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Phytochemicals from *Solanum surattense* Burm.f. have high binding affinities for C-3 like main protease of COVID-19 (SARS-CoV-2)

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Abstract
Corona virus SARS-CoV-2, otherwise known as COVID-19 has created a pandemic, which since its outbreak in late December 2019, till as of June 20, 2020 has infected 8,766,741 people throughout the world and caused deaths of 462,706 persons. Any fully effective drugs or vaccines against the virus remain to be discovered. The objective of the present study was to evaluate through molecular docking studies a number of compounds present in the plant *Solanum surattense* regarding their ability to bind to the main protease of COVID-19 [C3-like protease or $3CL^{pro}$, (PDB ID: 6LU7)]. Molecular docking (blind) were done with the help of AutodockVina. We observed that of the thirteen phytochemicals studied, eight showed very strong binding affinities to $3CL^{pro}$ and four showed moderate to strong binding affinities. Furthermore, the bindings were to the region to which the protease inhibitor N3 has been shown to bind. The high binding affinities of the phytochemicals to $3CL^{pro}$ merit further studies of these compounds as potential inhibitors against COVID-19, since the protease is indispensable for viral replication.

Keywords: Corona virus, COVID-19, C3-like protease, *Solanum surattense*, molecular docking

Introduction
Corona viruses are zoonotic, meaning that they can be transmitted from animals to humans. Several corona viruses affecting human beings cause mild flu-like symptoms. However, in late December 2019, a corona virus emerged in a seafood market in Wuhan, China, which quickly turned into a pandemic and as of June 20, 2020 has infected 8,766,741 people throughout the world and caused deaths of 462,706 persons. Since a previous infection by a corona virus causing severe acute respiratory syndrome was named SARS, the present virus, which is very similar to SARS has been named SARS-CoV-2 or otherwise COVID-19 [1]. The animal origin of the virus remains to be found. Also, despite the best efforts of scientists throughout the world any therapeutic for the virus in the form of drugs or vaccines remain to be discovered.

Corona viruses are enveloped positive strand RNA viruses. Among the proteases in both SARS and SARS-CoV-2 responsible for viral replication is a chymotrypsin like protease variously referred to as C3-like protease or $3CL^{pro}$ or M^{pro}. The two proteases in SARS and SARS-CoV-2 ($3CL^{pro}$) share a 96% identity [2] and are considered prime targets for inhibition and so stopping further viral replication. However, to screen new compounds against a highly contagious virus like SARS-CoV-2 ($3CL^{pro}$), one needs expensive and fully protected laboratories to perform anti-viral experiments or utilize molecular modeling approaches (molecular docking) for computer assisted drug design and/or discovery [3]. That any or all compounds found in molecular docking to bind to key proteins of the virus will prove their ability to inhibit the virus *in vivo* is incorrect; nevertheless molecular docking has proved a good tool to screen new compounds against crucial proteins of a number of pathogens or target proteins in the human body enabling researchers to do further work in discovering a therapeutic. The objective of the present study was to evaluate phytochemicals from a highly valued medicinal plant of Bangladesh, *Solanum surattense* Burm.f. (Solanaceae) for their ability to bind to the C3-like protease or $3CL^{pro}$ of SARS-CoV-2; the plant is known as Indian nightshade in English and Kontikari in Bengali.

Solanum surattense is a wild growing herb. In Ayurveda, the roots of the plant are used to prepare dashmularishta, used as a tonic for lactating mothers [4]. In a fairly recent review, the plant has been mentioned to contain a number of steroids (beta-solamargine, campesterol, cholesterol, cycloartanol, sitosterol, stigmasterol, sitosteryl glucoside, stigmasteryl glucoside) and steroidal alkaloids (solasodine, solasonine, solasurine, solanine) besides alkaloids and glycoalkaloids (alpha-solamargine, tomatidenol, solanocarpine), flavonoids, phenolics, coumarins, and triterpenoids (apigenin, coumarin, esculetin, esculin, diosgenin, lupeol). Various pharmacological activities have been reported in the review; among them the most relevant are antioxidant, antiasthmatic, anti-HIV, analgesic, anti-inflammatory, and cardioprotective activity [5]. Considering that low dose dexamethasone has recently been shown to cut deaths in COVID patients [6], the steroid phytochemicals of *Solanum surattense* posed special interest.

