THE COMPUTATIONAL INVESTIGATION OF SIXTEEN ANTIVIRAL DRUGS AGAINST MAIN PROTEASE (M<sup>PRO</sup>) AND SPIKE PROTEASE (S<sup>PRO</sup>) OF SARS-CoV-2

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ABSTRACT

In this research, the fourteen commonly used antiviral drugs were investigated through the computational tools against CoV-19 or SARS-2, as well as two small bioactive molecules from the cannabis plant, Tetrahydrocannabinol (THC) and Cannabinol (CBN). Thus, these were selected for molecular docking against main protein (5r7y) and spike protein (6xs6) of coronavirus. It was illustrated that the binding energies of M<sup>PRO</sup> for Pimodivir, Baloxavir Marboxil, Lopinavir, Baricitinib, Remdesivir, THC, Darunavir, Galidesivir, Nitazoxanide, CBN, Ritonavir, Penciclovir, Ribavirin, Favipiravir, Umifenovir, and Chloroquine were -8.6, -7.7, -7.6, -7.5, -7.3, -6.8, -6.6, -6.6, -6.5, -6.5, -6.3, -6.2, -6.0, -5.7 and -5.4 kcal/mol, respectively, which could be supported for good binding molecules against micropathogens, where it was -9.8, -6.9, -6.9, -7.1, -7.1, -7.1, -7.5, -6.0, -6.2, -7.4, -5.8, -5.9, -5.7, -5.6 and -5.4 kcal/mol, respectively, for S<sup>PRO</sup>. Among these, Pimodivir is a best-bonded molecule with M<sup>PRO</sup> and S<sup>PRO</sup> in view of molecular docking score. Secondly, the ligand interaction was accounted for this protein against required corona virus protein consisting of weak H bonding, hydrophobic bond and Van der Waal interaction. For justification of molecular docking, the molecular dynamics was calculated for top six scored drugs where the root mean square deviation (RMSD) and root mean square fluctuation (RMSF) were showed that the six drugs for both main protein and spike protein. Additionally, the chemical hardness and softness have calculated, and the lowest value of softness has found in sample 06 and 13 around 0.24. The HOMO-LUMO gap has calculated with a different value for all, but the lowest value has obtained for 01. Finally, the pharmacokinetics and Lipinski rule were calculated, and all of these molecules had satisfied the Lipinski rule. Finally, using the admetrs online data base, absorption, distribution, metabolism, excretion and toxicity have calculated.

Keywords: Corona virus, Antivirus drug, Molecular docking, Molecular Dynamics, and ADMET.

1. INTRODUCTION

In the concurrent time, our globe has been stopping their freshness activity and fear from death by an invisible enemy, SARS-CoV-19 from December 2019, which has considered the one of the greatest historical world pandemic disease although our globe faced some other outbreaks pandemics, such as SARS-1, ZIKA virus, Soyan flu, Spanish flu, HIV, AIDS, third plague pandemic, Asian flu, Hon Kong flu, third choleara pandemic and bird flu (1-3). First of all, the SARS-CoV-19 was introduced at Wuhan providence in China, December 2019 (4-6) which was caused as lethal endemic diseases, such as Extreme Acute Respiratory Syndrome (SARS) and Endemic Middle East Respiratory Syndrome (MERS) (7-8). Now it was exploited that the main protease(Mpro) strain of SARS-CoV-2 is a single-stranded with positive-sense RNA genome, subfamily Coronavirinae in the family Coronaviridae and the order Nidovirales, which is similar the genome of Mouse Hepatitis Virus (MHV) (9). The genomic structures of the COVID-19 is almost similar to human betacoronaviruses, such as SARS-CoV-2, SARS-CoV, and MERS-CoV, but also have a small variation in their genomic and phenotypic structure that can manipulate their pathogenesis (10). Chemically, it could be identified as a spherical or pleomorphic enveloped particles, which contains club-shaped glycoprotein projections, as RNA allied a nucleoprotein within a capsid comprised of matrix protein. Finally, COVID-19 virus comprises of at least six open reading frames, as spike glycoprotein, Envelope, small membrane protein, membrane protein, hem agglutinin- esterase, Nucleoprotein and Genomic protein. In general, there are two types of polypeptides, which are classified according to their length, and consist of hometryptsin-like protease (3CLpro) or main protease (Mpro). Though three or four type of abundant viral proteins are obtained in COV-19, the membrane (M) glycoprotein is most common whereas the a short unique N-terminal fragment (-NH2) is connected with the spike protein (outside), and a long -COOH terminus (cytoplasmic domain) is added with the virion (inside) (11).

In case of its activity, SARS-CoV-2 (CoV-19) binds to ACE2 (the angiotensin-converting enzyme 2 as cellular ligand) by its spike as virus receptor, and enters to the host cell while the spike protein has to be effected by an enzyme called a protease (TMPRSS2), a type 2 TM serine protease located on the host cell membrane, for finishing the process. During the time of RNA replication in host body, various symptoms, such as cellular immune deficiency, coagulation activation, myocardial injury, hepatic and kidney injury, and secondary bacterial infection were occurred (12). This infection has attacked the brain and spinal cord and especially damaged for weak nervous containing cell. As a result, the neuropath logical changes have occurred for fresh necrosis, neuronal death, glial nodules, and polymorphonuclear infiltrations (13-14). Therefore, more than a few kinds of vaccines and antiviral drugs have been designed and testing on base of spike protein or main protein. The protein of corona viruses was taken for the provided link https://www.rcsb.org/structure/5r7y of protein data bank (pdb) which was uploaded by Fearon, D. et al. (2020) in protein data bank (15). In addition, the spike protein was taken from pdb, linked https://www.rcsb.org/structure/6XS6.

In our work, some traditional drugs, used as antivirus drug, were simulated based on computational tools. Several drugs for the treatment of corona virus (CoV-19) have been used since last one and half years which have not been perfectly prescribed meditation from World Health Organization (WHO). Among of these, the most common drugs are Pimodivir as anti influenza drug (16), Baloxavir Marboxil as also anti influenza drug (17), Lopinavir and Ritonavir as novel protease inhibitors of HIV (18-23), Baricitinib as drug of rheumatoid arthritis (24-25), Remdesivir used for Ebola virus disease (EVD) as treating for RNA virus (26), Darunavir as antiretroviral-naive adults with HIV-1 (27-28), Galidesivir (BCX4430) used as broad-spectrum antiviral drug (29). Moreover, the Nitazoxanide had prescribed as a good candidate for the treatment of chikungunya virus (CHIKV) (30) while the Penciclovir and Ribavirin had been widely used for the treatment of herpesvirus infections and hepatitis C virus (HCV), respectively (31-32). In addition, Favipiravir,Umifenovir and Chloroquine are most three commonly used antivirus drug in all over the world (33). For the vast applications of selected drug for medication, these have been chosen for computational study against the CoV-19 virus stains to evaluate their activity as anti drugs for CoV-19. Once important point is that for evaluating drug activity from natural sources, cannabis is one of the most commons element from THC, CBD, CBG, and CBN have already used as a drug as antecedence, pain killer, increased anxiety, paranoia and impairment of memory (34-36). Although some vaccines have been started for medication and safe the human being from CoV-19, the demand of drugs is the crucial fact to remove this disease from our globe, which is why this study has designed for searching new drugs.

