraction of the viral RNA, an RT-PCR (real-time reverse transcription-polymerase chain reaction) was performed which showed a reduction in viral loadby 2-foldsat 1.25 mg/ml of the Datura seed (both cold aqueous and Soxhlet methanolic) extracts. These above findings confirm that phytocompounds in *D. metel* has potential antiviral action.

5. Conclusion

The present study concentrates on identification of phyto compounds inhibiting the main proteases of SARS-CoV-2 by molecular docking analysis. The druglikeness and ADMET properties of the selected compounds were performed. From the analysis, seven compounds, *i.e*., Withametelin I, Withametelin J, Withametelin K, Withametelin L, Withametelin M, Withametelin N and Withametelin O showed significant binding energies and significant ADMET values. Further studies are required to evaluate the *in vitro* and *in vivo* anti SARS-CoV-2 action and such compounds can be used for novel drugs for treatment of SARS-CoV-2 infections irrespective of the mutations.

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Conflict of interest

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

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