Methods

Three-dimensional structure of COVID-19 major protease (3C-like protease)

The pdb file (6LU7) of the main protease of SARS-CoV-2 3C-like protease or SARS-CoV-2 $3CL^{pro}$ published before [7] was used in the present study. An inhibitor (called N3) was removed from the pdb file before using the protein's structure in our molecular docking studies. The active residues of SARS-CoV-2 3C-like protease are His41 and Cys145. Monomeric form of protein was used for molecular docking. Binding of some selected phytochemicalss to SARS-CoV-2 $3CL^{pro}$ have been shown to illustrate the binding site of the phytochemicals to the protease binding domain and the amino acids involved in the binding.

Compounds used in docking studies

We have studied various classes of phytochemicals known to occur in *Solanum surattense*. Ligand molecules were downloaded from Pubchem [8] in sdf format. Optimization was done with the force field type MMFF94 using Openbable softwares and saved as pdbqt format. The names of the compounds present in *Solanum surattense* were obtained from published reports [5, 9].

Ligand molecular docking studies

Molecular docking (blind) was conducted using AutoDock Vina [10]. We report ΔG values as an average of six values from the docking program. We show the pose of phytochemicals bound to SARS-CoV-2 main protease in our figures as obtained from PyMOL and displayed in Discovery Studio [11].

Phytochemicals

The structures of the various phytochemicals screened are shown in Figure 1.

Results and Discussion

The SARS-CoV-2 3C-like protease has two domains. The upper domain is the catalytic domain and contains two key catalytic residues His41 and Cys145. It is of interest to see the binding of some of the phytochemicals to the 3C-like protease and whether His41 and Cys 145 were involved in the binding.

Regarding binding energies, the highest affinity of -10.8 kcal/mol was demonstrated by alpha-solamargine, an alkaloid found in *Solanum surattense*. Other alkaloids and steroidal alkaloids also gave high binding energies. The results are shown in Table 1. The alkaloids tomatidenol and carpesterol both gave binding energies of -8.3 kcal/mol each, while the three steroidal alkaloids solanine, solasodine, and solasurine gave binding energies of -9.0, -8.3, and -9.1 kcal/mol, respectively. The quinine, purpurin vand the triterpenoid diosgenin gave high binding energies of -9.2 and -8.1 kcal/mol, respectively. A glucoside derivative of sitosterol (beta-sitosterol) gave a binding energy of -7.7 kcal/mol. It is evident that the plant appears to contain a number of compounds with high binding energies to the 3C-like protease. The compounds merit special attention because their high binding energy raises the possibility of discovery of therapeutics against COVID-19.

Table 1: Binding energy of *Solanum surattense* phytochemicals to SARS-CoV-2 main protease.

Phytochemical	Nature	Binding energy (ΔG, kcal/mol)
Cycloartanol	Steroid	-7.1
Diosgenin	Triterpenoid	-8.1
Lupeol	Triterpenoid	-7.6
Purpurin	Quinone	-9.2
Sitosteryl glucoside	Steroid	-7.7
Solanine	Steroidal alkaloid	-9.0
Solasodine	Steroidal alkaloid	-8.3
Tomatidenol	Alkaloid	-8.3
Solasurine	Steroidal alkaloid	-9.1
Alpha-solamargine	Alkaloid	-10.8
Carpesterol	Alkaloid	-8.3
Esculetin	Flavanoid	-6.2
Esculin	Polyphenol	-7.1

The interaction of alpha-solamargine with the C3-like protease is shown in Figure 2. The same moiety of the compound binds with both catalytic residues His41 and Cys145, creating a strong binding force. Other interacting amino acids of the C3-like protease with alpha-solamargine are Ser46, Ser144, His163, Asn142, Glu166, Met49, and Gln189. It may be noted that the interacting amino acids with the inhibitor N3 of the C3-like protease have previously been shown to include amino acids His41, Met49, Phe140, Leu141, Asn142, Gly143, His163, His164, Glu166, Leu167, Pro168, Gln189, Thr190, and Ala191. Thus six of the amino acids of the protease that interact with N3 including a major catalytic residue His41 also interact with alpha-solamargine. Additionally, the interaction of alpha-solamargine with the other catalytic residue of the protease Cys145 probably creates a much stronger bond of the protease with the phytochemical than the inhibitor N3.