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Molecular Docking, initially introduced by Kuntz et al. 1982 (37), belongs to a computational method that virtually seeks to predict a complex of two binding partners, such as biological macromolecules and small molecules as drug. Moreover, it predicts how a drug can interact and bind to protein of pathogens as well as give the information about the binding energy as docking score (38-40). Regarding this fact, molecular docking tools have been used against sixteen antiviral drug against main protein of CoV-19 and molecular dynamic has performed for justify the accuracy of the docking method. Moreover, to fill up the computational literature study of sixteen antiviral drugs, the chemical activity indicator and AMDET study have included.

2. COMPUTATIONAL DETAILS

2.1 Preparation of ligand and calculation of Chemical reactivity and descriptors

The eighteen antiviral drugs were taken from the PubChem website in SDF form (41). The Material Studio 8.0 was used for geometry optimization (42). For the optimization, B3LYP of DMol code was used in the this software to calculate the chemical reactivity indicators using frequency calculation by DFT (43). After optimization, the molecular frontier orbital diagram of HOMO and LUMO were taken with its magnitude. It had then saved in PDB form, which was further used for molecular docking as ligand.

2.2 Method for molecular docking

The starting three-dimensional (3D) structure of RNA protein of coronavirus disease (CoV-19) is a new strain that was discovered in December, 2019 from Wuhan, China. It was found in Protein Data Bank (PDB) with ID: 5r7y, following link (https://www.rcsb.org/structure/5r7y), which was considered as one of the initial strain or main protease of CoV-19 virus and established as the RNA strain with all carried genetical characteristics. Moreover, the spike protease (6xs6) was taken from PDB with the link: https://www.rcsb.org/structure/6XS6 (44). After taking the protein from PDB, and it was viewed by the Pymol software version using PyMOL V2.3 (https://pymol.org/2) (45). All water molecules and unexpected ligands or heteroatoms were removed to get fresh protein, and it was saved as PDB files. The both of protein and drug PDB files were uploaded in PyRx software for molecular docking as the auto dock vina. After the molecular docking, the docked complex was taken Discovery Studio version 2017 for result analysis and view (46).

2.3 Determination the data of ADMET

The ADMET properties were completed by the online database amdetSar, http://lmmd.ecust.edu.cn/admetsar2, which is the most acceptable database for predicting the AMDET parameters (47-49).

2.4 Molecular Dynamic

To perform MD simulations, NAMD software was used using run interactively with live view or in batch mode on a desktop or laptop computer (50). MD simulation was devoted to underpin the docking results gained for the best antiviral drugs and CoV-19 protein up to 5000 ns for holo-form (drug-protein) applying AMBER14 force field (51). In the presence of a water solvent, the total system was equilibrated with 0.9% NaCl at 298 K temperature. A cubic cell was propagated within 20 Å on every side of process and periodic boundary circumstance during the simulation. After simulation, the RMSD and RMSF were analyzed using the VMD software.

3. RESULTS AND DISCUSSIONS

3.1 HOMO, LUMO and chemical reactivity descriptors

The computed rLUMO, rHOMO and \( \Delta E \) gap, chemical potential (\( \mu \)), electronegativity (\( \chi \)), hardness (\( \eta \)), softness (\( \kappa \)) and electrophilicity (\( \omega \)) of antiviral drugs are presented in table 01. These data have calculated by B3LYP functional. The chemical susceptibility of a molecule has determined by the HOMO-LUMO energy gap and a large HOMO-LUMO gap mentions the high kinetic and low chemical stability (52-58). From the table 1, it is found that the HOMO-LUMO gap is about 6.126 to 8.508 eV for all tested drugs while Pimodivir shows the lowest energy gap as well as having the highest the softness value (34, 59-61).

|   | rLUMO, eV | rHOMO, eV | rHOMO_lLUMO gap, eV | Ionization potential (I), eV | Electron affinity (A), eV | Chemical potential (\( \mu \)), eV | Hardness (\( \eta \)), eV | Electrons activity (x), eV | Electrophilicity (\( \omega \)), eV | Softness (S), eV |
|---|---------|---------|---------------------|-----------------|-----------------|----------------|----------------|----------------|----------------|----------------|
| 1 | -1.191  | -7.317  | 6.126               | 7.317           | 1.191           | -4.254         | 3.063          | 4.254          | -2.954         | 0.326          |
| 2 | -1.56   | -8.993  | 7.433               | 8.993           | 1.56            | -5.277         | 3.717          | 5.277          | -3.746         | 0.269          |
| 3 | -0.552  | -8.499  | 7.947               | 8.499           | 0.552           | -4.525         | 3.974          | 4.525          | -2.576         | 0.251          |
| 4 | -2.212  | -8.761  | 6.549               | 8.761           | 2.212           | -5.487         | 3.275          | 5.487          | -4.597         | 0.305          |
| 5 | -1.713  | -8.528  | 6.815               | 8.528           | 1.713           | -5.120         | 3.408          | 5.120          | -3.846         | 0.293          |
| 6 | -0.031  | -8.283  | 8.252               | 8.283           | 0.031           | -4.157         | 4.126          | 4.157          | -2.094         | 0.242          |
| 7 | -0.635  | -9.143  | 8.508               | 9.143           | 0.635           | -4.889         | 4.254          | 4.889          | 2.809          | 0.235          |
| 8 | -0.74   | -8.388  | 7.648               | 8.388           | 0.74            | -4.564         | 3.824          | 4.564          | -2.723         | 0.261          |
| 9 | -1.610  | -9.850  | 8.240               | 9.850           | 1.610           | -5.730         | 4.120          | 5.730          | -3.984         | 0.242          |
| 10| -0.623  | -8.066  | 7.443               | 8.066           | 0.623           | -4.345         | 3.722          | 4.345          | -2.536         | 0.269          |
| 11| -1.41   | -8.818  | 7.408               | 8.818           | 1.41            | -5.114         | 3.704          | 5.114          | -3.530         | 0.270          |
| 12| -0.996  | -8.615  | 7.619               | 8.615           | -0.996          | -4.806         | 3.809          | 4.806          | -3.031         | 0.263          |
| 13| -1.301  | -9.469  | 8.168               | 9.469           | 1.301           | -5.385         | 4.084          | 5.385          | -3.550         | 0.245          |
| 14| -2.126  | -9.007  | 6.881               | 9.007           | 2.126           | -5.567         | 3.441          | 5.567          | -4.503         | 0.291          |
| 15| -1.235  | -8.132  | 6.897               | 8.132           | 1.235           | -4.684         | 3.449          | 4.684          | -3.181         | 0.290          |
| 16| -1.007  | -8.137  | 7.130               | 8.137           | 1.007           | -4.572         | 3.566          | 4.572          | -2.931         | 0.280          |

