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Molecular dynamics analysis of phytochemicals from *Ageratina adenophora* against COVID-19 main protease (M^{pro}) and human angiotensin-converting enzyme 2 (ACE2)

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are found effective in treating COVID-19 (Neupane et al., 2020). Currently, several types of research and the clinical trial are going on worldwide to find the vaccine, but the success is still far away.

Structurally, SARS-CoV-2 consists of Spike glycoprotein (S), Envelope protein (E), Membrane protein (M), and Nucleocapsid protein (N). Coronavirus bear positive-sense, single-stranded RNA (+ssRNA) genetic material with approximately 30,000 nucleotides, the longest among all viruses. The viral polyprotein (Pp1a) and replicase polyprotein (Pp1ab) are found effective in treating COVID-19 (Neupane et al., 2020). Currently, several types of research and the clinical trial are going on worldwide to find the vaccine, but the success is still far away.

Structurally, SARS-CoV-2 consists of Spike glycoprotein (S), Envelope protein (E), Membrane protein (M), and Nucleocapsid protein (N). Coronavirus bear positive-sense, single-stranded RNA (+ssRNA) genetic material with approximately 30,000 nucleotides, the longest identified genome in RNA viruses till date (Malik, 2020). Viral genome of SARS-CoV-2 consists of 14 open reading frames (ORFs) (Bhosale et al., 2012). Among which the main reading frame ORF1ab encodes for two overlapping polyproteins 1a (pp1a) and replicase polyprotein 1ab (pp1ab) (Cowley et al., 2000). These polyproteins play a major role in the replication and transcription of the viral genome (Robb et al., 2009).

The virus has a protease class of hydrolytic enzyme known as Main protease (Mpro) also called as chymotrypsin-like protease (3CLpro). The entry of virus in the host has mediated binding Spike protein with human angiotensin-converting enzyme receptor-2 (ACE2) (Wan et al., 2020). Inside the host cell, proteolytic cleavage of pp1a and pp1ab by SARS-CoV-2 Mpro give rise to numerous non-structural proteins like RNA dependent RNA polymerase (RdRp), helicase and non-structural protein 3, 4, and 6 (nsp3, nsp4, and nsp6). These non-structural proteins are thought to be responsible for coronavirus replication. Thus, Mpro has emerged as important drug targets (Kirchdoerfer and Ward, 2019) and as in put ligand file for Autodock in docking.

The receptor and ligand interaction through virtual molecular docking of the Mpro with coordinates (X = 10.711388, Y = 12.411388, Z = 68.831286) and ACE2 receptor with coordinates (X = 44.98, Y = 20.98 and Z = 16.80) have been chosen as the active site. The active site of the COVID-19 main protease (Mpro) and human angiotensin-converting enzyme-2 (ACE2) related carboxypeptidase has been downloaded from protein data bank (PDB) website (http://www.rcsb.org/pdb) (Berman et al., 2000) and were prepared by using Autodock tools-1.5.6. Kollman charges were added to each atom, non-polar hydrogens were merged, atom types were defined. The structure of the ligands was saved in pdbqt format and used as in put ligand file for Autodock in docking.

The crystal structure of a COVID-19 main protease (Mpro) and human angiotensin-converting enzyme-2 (ACE2) related carboxypeptidase has been downloaded from protein data bank (PDB) website (http://www.rcsb.org/pdb) (Berman et al., 2000) and were prepared by using Autodock tools-1.5.6. Kollman charges were added to each atom, non-polar hydrogens were merged, atom types were defined. The structure of the ligands was saved in pdbqt format and used as in put ligand file for Autodock in docking.