Solanine (steroidal alkaloid) also interacts with Cys145 and His41 according to our best pose model (Figure 3). The compound appears to interact with two clusters of amino acids of the C3-like protease. The first cluster consists of His163, His164, Met165, and Pro168. The other cluster contains Asp187, Gln189, and Ala191. Additionally, solanine interacts with Met49 and Asn142. His164 and Met49 bond with the same moiety of solanine. Met49, His163 and His164 are interacting amino acids for inhibitor N#, which points to the possibility that both alpha-solamargine and solanine can be strong inhibitors of the C3-like protease. This assumption needs to be verified with viral inhibition studies *in vivo*. The docking results raise the possibility of further modifications of these compounds towards better therapeutics.

Solasurine (a steroidal alkaloid) interacts with the C3-like protease amino acids Phe8, Pro9, Ile152, Tyr154, Pro293, Phe294, Val297, and Arg298 (Figure 4). Multiple bonding of

amino acids to various moieties of solasurine can be seen. These multiple bonding to the same site include Phe8 and Pro9, Phe8 and Ile152, Tyr154 and Phe294, Pro293 and Val297, and Phe294 and Val297. To be noted is that solasurine does not interact with Cys145 and His41. However, the multiple bonding of eight different amino acids of the C3-like protease with solasurine can account for its high binding energy of -9.1 kcal/mol.

Another alkaloid, tomatidenol, besides binding to the catalytic residue Cys145, also binds to Ser144, Pro168 and Ala191 of the C3-like protease (Figure 5). The binding energy was also quite high at -8.3 kcal/mol. For brevity's sake the binding of the other nine phytochemicals have not been shown.

Cycloartanol from *Sutherlandia frutescens* has been reported to give immune potentiation effects [12]. The compound promoted interleukin-6 (IL-6) expression and suppressed IL-10 expression. Diosgenin reportedly exhibited antiviral activity *in vitro* against hepatitis C virus [13]. Lupane triterpenoids like lupeol, betulin and betulinic acid has been reported to exhibit antiviral activity against human immunodeficiency virus (HIV), herpes simplex virus (HSV), and Epstein-Barr virus (EBV) [14]. Strong antioxidant activity has been reported for purpurin, isolated from the common madder plant, *Rubia tinctoria* L. [15]. Beta-sitosterol has been shown to exhibit *in vitro* anti-HIV (anti-human immunodeficiency virus) activity by immunomodulatory mechanism though stabilization of $CD4^+$ T-lymphocyte counts and a significant decrease in interleukin-6 level [16].

Alpha-solanine is a common steroidal glycoalkaloid found in the *Solanum* genera plants, which include potato. The compound contains solanidine as aglycon. Another alkaloid, solamargine has a spirosolane basic skeleton and commonly found in *Solanum* genera plants. Steroidal glycosides found in *Solanum* genera plants reportedly exhibited antiviral activity against herpes simplex virus [17, 18]. Beta-sitosterol is reportedly active against plant viruses like tobacco mosaic virus or TMV [19].

Around 200 alkaloids have been reported from many *Solanum* species [20]. All these alkaloids possess the C27 cholestane skeleton and are divided into five structural types – solanidine, spirosolanes, solacongestidine, solanocapsine, and jurbidine. Although more attention has been focused on the anti-cancer activities of the alkaloids, at least a number of them need investigation as anti-viral agents [21]. The alkaloid, carpesterol gave a binding energy of -8.3 kcal/mol with the C3-like protease. It interacted with the amino acids Arg40, Cys85, Phe 134 and Pro 184 (Figure 6). Interestingly, the compound has been identified as a lead compound against human hepatitis B viral capsid protein through *in silico* method [22].