The frontier molecular orbital(FMO) has determined the chemical reactivity and active sites where the protein can be banded. The lower magnitude of energy gap contributes to form an interaction with SARS-2 protein with drugs. From the figure 1, the FMO has presented. In case of LUMO, the yellow color indicates the negative node and blue color indicates the positive node of orbitals. On the other hand, the violet color for HOMO indicates positive node of orbital and light greenish color expresses the negative node of orbitals. It must be written that the protein can be attached the part of LUMO.
3.2 Molecular docking score

Molecular docking studies were conducted in order to validate the obtained pharmacological data and provide evidence for binding affinity of drug compounds with protein of CoV-19 or SARS-2 (62-63).

As the protein-ligand interaction plays a significant role in structural based drug designing, the H bonding and hydrophobic bonding are the main cause for docking score where the docking score above 6.00 kcal/mol has been considered as standard drug (63-65).

Molecular docking study is a well-established technique to determine the interaction of two molecules and find the best orientation of ligand, which would form a complex with overall minimum energy. In Silico studies revealed that all drug molecules showed good binding energy toward the target protein ranging from -8.60 to -5.44 kcal/mol shown in table 02 while the Pimodivir, Baloxavir-Marboxil, Lopinavir, Baricitinib, Remdesivir could be considered as the standard drug although THC, natural occurring molecule, has its also standard docking score in term of binding energy.
Table 2. Data of binding energy and name of interacted ligand for main protease (Mpro)

| Ligand          | Binding Affinity (kcal/mol) | No of H bond | No of Hydrophobic bond | No of van der Waal bond | Total bonds |
|-----------------|-----------------------------|--------------|------------------------|-------------------------|-------------|
| Pimodivir       | -8.6                        | 02           | 06                     | absent                  | 08          |
| Baloxavir-Marboxil | -7.7                       | 08           | 02                     | absent                  | 10          |
| Lopinavir       | -7.6                        | 08           | 04                     | absent                  | 12          |
| Baricitinib     | -7.5                        | 05           | 01                     | absent                  | 06          |
| Remdesivir      | -7.3                        | 08           | 03                     | absent                  | 11          |
| THC             | -6.8                        | absent       | 09                     | absent                  | 11          |
| Darunavir       | -6.6                        | 01           | 02                     | absent                  | 03          |
| Galidesivir     | -6.6                        | 06           | absent                 | absent                  | 06          |
| Nitazoxanide    | -6.6                        | 04           | 03                     | absent                  | 07          |
| CBN             | -6.5                        | 01           | 05                     | absent                  | 06          |
| Ritonavir       | -6.5                        | 07           | 06                     | absent                  | 13          |
| Penciclovir     | -6.3                        | 05           | 01                     | absent                  | 06          |
| Ribavirin       | -6.2                        | 05           | absent                 | absent                  | 05          |
| Favipiravir     | -6.0                        | 07           | 02                     | absent                  | 09          |
| Umifenovir      | -5.7                        | 04           | 02                     | Absent                  | 06          |
| Chloroquine     | -5.4                        | 01           | 06                     | absent                  | 07          |

In case of spike protease, the Pimodivir can show the highest docking score, -9.8 kcal/mol which is more than the main protease. The Baricitinib, Remdesivir and THC have shown from the table 3 the similar docking score, -7.1 kcal/mol and Darunavir and CBN have obtained the -7.5 and -7.4 kcal/mol shown in table 3. It could be said that the THC and CBN are highly active inhibitor against Spro than Mpro and the activity of Pimodivir has the towering among all drugs although it is higher against Spro than Mpro. There are small change in H bonding and hydrophobic bonding between Spro and Mpro that more H bonding has created for Spro.

Table 3. Data of binding energy and name of interacted ligand for spike protein (Spro)

| Ligand          | Binding Affinity (kcal/mol) | No of H bond | No of Hydrophobic bond | No of van der Waal bond | Total bonds |
|-----------------|-----------------------------|--------------|------------------------|-------------------------|-------------|
| Pimodivir       | -9.8                        | 04           | 02                     | absent                  | 06          |
| Baloxavir-Marboxil | -6.9                       | 07           | 04                     | absent                  | 11          |
| Lopinavir       | -6.9                        | 02           | 06                     | absent                  | 08          |
| Baricitinib     | -7.1                        | 05           | 03                     | absent                  | 08          |
| Remdesivir      | -7.1                        | 01           | 05                     | absent                  | 06          |
| THC             | -7.1                        | 01           | 08                     | absent                  | 09          |
| Darunavir       | -7.5                        | 03           | 12                     | absent                  | 15          |
| Galidesivir     | -6.0                        | 05           | 02                     | absent                  | 07          |
| Nitazoxanide    | -6.2                        | 05           | 02                     | absent                  | 07          |
| CBN             | -7.4                        | absent       | 11                     | absent                  | 11          |
| Ritonavir       | -7.5                        | 05           | 08                     | absent                  | 13          |
| Penciclovir     | -5.8                        | 05           | 02                     | absent                  | 07          |
| Ribavirin       | -5.9                        | 04           | absent                 | absent                  | 04          |
| Favipiravir     | -5.7                        | 04           | 02                     | absent                  | 06          |
| Umifenovir      | -5.6                        | 02           | 07                     | absent                  | 09          |
| Chloroquine     | -5.4                        | 01           | 08                     | absent                  | 09          |