2.2. Ligand preparation

The list of the major phytochemicals of A. adenophora were retrieved from the earlier reported literature (Poudel et al., 2020). The structures of known major chemical components of the plant were prepared using Chemdraw 3D pro12.0. software (Cousins 2005) and built - and - edit module in Open Babel 2.2.3 tool (O’Boyle et al., 2011). MMF F94s force fields parameters were assigned to ligands atoms and then the energy has been minimized. Kollman charges were added to each ligand atoms. However, nonpolar hydrogen atoms were merged, and rotatable bonds defined. The structure of the ligands was saved in pdbqt format and used as in put ligand file for Autodock in docking.

2.3. Active site selection

The active site of the COVID-19 Mpro protein (PDB ID: 6LU7) and Human ACE2 protein (PDB ID: 1R42) has been predicted from different receptor cavities available. The different active site was identified from Discovery Studio 2020 Client (BIOVIA) and re-docking of all the complexes and apo forms of the Mpro with coordinates (X = −10.711837, Y = 12.411388 and Z = 68.831286) and ACE2 receptor with coordinates (X = 44.98, Y = 20.98 and Z = 16.80) have been chosen as the active site.

2.4. Virtual molecular docking

The receptor and ligand interaction through virtual molecular docking have been performed through AutoDock Tools-1.5.6. All the molecules have been docked to active site 1 of COVID-19 Mpro and active site 1 of ACE2 receptor. Ligand-receptor interaction was viewed through Discovery Studio 2020 Client (BIOVIA) and re-docking of all the compounds was done to assure reproducibility (Puthak et al., 2020).

2.5. Molecular dynamic simulation

The effects of the ligands on the structural dynamics of proteins were studied on GROMACS 5.1.4 version (Abraham et al., 2015). Each complex and apo forms of the Mpro and ACE2 proteins were considered for the study. Additionally, the protein and water topology were defined by
GROMOS43A2 force field (van Gunsteren et al., 1996) and SPC/E water model (Berendsen et al., 1987), respectively. Each ligand topology was generated through the same force field using the PRODRG server (http://prodrg2.dynndns.org/submit.html). The charge of each simulating system was neutralized by an appropriate number of sodium ions (Na\(^+\)). Subsequently, the energy of the simulating systems was minimized by the steepest descent algorithm in 50,000 steps. The two-phase equilibration of 100 ps was carried out by NVT (at constant 300 K) and NPT (at constant 1 bar) ensemble equilibrations for each system. Consequently, MD simulation of 50 ns was carried out for each system and the data was used for the enumeration of RMSD, RMSF and Rg. Furthermore, the binding energy was enumerated by the gMMPBSA package (Kumari et al., 2014) of GROMACS for every 0.1 ns frame of the last 20 ns simulation of each protein-compound complex.

2.6. Drug likeness property

Physicochemical and pharmacokinetic properties to different phytochemical present in A. adenophora were studied using Swiss ADME a free online web tool (Zoete et al., 2016) (http://swissadme.ch/) by submitting their respective structures.

3. Result and discussion

3.1. Virtual screening through molecular docking

The SARS-CoV-2 M\(^{\text{pro}}\) with N3 inhibitor is divided into three domains. Domain I (from Phe 8 to Try 101), domain II (from Lys 102 to Pro 184) and domain III (from Thr 201 to Val 303). Domain I and II have an anti-parallel β-barrel structure. Domain III contains five α-helices arranged into the large anti-parallel globular cluster and is connected with domain II through loop region, which consist residue from Phe 185 to Ile 200. The substrate-binding site of M\(^{\text{pro}}\) of SARS-CoV-2 has Cys-His catalytic dyad, where N3 inhibitors bind. This is located in the cleft between domain I and domain II. Fig. 1 represents the crystal structure of COVID-19 main protease (M\(^{\text{pro}}\)) in complex with an inhibitor N3 and three domains of M\(^{\text{pro}}\).