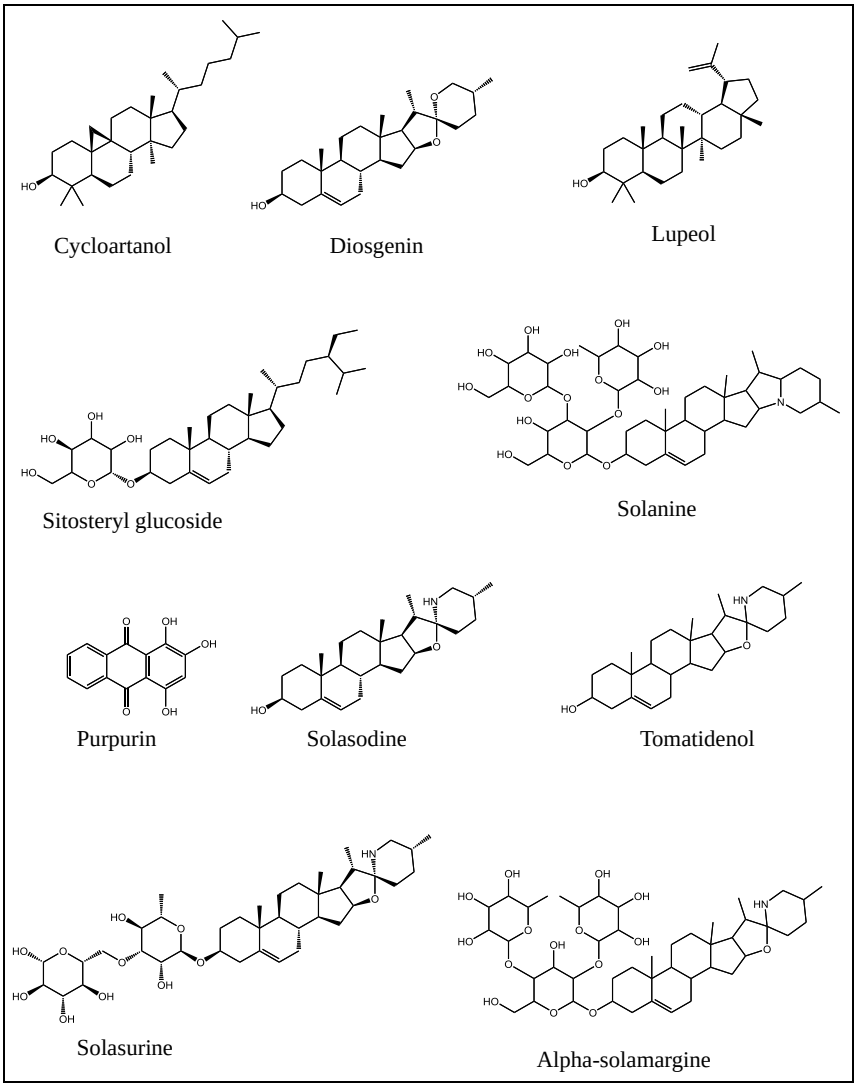

Fig 1: Various phytochemicals of *Solanum surattense*.

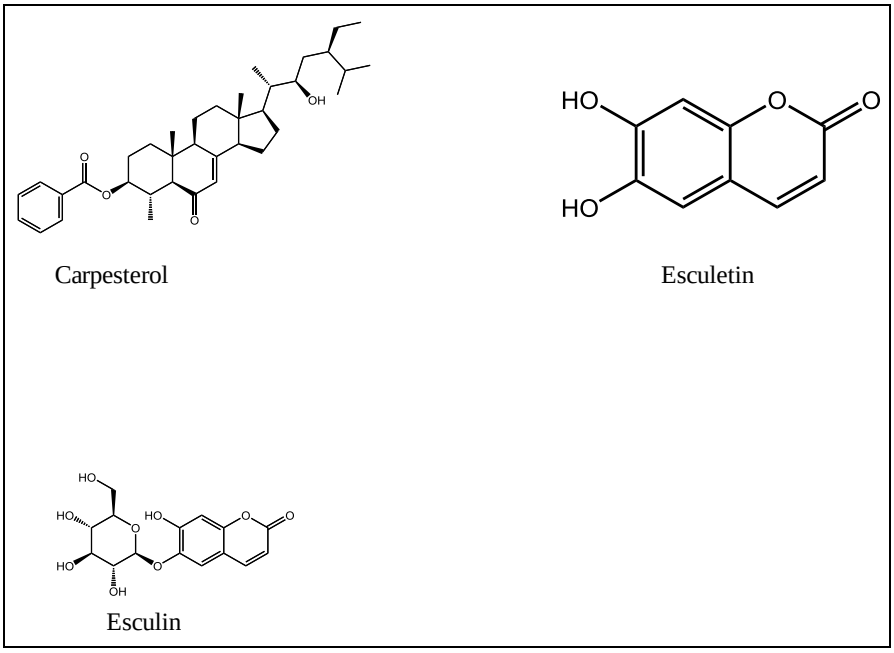

Fig 1: (*continued*): Various phytochemicals of *Solanum surattense*.