3.3 Protein - Ligands Interaction

To design a new drug, the main key factor is ligand-protein interaction that provides the information of binding or bonding of drugs with the protein of virus or micro pathogens. The interaction of drug molecule with the main protease, 3r7y, of corona virus, has been investigated with bond distance. From table 04, it is illustrated that there are two types of bonds, H- bond and hydrophobic bond but Van der Waal bond is not presented for all drugs. For the Pimodivir drug, three H bonds and six hydrophobic bonds are formed with CoV-19 protein whereas the hydrogen bonds distance is lower than hydrophobic bond distance. Similarly, the type of bond interaction with bond distance for all drugs is listed in table 04.
### Table 4. Protein-Ligands Interaction with amino acid residues and their bond distance

| PubChem Code | Hydrogen bond | Hydrophobic bond | Van der Waals bond |
|--------------|---------------|-----------------|--------------------|
|              | Interacting residue of amino acid | Distance, Å | Interacting residue of amino acid | Distance, Å |                      |
| 1 Pimodivir  | ASP – 289 | 2.45 | TYR – 237 | 5.16 | absent |
| 67286591     | LEU – 287 | 3.18 | TYR – 237 | 5.40 |                      |
| 1 Pimodivir  | LEU – 287 | 2.45 | LEU – 272 | 4.79 |                      |
| 1 Pimodivir  | LEU – 287 | 4.19 | LEU – 272 | 5.05 |                      |
| 1 Pimodivir  | LEU – 286 | 2.96 | LEU – 286 | 4.27 |                      |
| 1 Pimodivir  | LEU – 286 | 3.01 | LEU – 286 | 4.83 |                      |
| 2 Baloxavir-Marboxil | ARG – 298 | 4.55 | ARG – 298 | 3.92 | absent |
| 124081896    | ARG – 298 | 3.43 | ARG – 298 | 4.55 | absent |
| 2 Baloxavir-Marboxil | ARG – 298 | 4.37 | ARG – 298 | 4.55 | absent |
| 2 Baloxavir-Marboxil | LEU – 287 | 2.65 | LEU – 286 | 4.82 |                      |
| 2 Baloxavir-Marboxil | LEU – 287 | 4.19 | LEU – 286 | 4.82 |                      |
| 2 Baloxavir-Marboxil | THR – 199 | 3.13 | THR – 199 | 4.57 |                      |
| 2 Baloxavir-Marboxil | THR – 199 | 2.60 | THR – 199 | 4.57 |                      |
| 2 Baloxavir-Marboxil | LYS – 236 | 5.00 | LYS – 236 | 5.00 |                      |
| 3 Lopinavir  | TYR – 237 | 1.91 | TYR – 237 | 3.99 | absent |
| 92727        | TYR – 237 | 2.07 | LYS – 236 | 4.64 |                      |
| 3 Lopinavir  | ASP – 289 | 2.68 | LYS – 236 | 5.00 |                      |
| 3 Lopinavir  | LEU – 287 | 2.65 | LEU – 286 | 4.82 |                      |
| 3 Lopinavir  | LEU – 287 | 4.19 | LEU – 286 | 4.82 |                      |
| 3 Lopinavir  | THR – 199 | 3.13 | THR – 199 | 4.57 |                      |
| 3 Lopinavir  | THR – 199 | 2.60 | THR – 199 | 4.57 |                      |
| 3 Lopinavir  | LYS – 236 | 5.00 | LYS – 236 | 5.00 |                      |
| 4 Baricitinib | GLN – 189 | 2.90 | CYS – 145 | 4.63 | absent |
| 44205240     | HIS – 41  | 3.00 |                       |                |                      |
| 4 Baricitinib | PHE – 140 | 2.75 |                       |                |                      |
| 4 Baricitinib | GLU – 166 | 3.39 |                       |                |                      |
| 4 Baricitinib | HIS – 163 | 3.32 |                       |                |                      |
| 5 Remdesivir | GLU – 290 | 2.74 | LYS – 137 | 4.98 | absent |
| 12130416     | GLU – 288 | 2.96 | LEU – 287 | 3.88 |                      |
| 5 Remdesivir | TYR – 239 | 2.84 | MET – 276 | 5.98 |                      |
| 5 Remdesivir | THR – 199 | 2.19 |                       |                |                      |
| 5 Remdesivir | THR – 199 | 3.17 |                       |                |                      |
| 5 Remdesivir | ARG – 131 | 3.18 |                       |                |                      |
| 5 Remdesivir | ASP – 289 | 2.88 |                       |                |                      |
| 5 Remdesivir | ASP – 289 | 3.72 |                       |                |                      |
| 6 THC        | absent    |                |                       |                | absent |
| 16078        |                        |                |                       |                | absent |
| 6 THC        | PRO – 108 | 5.16 |                       |                | absent |
| 6 THC        | PRO – 108 | 4.51 |                       |                | absent |
| 6 THC        | PRO – 108 | 5.01 |                       |                | absent |
| 6 THC        | ILE – 200 | 4.14 |                       |                | absent |
| 6 THC        | PRO – 132 | 4.25 |                       |                | absent |
| 6 THC        | HIS – 246 | 4.58 |                       |                | absent |
| 6 THC        | HIS – 246 | 4.59 |                       |                | absent |
| 6 THC        | PRO – 293 | 4.31 |                       |                | absent |
| 6 THC        | PHE – 294 | 4.45 |                       |                | absent |
| 7 Darunavir  | THR – 199 | 2.71 | LYS – 137 | 3.96 | absent |
| 213039       |                        |                |                       |                | absent |
| 7 Darunavir  |                        |                |                       |                | absent |
| 8 Galidesivir | PHE – 140 | 2.91 |                       |                | absent |
| 10445549     | GLN – 189 | 3.67 |                       |                | absent |
| 8 Galidesivir | HIS – 41  | 2.59 |                       |                | absent |
| 8 Galidesivir | HIS – 164 | 2.17 |                       |                | absent |
| 8 Galidesivir | CYS – 145 | 2.88 |                       |                | absent |
| 8 Galidesivir | HIS – 163 | 3.34 |                       |                | absent |
| 9 Nitazoxanide | LYS – 137 | 2.88 |                       |                | absent |
| 41684        | THR – 199 | 3.09 |                       |                | absent |
| 9 Nitazoxanide | TYR – 239 | 2.88 |                       |                | absent |
| 9 Nitazoxanide | LEU – 287 | 2.22 |                       |                | absent |
| 10 CBN       | ARG – 298 | 2.80 |                       |                | absent |
| 2543         |                        |                |                       |                | absent |
In the view of SPP, the H bonding interaction and hydrophobic bonds are illustrated in the table 5. Overall, the H bonds are more interacted with protein because its bond distance is less than hydrophobic bond and Van der Waal bonds are absent in all case. For the CBN, no hydrogen bond was formed although its docking score almost near to highest inhibitor. On the other hand, the Ribavirin could not form the hydrophobic bonds as a result its docking score is low. From the protein-drug interaction, it could be difficult to say about the effect of specific bonds on docking score that which bond is directly involved to forming the molecular docking score but it has observed that the bond distance of H bonding is less than hydrophobic bond.