The validation of the docking calculation was evaluated by redocking M\(^{\text{pro}}\) inhibitor remdesivir on the main protease protein of SARS-CoV-2 (PDB ID: 6LU7). It displayed that remdesivir is able to bind in the almost same pose in the same binding pocket with a binding affinity of −7.8 kcal/mol. The study showed that remdesivir interacts with M\(^{\text{pro}}\) through various types of interaction with different amino acid residues by making hydrogen bond and Van der Waals bonds. However, it was noticed that the tested ligands interact with Glu A:166, Leu A:141, Gly A:143, Ser A:144, and Cys A:145 amino acids through hydrogen bonds. The interaction between phyto compound 5GDE and M\(^{\text{pro}}\) receptor is displayed in Fig. 2.

These interactions are compared with native inhibitor N3 and it was found that 90.90% amino acid showed similarity with that of a co-crystal ligand, which was found acceptable. Thus, the protein was further utilized for docking 34 different compounds reported in A. adenophora and docking score is displayed in Table 1 (Poudel et al., 2020).

It was found that among these only three compounds (5GDE, 3-CQA and MDCQ) have better binding affinities than remdesivir. Moreover, 5GDE showed the highest docking affinity (−8.1 kcal/mol) in the entire set of molecules. The comparison between remdesivir and phyto compound 5GDE complex displayed 100% similarity in interaction pattern, illustrated in Table 2. Among all the interacting amino acids of 3-CQA and MDCQ it was found that 94.11% and 94.73% amino acid interactions are similar with remdesivir, respectively. The docking score along with hydrogen bond and Van der Waals interactions of these three compounds with M\(^{\text{pro}}\) is shown in Table 2.

The human ACE2 enzyme is composed of two domains; the first is zinc metallopeptidase domain depicted in Fig. 3(residues 19–611) and the second C terminus domain (residues 612–740). The first domain is 42% identical to the corresponding domains of humans ACE. The first zinc metallopeptidase domain is located near the bottom and on one side of the large active site cleft. The zinc is coordinated by His374, His 378, Glu402 and single water molecules (in the native structure). The second domain is identical to human collectrin by 48%. The ACE2 metallopeptidase domain was divided into two subdomains (I and II), that formed the two sides of a long deep cleft with dimensions of 40 Å long by 15Å wide by 25Å deep. The catalytic subdomains are only connected at the floor of the active site cleft.

Initially, re-docking of the endogenous or native co-crystal ligand has been performed for the validation of the whole docking procedure ensuring its reproducibility. A total of 34 phytochemicals of A. adenophora have been docked with human ACE2. The receptor-ligand interactions have indicated that all the compounds used for docking procedure have a substantial binding affinity among them top 5 high scoring compounds are listed in Table 3.

Top 5 high scoring compounds has been taken into consideration for further detailed analysis as reflected in Table 3. BODO has shown the best binding affinity towards the human ACE2 receptor with a binding energy of −8.7 kcal/mol. This binding energy is higher than best fit inhibitor (Hydroxychloroquine) binding affinity, which is −6.3 kcal/
mol. The best fit inhibitor was selected by comparing binding affinity of several drugs that have shown activity against COVID-19. The interaction of the compound with the human ACE2 receptor is depicted in Fig. 4. Docking study has exhibited that BODO interacts with 11 amino acid residues among which 7 residues (GLU A:495, ASP A:494, PRO A:492, HIS A:493, TRP A:478, TYR A:613, GLUA:489) matches with that to the inhibitor hydroxychloroquine. Thus, can be predicted compound binds to the receptor properly to inhibit human ACE2 protein.

MDPC, a phytochemical of *A. adenophora*, has shown a binding energy score of −7.5 kcal/mol, which is higher than the native inhibitor. The study stated that MDPC interacted with 10 amino acid residues (TYR A:613, ARG A:482, GLU A:489, ASP A:494, ASP A:471, HIS A:493, TRP A:478, GLN A:472, GLU A:495 and GLU A:479), which matches with the hydroxychloroquine. Further, it was also noticed that 5GDE have higher binding affinity (−6.7 kcal/mol) with human ACE2 than native inhibitor hydroxychloroquine. Additionally, the careful study of interaction emphasized that the compound 5GDE interacts with two amino acids through hydrogen and π-alkyl bonds, where one amino acid residue HIS A: 493 found common to the native inhibitor hydroxychloroquine.