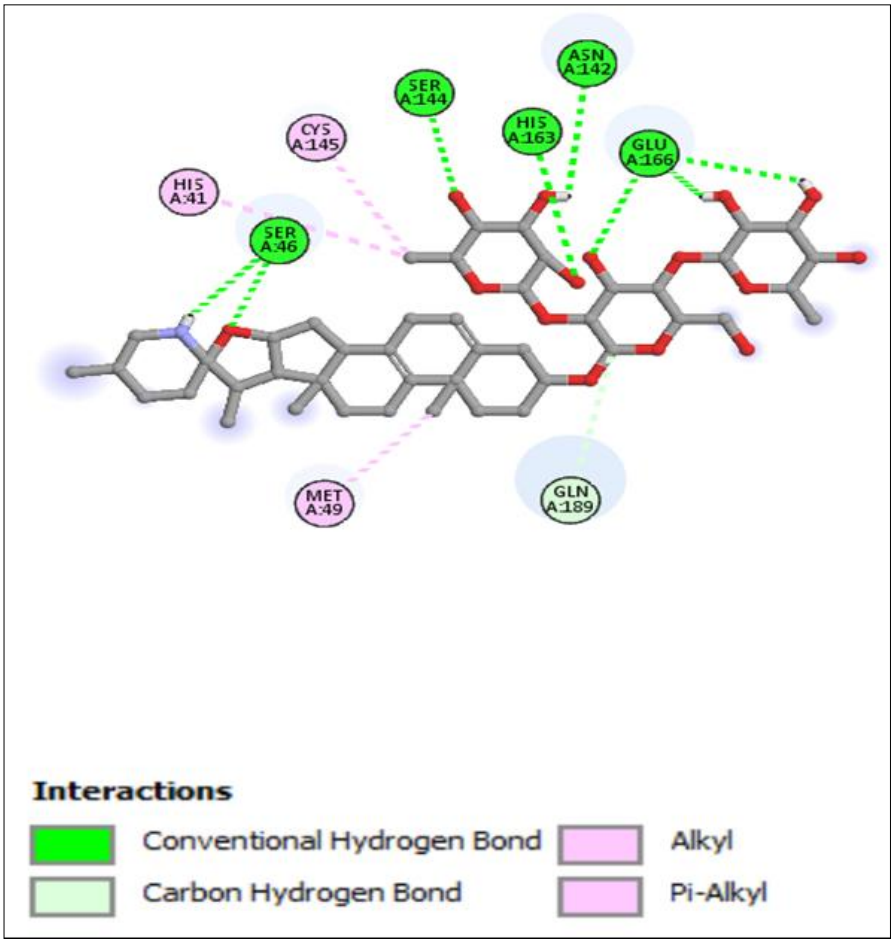

Fig 2: Interaction of alpha-solamargine with C3-like protease.