**Table 5. Spike Protein- Ligands Interaction with amino acid residues and their bond distance**

| PubChem Code | Hydrogen bond Interacting residue of amino acid | Hydrophobic bond Interacting residue of amino acid | Van der Waal bond |
|--------------|-----------------------------------------------|-----------------------------------------------|-----------------|
|              | Distance, Å  |                                  | Distance, Å  |                                  |                |
| 1 Pimodivir  | ALA-123   | 2.49                                    | ILE-119      | 4.94                                  | absent         |
| 67286591     | ASN-121   | 3.29                                    | ILE-119      | 4.70                                  |                |
|              | ARG-190   | 3.17                                    |               |                                       |                |
|              | (Halogen) | 3.24                                    |               |                                       |                |
| 2 Baloxavir-Marboxil | THR-791 | 3.02                                    | PRO-807      | 5.28                                  | absent         |
| 124081896    | LYS-900   | 5.28                                    | PRO-807      | 4.76                                  |                |
|              | LYS-814   | 3.34                                    | PRO-809      | 5.29                                  |                |
|              | LYS-814   | 3.19                                    | ALA-871      | 3.76                                  |                |
|              | LYS-814   | 3.63                                    |               |                                       |                |
|              | SER-875   | 3.12                                    |               |                                       |                |
|              | SER-875   | 3.01                                    |               |                                       |                |
| 3 Lopinavir  | THR-33    | 3.08                                    | PHE-32       | 5.42                                  | absent         |
| 92727        | LYS-300   | 3.06                                    | PHE-59       | 4.82                                  |                |
|              |           |                                         | VAL-289      | 5.43                                  |                |
|              |           |                                         | VAL-289      | 5.43                                  |                |
|              |           |                                         | LEU-296      | 5.47                                  |                |
|              |           |                                         | LYS-300      | 3.40                                  |                |
| 4 Baricitinib| THR-778   | 1.88                                    | PRO-863      | 4.99                                  | absent         |
| 44205240     | ALA-1056  | 2.44                                    | HIS-1058     | 4.82                                  |                |
|              | ALA-1056  | 3.49                                    | HIS-1058     | 5.17                                  |                |
|              | SER-730   | 3.81                                    |               |                                       |                |
|              | HIS-1058  | 3.54                                    |               |                                       |                |
| 5 | Remdesivir | ASP867 | 2.97 | VAL-860 | 5.33 | absent |
|   |           | 121304016 |      | VAL-860 | 4.75 |        |
|   |           |         |      | PRO-863 | 5.42 |        |
|   |           |         |      | HIS-1058 | 4.67 |        |
|   |           |         |      | PHE-823 | 4.33 |        |
| 6 | THC | ASN-121 | 3.37 | VAL-126 | 3.76 | absent |
|   |       |         |      | ILE-203 | 5.08 |        |
|   |       |         |      | ILE-203 | 4.78 |        |
|   |       |         |      | ILE-128 | 4.34 |        |
|   |       |         |      | ILE-119 | 3.95 |        |
|   |       |         |      | PHE-192 | 5.39 |        |
|   |       |         |      | PHE-192 | 5.39 |        |
|   |       |         |      | TRP-104 | 4.71 |        |
| 7 | Darunavir | ASN-121 | 3.07 | ILE-203 | 5.50 | absent |
|   |       | THR-124 | 2.37 | ILE-119 | 5.15 |        |
|   |       | HIS-207 | 2.90 | HIS-207 | 5.28 |        |
|   |       |         |      | TRY-170 | 5.24 |        |
|   |       |         |      | TRY-170 | 5.00 |        |
|   |       |         |      | TRP-104 | 4.66 |        |
|   |       |         |      | TRP-104 | 4.59 |        |
|   |       |         |      | VAL-227 | 3.80 |        |
|   |       |         |      | VAL-227 | 5.00 |        |
|   |       |         |      | VAL-126 | 3.80 |        |
|   |       |         |      | VAL-126 | 5.33 |        |
|   |       |         |      | PHE-192 | 4.84 |        |
| 8 | Galidesivir | ARG-1014 | 2.99 | THR-961 | 3.57 | absent |
|   |       | GLN-957 | 2.05 | ALA-958 | 4.91 |        |
|   |       | GLN-957 | 3.45 |       |      |        |
|   |       | ALA-958 | 3.06 |       |      |        |
|   |       | SRE-1003 | 2.65 |       |      |        |
| 9 | Nitazoxanide | SER-205 | 2.87 | ILE-203 | 5.30 | absent |
|   |       | ARG-190 | 3.18 | HIS-207 | 5.25 |        |
|   |       | ASN-99 | 3.18 |       |      |        |
|   |       | ASN-121 | 2.92 |       |      |        |
|   |       | ASN-121 | 3.32 |       |      |        |
| 10 | CBN |    | | TYR-170 | 3.73 | absent |
|   |       | |      | LEU-226 | 3.89 |        |
|   |       | |      | HIS-207 | 4.70 |        |
|   |       | |      | ILE-119 | 4.96 |        |
|   |       | |      | ILE-203 | 4.42 |        |
|   |       | |      | PHE-192 | 5.22 |        |
|   |       | |      | PHE-192 | 4.43 |        |
|   |       | |      | PHE-194 | 5.26 |        |
|   |       | |      | VAL-126 | 5.07 |        |
|   |       | |      | VAL-227 | 4.33 |        |
|   |       | |      | TRP-104 | 4.63 |        |
| 11 | Ritonavir | TRY-170 | 2.25 | ILE-119 | 5.30 | absent |
|   |       | TRY-170 | 2.91 | ILE-128 | 5.27 |        |
|   |       | TRY-170 | 3.26 | LEU-229 | 5.42 |        |
|   |       | SER-172 | 3.14 | LEU-229 | 5.31 |        |
|   |       | ASN-121 | 3.42 | VAL-227 | 5.35 |        |
|   |       |         |      | VAL-227 | 4.29 |        |
|   |       |         |      | VAL-126 | 4.90 |        |
|   |       |         |      | PHE-168 | 4.83 |        |
| 12 | Penciclovir | THR-778 | 2.89 | HIS-1058 | 5.01 | absent |
|   |       | GLY-1059 | 2.56 | ILE-870 | 5.10 |        |
|   |       | ALA-1056 | 2.46 |       |      |        |
|   |       | ALA-1056 | 2.59 |       |      |        |
|   |       | ASP-867 | 3.34 |       |      |        |
| 13 | Ribavirin | LEU-966 | 2.17 | absent |      | absent |
|   |       | SER-975 | 3.65 |      |      |        |
|   |       | SER-975 | 2.80 |      |      |        |
|   |       | GLY-744 | 3.25 |      |      |        |
### Table 1. Interactions between Ligands and Proteins

|  | Ligand | Interaction Site | Distance (Å) | Protein Residue | Distance (Å) |
|---|---|---|---|---|---|
| 14 | Favipiravir | MET-731 | 2.55 | THR-778 | 2.98 |
|  |  | SER-730 | 3.93 |  |  |
| 15 | Umifenovir | GLU-1092 | 2.59 | LYS-1038 | 3.30 |
|  |  | ARG-1107 | 4.57 |  |  |
|  |  | ARG-1107 | 4.76 |  |  |
|  |  | LYS-1038 | 3.66 |  |  |
|  |  | TYR-1047 | 4.78 |  |  |
|  |  | TYR-1047 | 4.80 |  |  |
| 16 | Chloroquine | LEU-226 | 2.95 | PHE-192 | 5.24 |
|  |  | LEU-226 | 4.65 |  |  |
|  |  | ILE-203 | 4.63 |  |  |
|  |  | ILE-119 | 4.51 |  |  |
|  |  | TRP-104 | 4.85 |  |  |
|  |  | VAL-227 | 4.77 |  |  |
|  |  | TYR-170 | 3.92 |  |  |
|  |  | TYR-170 | 4.02 |  |  |