*A. adenophora* phytochemical have already proven anti-TMV and anti-HIV activity. In our in-silico study molecular dynamics of phytochemicals of *A. adenophora* done with M<sup>pro</sup> and ACE2 virtually and found that phytochemicals BODO and 5GDE, were potential blockers of M<sup>pro</sup> and ACE2. These plant materials are extremely abundant, convenient to harvest and easy to collect. This will lead to cost effective drug can be develop.

3.2. Molecular dynamic simulation

To elucidate the effects of the selected compounds (BODO and 5GDE) on the structural attributes of the respective protein (ACE2 and M<sup>pro</sup>), the comparative MD analysis was carried out between each protein complex and its apo form. The average RMSD of M<sup>pro</sup> complex and apo form was enumerated as 0.34, and 0.25 nm that delineate lesser deviations in backbone atoms of the ACE2-compound complex in comparison to its apo structure. The effect on compactness of the ACE2 after accommodating the BODO was analyzed through Rg analysis. The average Rg value for the ACE2 apo and complex form was found to be 2.47 and 2.46 nm, respectively, indicating that both apo and complex forms of ACE2 protein attained a similar level of compactness. The Rg graph is displayed in Fig. 6.

The backbone atom fluctuation of the ACE2 residues was analyzed by the RMSF data, which showed similar levels of fluctuation in apo and complex forms with an average RMSF of 0.15 and 0.14 nm, respectively. The MD analysis showed that the ACE2 complex structure retains similar compactness like its apo structure, but with increased structural stability during the simulation.

Further, the effect of interaction between compound and M<sup>pro</sup> protein on its compactness was analyzed by Rg analysis. The respective average Rg values were computed as 2.14 and 2.15 nm for apo and complex form, suggesting that both forms exhibited a similar level of compactness during simulation. The backbone atom fluctuation of the M<sup>pro</sup> residues in both forms was analyzed by the RMSF data, which showed that apo and complex form have an average RMSF of 0.21 and 0.15 nm, respectively. It indicates that backbone atoms of M<sup>pro</sup> residues showed low fluctuation in complex form in comparison to the apo form.

The MD analysis showed that the M<sup>pro</sup> complex structure retains similar compactness like its apo structure, but with increased structural stability and low residue fluctuation in comparison to the apo form during the simulation. Analysis also depicts the stability of interactions between 5-β-glucosyl-7-demethoxy-enecalinand protein during the dynamics. Simultaneously, the average RMSD of the respective ACE2 complex and apo form was enumerated as 0.34, and 0.25 nm which delineate lesser deviations in the backbone atoms of the ACE2-compound complex in comparison to its apo structure. The effect on compactness of the ACE2 after accommodating the BODO was analyzed through Rg analysis. The average Rg value for the ACE2 apo and complex form was found to be 2.47 and 2.46 nm, respectively, indicating that both apo and complex forms of ACE2 protein attained a similar level of compactness. The Rg graph is displayed in Fig. 6.

In addition, the interface affinity of the protein and compound was analyzed by calculating the binding energy of the protein complex. The average binding energy calculated for ACE2 (BODO) and M<sup>pro</sup>-(5GDE) complex is presented in Table 4 which represents that Van der Waals energy played a major role in maintaining the binding of compounds with protein in both of the complexes during the dynamics.

Drug likeness is a crucial step in the initial step of drug discovery. The pharmacological properties of 4 high scoring phytochemicals of *A. adenophora* were studied. The pharmacokinetics profiling and toxicity predictions need to assess its drug-likeness property using Swiss ADME, which works on interpreting the molecular fingerprint of the submitted query structure, and analyze the presence or absence of chemical features in a molecule to publish pharmacokinetic data. The *in silico* pharmacokinetic predictions of the top 10 compounds of *A. adenophora* are depicted in Table 5.