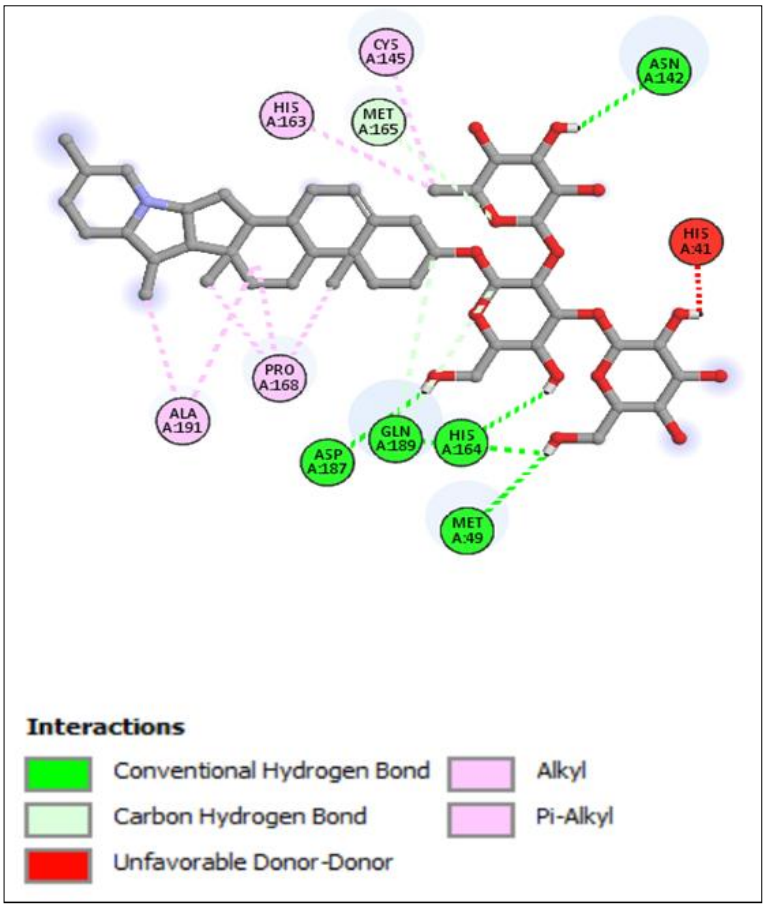

Fig 3: Interaction of solanine with C3-like protease.

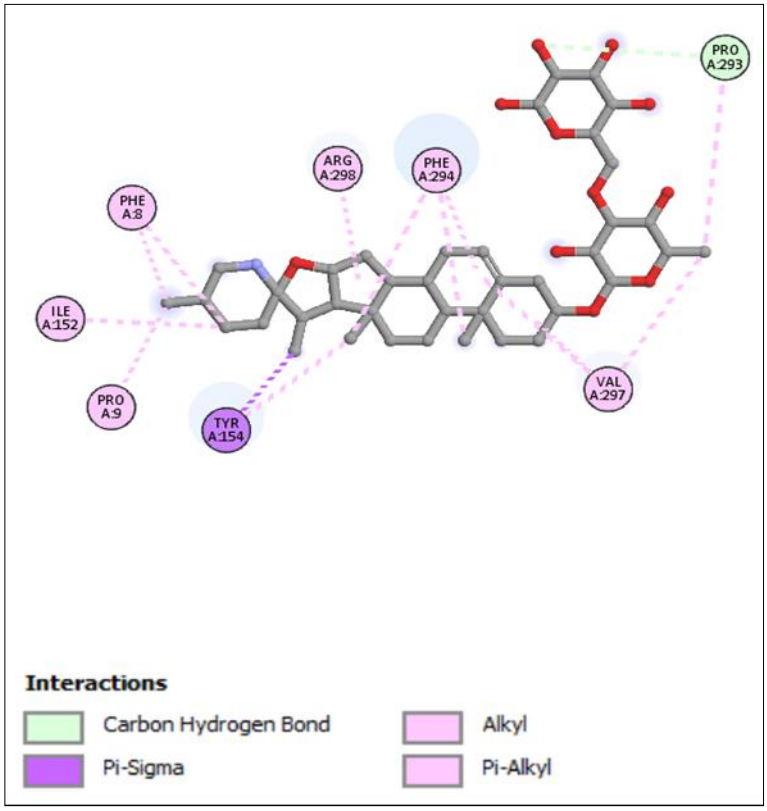

Fig 4: Interaction of solasurine with C3-like protease.