[Note: TRP = TRPptophan, ASP = Aspartic acid, GLU = Glutamic acid, LEU = Leucine, THR = Threonine, ASN = Asparagine, GLN = Glutamine, PHE = Phenylalanine, ILE = Isoleucine, ARG = Arginine, VAL = Valine, SER = Serine, PRO = Proline, GLY = Glycine, HIS = Histidine, LYS = Lysine, TRP = TRPosine, CYS = Cysteine, MET = Methionine.]

#### 3.4 Aromaticity

The ability to design and fine-tune non-covalent interactions between organic ligand and proteins is indispensable to rational drug development. Aromatic stacking has long been recognized as one of the key constituents of ligand-protein interfaces providing the \( \pi-\pi \) interactions. From figure 2, it finds the edge and face of interaction between drugs as ligand and protein of coronavirus as well as the pocket show how the ligand has interacted with protein and where it is formed a bond. Besides, the maps binding pocket by employing a voxel/grid-based 3D pocket represents its flexibility action between drugs and amino acids of protein and is also useful for the visualization of the active binding site by a selection of representative structures for ensemble docking effect.

#### 3.5 Hydrogen bonding and Hydrophobicity

Hydrogen bonding is an exchange reaction whereby the hydrogen bond donors and acceptors of the free protein and ligand break their hydrogen bonds with water and form new ones in the protein-ligand complex. We evaluated the Hydrogen bond accepting and donating region in figure 3. In table 5, it was found that there was a strong H bond distance, weak H bond distance, the hydrophobic bond distance for all molecules.

**Figure 1. Aromaticity**

**Pimodivir**

**Baloxavir-Marboxil**

**Lopinavir**

**Figure 2. Hydrogen bonding**

**Pimodivir**

**Figure 3. Hydrophobicity**

**Pimodivir**
3.6 Pharmacokinetics and Druglikeness study

According to Christopher A. Lipinski rule for drug molecules in 1997 stated that first of all, it has less the 5 hydrogen bond donors and less than 10 hydrogen bond acceptors whereas the no of rotatable bonds is three or more, but the molecular mass is less than 500 Daltons (66). The fifth view is the octanol-water partition coefficient expressed as log P0/w and it is not greater than 5.

Table 6. Data of Lipinski rule, Pharmacokinetics and Druglikeness

|     | NBR | HBA | HBD | TPSA, Å² | Consensus Log Po/w | Log Kp (skin permeation) | Lipinski rule | MW     | Bioavailability Score | GI absorption |
|-----|-----|-----|-----|----------|--------------------|--------------------------|---------------|--------|-----------------------|---------------|
| Pimodivir | 4   | 7   | 3   | 103.79   | 3.18               | -6.05                    | Yes           | 399.39 | 0.56                  | High          |
| Baloxavir-Marboxil | 6   | 11  | 0   | 123.15   | 2.59               | -7.73                    | Yes           | 575.58 | 0.55                  | High          |
| Lopinavir | 17  | 5   | 4   | 120.00   | 4.37               | -5.93                    | Yes           | 628.80 | 0.55                  | High          |
| Baricitinib | 4   | 7   | 1   | 128.94   | 0.42               | -8.61                    | Yes           | 357.39 | 0.55                  | High          |
| Remdesivir | 14  | 11  | 4   | 189.57   | 2.03               | -8.65                    | Yes           | 591.59 | 0.17                  | Low           |
| THC   | 4   | 2   | 1   | 29.46    | 5.28               | -3.27                    | Yes           | 314.46 | 0.55                  | High          |
| Darunavir | 12  | 8   | 3   | 148.80   | 1.95               | -7.84                    | Yes           | 533.64 | 0.55                  | Low           |
| Galidesivir | 2   | 6   | 6   | 140.31   | -1.55              | -9.38                    | Yes           | 265.27 | 0.55                  | Low           |
| Nitzoxanide | 6   | 6   | 2   | 142.35   | -0.07              | -7.07                    | Yes           | 308.29 | 0.55                  | Low           |
| CBN   | 4   | 2   | 1   | 20.23    | 5.21               | -3.86                    | Yes           | 310.43 | 0.55                  | High          |
| Ritonavir | 22  | 7   | 4   | 225.95   | 5.18               | -6.53                    | Yes           | 708.98 | 0.55                  | Low           |
| Penciclovir | 5   | 5   | 4   | 130.05   | -0.77              | -8.97                    | Yes           | 253.26 | 0.55                  | Low           |
| Ribavirin | 3   | 7   | 4   | 143.72   | -2.05              | -9.10                    | Yes           | 244.20 | 0.55                  | Low           |
| Favipiravir | 1   | 4   | 3   | 88.84    | -0.93              | -7.74                    | Yes           | 159.12 | 0.55                  | High          |
| Umifenovir | 8   | 4   | 1   | 80.00    | 4.26               | -6.07                    | Yes           | 477.41 | 0.55                  | High          |
| Chloroquine | 8   | 2   | 1   | 27.30    | 4.15               | -4.96                    | Yes           | 319.87 | 0.55                  | High          |

Using the Swiss Institute of Bioinformatics online database was used to evaluate the Pharmacokinetics and drug-likeness applying Lipinski rule from the log in the mentioned link https://www.sib.swiss/, and make a comparison study as drug activity (67-68). From the table 06, it demonstrates that all molecules follow the Lipinski rule as a drug.
3.7 In silico Pharmacokinetics study by ADMET

ADMET stands for absorption, distribution, metabolism, excretion, and toxicity, which are considered as the vital parts of any drug development program and essential for compliance with regulatory guidelines. Both of these conducted for chemical optimization, process development, and pharmacological profile. This study belongs to invariably involved whole-animal models, and it is highly time-consuming and expensive. In order to minimize the cost and time, the ADME study helps to design a new drug for drug preparation or even in the clinic. Such events created a serious disruption of the development process and often resulted in the closure of the project and a lost opportunity. As a result, the situation of drug discovery has been changing rapidly and dramatically. ADME and toxicology technologies have evolved to permit the use of rapid and less expensive methods that have made the early assessment of drug candidates very attractive to the pharmaceutical industry. The absorption, distribution, metabolism, excretion, and toxicity parameters have listed in table 05.