Table 5: Top 10 compounds of *A. adenophora*.

| Compound | MW | n-Rotb | n-HbA | n-HbD |
|----------|----|--------|-------|-------|
| BODO     | 327 | 20      | 9     | 10    |
| 5GDE     | 327 | 20      | 9     | 10    |
| A. adenophora | 260 | 12      | 7     | 9     |
| A. adenophora | 260 | 12      | 7     | 9     |

Number of hydrogen bond acceptor, n-HbA: Number of hydrogen bond donors, n-HbD: Number of hydrogen bond donors.

Four compounds depicted in the table are high scoring compounds in 2 different receptors ACE2 and M<sup>pro</sup> but BODO and 5GDE are the top-scoring compounds, respectively. These compounds also have single
lead likeness violations. Therefore, these molecules can be considered for the further drug development steps. Among these two 5GDE has a molecular weight less than 500, which follow Lipinski’s rule of five. This can propound that the compounds are safer and permissible for further study. The computational activity predication for expressed that

| S. N | Phytochemicals | Docking score of MDCQ (affinity Kcal/mol) | Docking score of human ACE2 (affinity Kcal/mol) |
|------|----------------|------------------------------------------|-----------------------------------------------|
| 1    | 7-hydroxy-dehydrotretemone | -6.3 | -5.7 |
| 2    | 7,10,11-trihydroxydehydrotretemone | -6.6 | -6.2 |
| 3    | 10-oxo-7-hydroxy-3-nordihydrotretemone | -6.2 | -5.7 |
| 4    | 2amethoxyl-3β-methyl-6-(acetyl-O-methyl)-2,3-dihydrobenzofuran | -5.7 | -5.3 |
| 5    | 5-b-glucosyl-7-demethoxy-encecalin (5GDE) | -8.1 | -6.5 |
| 6    | 8-hydroxy-8-b-glucosyl-2-carene | -6.6 | -5.7 |
| 7    | (4S,4aR,6R)-1-acetyl-6-(acetyl-oxy)-4,4a,5,6-tetrhydro-4,7-dimethylcyclohexalen-2(1H)-one | -6.6 | -5.7 |
| 8    | 2-deoxo-2-(acetyl-oxy)-9 oxoaporphorone(DAODA) | -6.2 | -6.0 |
| 9    | 9-oxoxaporphorone(ODA) | -5.9 | -5.3 |
| 10   | 9-oxo-10,11-dehydro-agerophorone (ODA) | -6.0 | -5.9 |
| 11   | 9β-hydroxy-agerophorone | -5.8 | -5.4 |
| 12   | Murol-4-en-7-β | -5.7 | -5.5 |
| 13   | 8-beta-hydroxy-9,12-dehydroverbocociolenten | -5.5 | -5.2 |
| 14   | 2β-acetoxy-(7α, β)-3,16(11)-cadinadien-12(7)-olide | -6.9 | -6.4 |
| 15   | 3-hydroxymurol-4-7(11)-dien-8-one | -6.1 | -5.5 |
| 16   | (1) 5,7,9(10S)-2-oxocandinan-3,6(11)-dien-12,7-olide (ODDO) | -6.8 | -6.5 |
| 17   | (1) 7,7,7-bis(5R,7R,9R,10S)-2-oxocandinan-3,6(11)-dien-12,7-olide (BODO) (He et al., 2008) | -6.3 | -8.8 |
| 18   | (1) 5,7,9(10S)-7-hydroxy-7,12-epidoxycadinan-3,6(11)-dien-2-one (HEDO) | -6.7 | -6.3 |
| 19   | (1) 5,7,9(10S)-7-cadinan-3-ene-6,7-diol (CED) | -5.8 | -5.5 |
| 20   | (1) (5R,7R,9R,10S)*5,6-dihydroxyxcadinan-3-ene-2,7-diol | -6.0 | -5.7 |
| 21   | 7-hydroxycadinan-3-ene-2-one | -5.6 | -5.4 |
| 22   | 5,6-dihydroxyxadinan-3-ene-2,7-dione | -6.5 | -5.9 |
| 23   | 2-acetyl-cadinan-3,6-diene-7-one | -6.1 | -6.1 |
| 24   | Cadinan-3-ene-2,7-dione | -5.8 | -5.3 |
| 25   | Cadinan-3,6-diene-2,7-dione | -6.2 | -5.6 |
| 26   | 1,6-dihydroxy-1-isopropyl-4,7-dimethyl-3,4-dihydrobenzofuran-2(1H)-one | -6.4 | -5.8 |
| 27   | (4R,5S)-4-Hydroxy-5-isopropyl-2-methyl-2-cyclohexene | -4.9 | -4.6 |
| 28   | 5-O-caffeyloquinic acid (5-CQA) | -7.2 | -6.3 |
| 29   | 3-O-caffeyloquinic acid (3-CQA) | -8.0 | -6.4 |
| 30   | 4-O-caffeyloquinic acid (4-CQA) | -7.6 | -6.4 |
| 31   | 5-O-trans-o-cafeyloquinic acid methyl ester | -7.0 | -6.3 |
| 32   | methyl (1R,3S,5S,S)-3-(3,4-dihydroxyphenyl)prop-2-enoyloxy-1,4,5-trihydroxyxyclohexane-1-carboxylate | -7.3 | -6.2 |
| 33   | methyl 3,4-bis[(3,4-dihydroxyphenyl)prop-2-enoyloxy]-1,5,6-dihydroxyxyclohexane-1-carboxylate (MDPC) | -7.4 | -7.3 |
| 34   | Methyl 3,5-di-O-caffeylo quinate (MDCQ) | -8.0 | -6.8 |