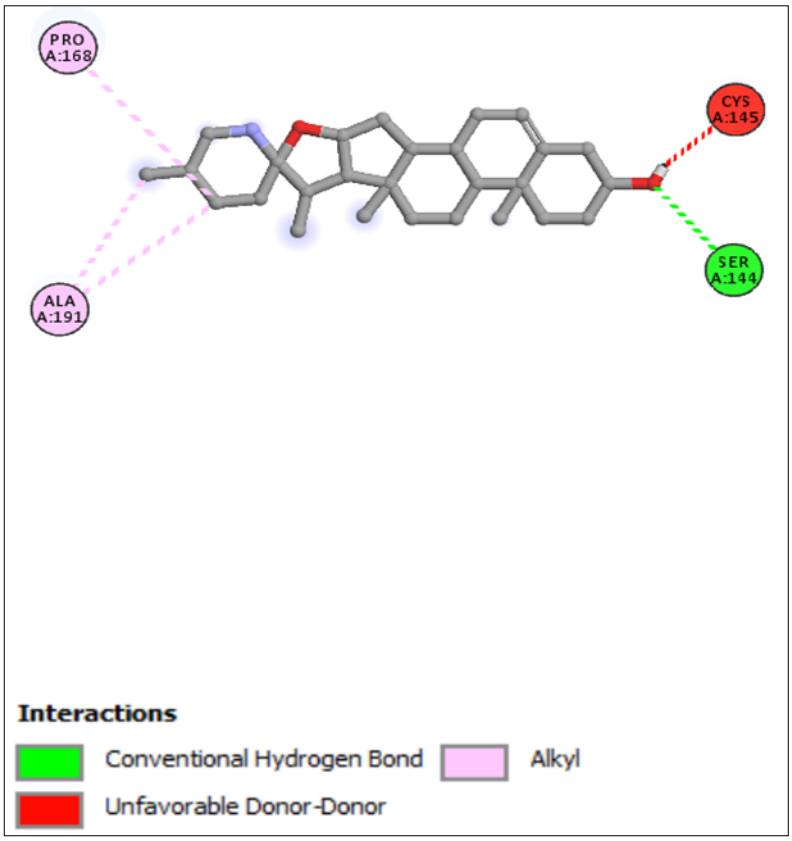

Fig 5: Interaction of tomatidenol with C3-like protease.

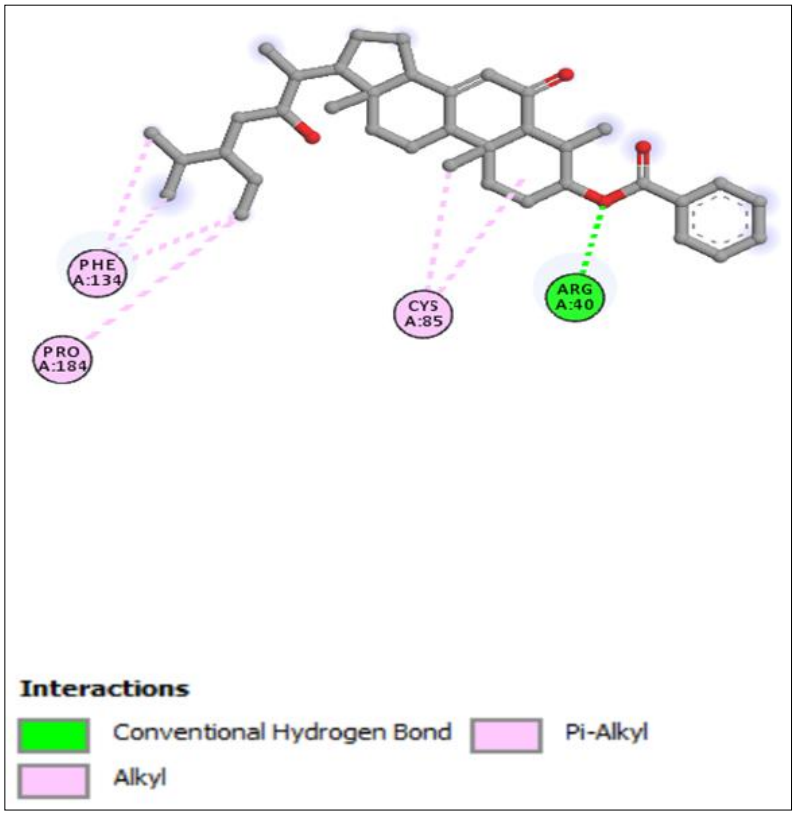

Fig 6: Interaction of carpesterol with C3-like protease.

Conclusion

Molecular docking studies demonstrate that a number of phytochemicals of *Solanum surattense* can bind strongly to the C3-like protease of SARS-CoV-2 raising the possibility of their acting as therapeutic(s) against the virus.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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