**Table 7. Data of pharmacokinetics study by ADME**

| Drugs/ADME  | Human Intestinal Absorption | Caco-2 Permeability | Blood Brain Barrier | P-I glycoprotein inhibitor | P-II glycoprotein substrate | Renal Organic Cation Transporter | Sub-cellular localization | CYP450 2C9 Substrate | CYP450 1A2 Inhibitor |
|-------------|-----------------------------|---------------------|--------------------|------------------------------|-----------------------------|--------------------------------|-----------------------------|----------------------|----------------------|
| Pimodivir   | 0.9853                      | -6.05               | Yes                | No                           | Yes                         | 0.8448                         | Mitochondrion              | No                   | Yes                  |
| Baloxavir-Marboxil | 0.9943                  | -7.73               | Yes                | Yes                          | Yes                         | 0.7167                         | Mitochondrion              | No                   | No                   |
| Lopinavir   | 0.6593                      | -5.99               | Yes                | Yes                          | Yes                         | 0.8578                         | Mitochondrion              | No                   | No                   |
| Baricitinib | 1.0000                      | -8.61               | Yes                | No                           | No                          | 0.7387                         | Lysosomes                   | No                   | No                   |
| Remdesivir  | 0.9005                      | -8.65               | Yes                | No                           | No                          | 0.9580                         | Lysosomes                   | No                   | No                   |
| THC         | 0.9949                      | -3.27               | Yes                | No                           | Yes                         | 0.8169                         | Mitochondrion              | No                   | Yes                  |
| Darunavir   | 0.9287                      | -7.84               | Yes                | Yes                          | No                          | 0.8724                         | Lysosomes                   | No                   | No                   |
| Galidesivir | 0.9932                      | -9.38               | Yes                | No                           | No                          | 0.8965                         | Nucleus                     | No                   | No                   |
| Nitazoxamide| 0.8581                      | 0.6231              | No                 | No                           | No                          | 0.9343                         | Mitochondrion              | No                   | No                   |
| CBN         | 0.9922                      | 1.7659              | Yes                | No                           | Yes                         | 0.8345                         | Mitochondrion              | No                   | Yes                  |
| Ritonavir   | 0.8344                      | 0.0975              | No                 | Yes                          | No                          | 0.8140                         | Lysosomes                   | Yes                  | No                   |
| Penclovir   | 0.9885                      | 0.8545              | Yes                | No                           | No                          | 0.7342                         | Nucleus                     | No                   | No                   |
| Ribavirin   | 0.9852                      | 0.2286              | Yes                | No                           | No                          | 0.9574                         | Mitochondrion              | No                   | No                   |
| Favipiravir | 0.8416                      | 0.5807              | Yes                | No                           | No                          | 0.8851                         | Mitochondrion              | No                   | No                   |
| Umifenovir  | 0.9969                      | 1.4823              | Yes                | No                           | Yes                         | 0.5189                         | Lysosomes                   | Yes                  | No                   |
| Chloroquine | 0.9939                      | 0.8736              | Yes                | Yes                          | Yes                         | 0.6046                         | Lysosomes                   | Yes                  | No                   |

The table 8 represents the toxicity of required drugs in case of acute and non acute species, testing on rat and fish, which was obtained by online data base for computational prediction. It is observed that all drugs have more solubility in water medium. As a result, most of drugs are toxic on fish where the LD50 score is about 1.814 to 2.954 mol/kg as non aquatic species, rat. Finally, It can be said that all drugs are non carcinogenic, as well as no responsible for AMES toxicity.

**Table 8. Data of pharmacokinetics study by toxicity**

| S.L  | AMES toxicity | Carcinogenicity (trinary) | Water solubility, Log, S | Plasma protein binding | Fish Toxicity, (Yes/No) | Acute Oral Toxicity, kg/mol | Oral Rat Acute Toxicity (LD50) (mol/kg) | Fish Toxicity pLC50 mg/L | T.Pyriformis toxicity (log ug/L) |
|------|---------------|--------------------------|--------------------------|------------------------|-------------------------|----------------------------|------------------------------------------|---------------------------|-----------------------------|
| Pimodivir | No            | No                       | -3.986                   | 0.872                  | Yes                     | 1.72                       | 2.881                                     | 1.129                     | 0.557                       |
| Baloxavir-Marboxil | No            | No                       | -3.719                   | 1.100                  | Yes                     | 3.053                     | 2.582                                     | 1.346                     | 0.618                       |
| Lopinavir  | No            | No                       | -3.414                   | 1.001                  | No                      | 3.430                     | 2.250                                     | 1.747                     | 0.385                       |
| Baricitinib| No            | No                       | -3.079                   | 0.766                  | Yes                     | 2.716                     | 2.673                                     | 1.690                     | 0.359                       |
| Remdesivir| No            | No                       | -3.469                   | 1.057                  | Yes                     | 3.939                     | 2.716                                     | 1.251                     | 0.548                       |
| THC       | No            | No                       | -4.322                   | 1.009                  | Yes                     | 3.030                     | 2.594                                     | -0.110                    | 1.778                       |
| Darunavir  | No            | No                       | -3.512                   | 0.957                  | Yes                     | 4.044                     | 2.527                                     | 1.430                     | 0.431                       |
| Galidesivir| No            | No                       | -1.790                   | 0.494                  | No                      | 2.360                     | 2.176                                     | 1.918                     | 0.019                       |
| Nitazoxamide| Yes          | No                       | -1.630                   | 0.660                  | Yes                     | 2.340                     | 1.814                                     | 1.506                     | 0.637                       |
| CBN       | No            | No                       | -3.975                   | 0.997                  | Yes                     | 3.033                     | 2.515                                     | 0.368                     | 1.867                       |
| Ritonavir  | No            | No                       | -3.256                   | 0.892                  | Yes                     | 3.095                     | 2.734                                     | 1.496                     | 0.541                       |
| Penclovir  | No            | No                       | -2.654                   | 0.179                  | No                      | 2.381                     | 2.142                                     | 1.867                     | 0.180                       |
| Ribavirin  | No            | No                       | -1.173                   | 0.237                  | No                      | 2.774                     | 1.987                                     | 1.798                     | 0.150                       |
| Favipiravir| No            | No                       | -2.251                   | 0.319                  | No                      | 3.395                     | 2.413                                     | 2.113                     | 0.254                       |
| Umifenovir | No            | No                       | 4.368                    | 0.980                  | Yes                     | 2.885                     | 2.245                                     | 0.878                     | 0.828                       |
| Chloroquine| Yes           | No                       | -4.348                   | 0.580                  | Yes                     | 2.827                     | 2.954                                     | 0.943                     | 0.808                       |
### 3.8: Molecular Dynamics

The molecular dynamics is an avenue for testing the accuracy docking procedure in terms of the average root-mean square deviation (RMSD) and root-mean-square fluctuation (RMSF) which provide information about their binding pose in the respective crystal structures, ligand and protein interaction complex structure (69). It is revealed that the RMSD of docking complex is less than 2 Å for becoming a good fitting pose of ligand in drug pocket and proving that software is able to accurately dock the compounds (70-71). Then simply make parallel both docked poses with that of docked complex by RMSD; lower value indicates the accuracy and stability of the docking method (72-73).