Table 1 Docking score of 34 phytochemicals present in A. Adenophora with Main protease protein (MDCQ) and human ACE2.

Table 2 Molecular interaction of top 3 high scoring compounds with Main protease protein (MDCQ) of SARS-CoV-2.

| S. N | Compounds | H-bond interactions | Van der waals interactions |
|------|-----------|---------------------|---------------------------|
| 1    | 5GDE      | LEU A:141, GLU A:166 | MET A:49, TRP A:54, ARG A:188, ASP A:187, GLN A:189, SER A:144, HIS A:163, PHE A:140, HIS A:172, GLY A:143 |
| 2    | 3-CQA     | GLU A:166, CYS A:145, THR A:190 | HIS A:172, PHE A:140, LEU A:141, ASN A:142, SER A:144, GLN A:189, ARG A:188, GLN A:192, ALA A:191, PRO A:168, HIS A:164 |
| 3    | MDPC      | LEU A:141, HIS A:163, SER A:144, SER A:144, GLN A:192 | PHE A:140, ASN A:142, GLY A:143 TRY A:54, ASP A:187, ARG A:188, GLN A:189, THR A:190, LEU A:167, GLN A:166 |

3.3. Probable mechanism of action

The coronavirus is positive-strand RNA viruses (Weiss and Navas-Martin 2005). The process of viral replication and transcription is selected phyto-compounds have mild to moderate potency against COVID-19 proteins.
controlled by two overlapping polyproteins, the pp1a (replicase 1a, 450KD) and pp1ab (replicase 1ab, 750KD) (Yang et al., 2003). Frame shifting of the ribosome is essential for the expression of the C-proximal of pp1ab polyprotein (Kjær and Belsham 2018). The release of functional polypeptides from both polyproteins is controlled by M\textsuperscript{pro}, and necessary for proteolytic processing of polyproteins translated from viral RNA. The main protease slices the polyprotein by autolytic cleavage of the enzymes. This indicates blocking the activity of the main proteases could lead to inhibition of viral replication. 5GDE, inhibits the M\textsuperscript{pro} with more binding affinity than native inhibitor through the multiple types of interactions.