The stability of these six docked complexes was evaluated using protein–ligand RMSD, ligand protein interaction and hydrogen bonding and ligand RMSF among others. In our study, the RMSD was calculated with respect to time (0-5000 ns) and interaction of amino acid residues of protein. Firstly, it is noted that the RMSD illustrates in the figure 4 (a) to (f) in terms of time and amino acid residue dependent where an innovative relationship is found for first three figures. The RMSD is obtained less than 2 Å within time, 2000 ns but it has increased 2.4 Å at 5000 ns time for no bond or interaction. But the RMSD has changed after formation of backbone or hydrogen bond. The RMSD has decreased from 2.4 Å to below 0.9 Å in terms of backbone bond interaction after docking, indicating high accuracy and stability of docked complexes, but the hydrogen bonding shows the little reducing of RMDS value from on bond. It could be said that hydrogen bonds are little response for molecular docking and stability of docked complex, showing RMSD is at about 2.2 Å, but interaction of protein-ligand leads the major role which shows the value less than 0.9 Å where THC compound has less than 0.7 Å. In case of amino acid residue interaction with ligand, the same phenomenon of RMSD has obtained.

The RMSF of docked complex indicates the stability. Lower value of RMSF mentions the higher stability. From figure (g), it has found that the RMSF lays about 2 Å when it has no bonding or interaction as ligand-protein interaction. In case of hydrogen bond, it puts down 2.2 Å which means that hydrogen bond are little response for stability. But it has shifted down 0.8 Å due to backbone interaction while the THC shows the minimum RMSF is about 0.6 Å, meaning the highest stability of docked complex.

In case of Spro, the MD was performed on basis of RMSD and RMSF for the protease and ligand complex after docking. The RMSD value is about 3.0 Å which has occurred without no bond between protein and ligand interaction. It was decreased in 1.3 Å which indicated the standard for drugs discovery. When H bond is created, the RMSD is about 2.9 Å while the RMSF was about 3.0 Å which are not good result for standard drugs. But, when bonds were created as backbone bond with protein residue, the RMSD was in 1.4 to 1.1 Å and RMSF was about 1.5 to 1.2 Å for first six drugs. In case of H bonds, the both of RMSD and RMSF were in about 3.0 Å shown figure 5(I to VI).

![Figure 2](image-url)
CONCLUSIONS

On the basis of molecular docking study, it can be concluded that all drugs show an excellent binding affinity with corona viruses protein. At first, Pimodivir, Baloxavir-Marboxil, Lopinavir, Baricitinib, and Remdesivir showed the docking score as binding energy at -8.6, -7.7, -7.6, -7.5, and -6.8 kcal/mol for Mpro whereas above -6.0 kcal/mol binding energy can be considered as an efficient drug against any micro-pathogens. In case of Spro, the docking score is slightly higher than Mpro. Moreover, for testing the accuracy of docking and stability of docked compound, the molecular dynamic study was performed where the RMSD and RMSF were calculated in term of protein ligand interaction, H bonding and hydrophobic bonding. In case of no bonding, the RMSD and RMSF were about 2.4 Å where the ligand-protein interaction for Mpro had the vast contribution for stability, showing the value below 0.9 Å, and it was same for Spro. Moreover, the H bonding contribution is very poor in docking score which is obtained from both of interaction and RMSD or RMSF value. Finally, it could be said that the docking protocol was highly accurate in term of MD. On the other hand, the HOMO, LUMO and LUMO HOMO gap mention about their chemical reactivity, as well as softness and hardness for becoming a drug. The pharmacokinetic study shows that they have different values, but all drugs can satisfy the Lipinski rule. Lastly, the ADMET data shows the essential information as a drug and its application in a human cell with comparative low toxicity even all of drugs are non carcinogenic materials.

CONFLICTS OF INTEREST

There are no conflicts to declare.

AUTHOR CONTRIBUTIONS

AK designed, optimized and docking of molecules, wrote the manuscript; UC performed the molecular dynamic and analyzed the obtained data; DH and MTI analyzed the obtained data, and took 2D and 3D picture; and TH gave all technical supports. All authors gave final approval for publication.

Figure 3. Various picture of RMSD and RMSF for spike protein (Spro)

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REFERENCES

1. Samal JS, Presently MPH.; 2014. International Journal of Health Sciences and Research 4: 165-9.
2. Snowden FM. 2008. Immunological reviews 225: 9-26.
3. Patterson KD. 1986. Pandemic influenza, 1700-1900: a study in historical epidemiology: Rowman & Littlefield Totowa, NJ, USA.
4. Xu XC, Ping; Wang, Jingfang; Feng, Jiannan; Zhou, Hui; Li, Xuan; Zhong, Wu; Hao, Pei. 2020. Science China Life Sciences 63: 457-60.
5. Wang WT, Jianning; Wei, Fangqiang. 2020. Journal of medical virology 92: 441-7.
6. Singhal T. 2020. The indian journal of pediatrics 87: 281-6.
7. Azhar EIH, David SC; Memish, Ziad A; Drosten, Christian; Zumla, Alimuddin. 2019. Infectious Disease Clinics 33: 891-905.
8. Zumla AH, David S;Perlman, Stanley. 2015. The Lancet 386: 995-1007.
9. Miura TAT, Emily A'; Oko, Lauren; Bielefeldt-Ohmann, Helle; Weiss, Susan R;Beauchemin, Nicole; Holmes, Kathryn V. 2008. Journal of virology 82: 755-63.
10. Mousavizadeh LG, Sorayya. 2020. Journal of Microbiology, Immunology and Infection In press.
11. De Haan CAK, Lili; Masters, Paul S; Vennema, Harry; Rottier, Peter JM. 1998. Journal of virology 72: 6838-50.
12. Chen NZ, Min; Dong, Xuan; Qu, Jieming; Gong, Fengyun; Han, Yang; Qiu, Yang; Wang, Jingli; Liu, Ying; Wei, Yuan. 2020. The Lancet 395: 507-13.
13. Waksman BHA, Raymond D. 1962. Journal of Neuropathology & Experimental Neurology 21: 491-518.