Coronavirus also presents on protein S a specific binding site for ACE2 which serves as an entry point into the host cell. Various researches on ACE2 suggest, blocking the ACE2 receptor could make it more difficult for coronavirus to enter cells. BODO binds to the ACE2 receptor more effectively with higher binding affinity and most of the amino acid residue (GLU A:495, ASP A:494, PRO A:492, HIS A:493, TRP A:478, TYR A:613, GLUA:489) matches with native inhibitor hydroxychloroquine. 5GDE and BODO are phytochemicals of A. adenophora inhibit the viral replication and block the entry of SARS-CoV-2 through M\textsuperscript{pro} and ACE2 receptors. Phytochemicals of these two A. adenophora phytochemicals have shown more effective binding energy than its native inhibitors remdesivir and hydroxychloroquine.

Fig. 4. (A) The phytocompound BODO ACE2 complex. (B) Detail amino acid interaction of BODO with ACE2 receptor in 2D.

Fig. 5. A and B displayed RMSD of ACE2 and M\textsuperscript{pro}.

Fig. 6. (A) and (B) displayed Rg of ACE2 and M\textsuperscript{pro}.
4. Conclusion

Our aim of the study was to investigate efficiency of the phyto-compounds against coronavirus. Therefore, the phytochemicals of *A. adenophora* are in-silico tested against M<sub>pro</sub> and ACE2 receptor. Furthermore, the docking calculation confirmed that the phyto-compound 5GDE consist significant identical interaction with selected protein as referenced compounds. However, the binding energy was measure slightly above than standard drug remdisivir and hydroxychloroquine. The MD analysis of M<sub>PRO</sub> complex structure found to retain similar compactness like its apo structure, but with increased structural stability during the simulation. Whereas, phytochemical BODO has shown high binding affinity (score), almost stable interaction with ACE2 receptor, retain similar compactness, and residues motion like its apo structure, but with increased structural stability during the simulation.

Our study showed natural compounds from *A. adenophora* have either similar or greater binding affinity than that of natural inhibitor remdesivir and hydroxychloroquine. Hence, 5GDE and BODO can be further developed as drug candidates against M<sub>pro</sub> and ACE2 receptor of coronavirus, responsible for ongoing pandemic. Finally, we suggest from this in-silico study that *A. adenophora* phytochemicals block both M<sub>pro</sub> and ACE2 receptors.

### Table 4

The Binding energy of the protein-compound complex. Drug likeness property.

| Complex | Van der Waal energy (kJ/mol) | Electrostatic energy (kJ/mol) | Polar salvation energy (kJ/mol) | SASA energy (kJ/mol) | Binding energy (kJ/mol) |
|---------|-----------------------------|-------------------------------|-------------------------------|----------------------|------------------------|
| ACE2-Comp | -181.67 ± 7.39 | 98.33 ± 15.75 | -106.52 |
| M<sub>PRO</sub>-Comp | -166.48 ± 40.96 | 108.23 ± 17.03 | -116.31 |

### Table 5

In silico pharmacokinetics prediction (Lipinski parameters) for the top 4 phytochemicals of *A. adenophora*.

| Pharmacological properties | BODO | 5GDE | MDCQ | MDPC |
|---------------------------|------|------|------|------|
| MW                        | 504.61 | 382.40 | 532.49 | 516.49 |
| n-rotb                    | 1     | 4    | 11   | 10   |
| n-HBA                     | 6     | 8    | 12   | 11   |
| n-HBD                     | 0     | 4    | 6    | 6    |
| Log P                     | 3.12  | 2.45 | 2.92 | 2.99 |
| Lipinski violations       | 1     | 0    | 3    | 3    |
| Lead likeness violations  | 1     | 1    | 2    | 2    |

### Declaration of competing interest

Authors have no conflict of interest regarding this article.

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