



Target SARS-CoV-2: theoretical exploration on clinical suitability of certain drugs

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ABSTRACT

We propose a unique theoretical methodology because of the global high priority rating to search for the repurposed drugs that outfit clinical suitability to SARS-CoV-2. The approach is based on the exploration of structural analysis, computation of biothermodynamics, interactions and the prediction of entropy sign successively via molecular dynamics. We tested this methodology for Favipiravir/Dolutegravir drugs on the apo form of SARS-CoV-2 main protease. This theoretical exploration not only suggested the presence of strong interactions between (SARS-CoV-2 + Favipiravir/Dolutegravir) but also emphasized the clinical suitability of Favipiravir over Dolutegravir to treat SARS-CoV-2 main protease. The supremacy of Favipiravir over Dolutegravir is well supported by the results of global clinical trials on SARS-CoV-2 infection. Thus, this work will pave the way for incremental advancement towards future design and development of more specific inhibitors to treat SARS-CoV-2 infection in humans.

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1. Introduction

In recent times, myriads of people have been suffering from a novel SARS-CoV-2 (COVID-19) infection, and the death rate toll has reached thousands and been heading step by step, which is a topmost crisis across the globe (Chen, 2020). Accordingly, the demand for an investigation of the drug to forestall SARS-CoV-2 is of enormous interest for all scientific communities worldwide. The vital topic appropriate to annihilating activity of SARS-CoV-2 virus is concomitant to a variety of viruses which caused MERS (Middle East respiratory syndrome), SARS (Severe acute respiratory syndrome) (Roberts et al., 2007). These viruses, which inception the common cold in human beings over and over again. However, the new COVID-19 cause earnest evidence compared to Middle East respiratory syndrome and severe acute respiratory syndrome (Chen, 2020).

SARS-CoV-2 is a betacoronavirus, such as SARS-CoV and MERS-CoV, all of which have their beginning in chiropterans. For the aesculapian indicant, SARS-CoV-2 pathologic process reason out in fatal pneumonia with the technological provision aggravated similar to SARS-CoV-2 malady. Endure infected with COVID-19 might likewise fortify acute respiratory distress syndrome, leading to a full admittance rate to an intensive care unit and finally death in austere cases (Chen et al., 2020).

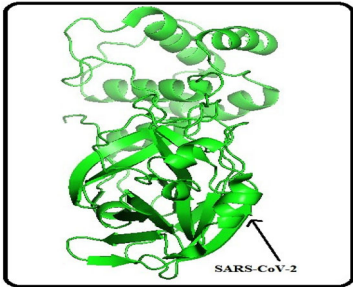
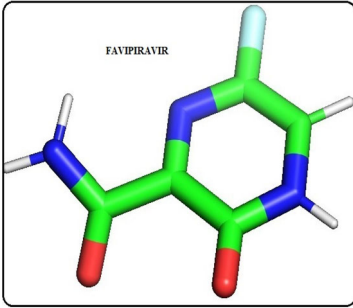
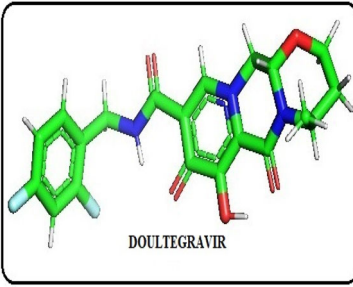
The COVID-19 virus is suited to the cysteine protease family unit. Hitherto, various business firms and scholarly people followed a line of the probe on the globe paying care on inquisitory and processing the monosemous vaccine or

antiviral drug to obviate or pull off the budding pathological process of SARS-CoV-2. Conversely, such selections need much time for the developing procedure. For the imperative prerequisite to get rid of the SARS-CoV-2 virus, the use of repurposed on hand antiviral drugs is authorized to cure another viral contagion for example HIV, hepatitis B/C and influenza is to some degree anticipatory. It is based on the early action of healing after administration relevant to viruses of Middle East respiratory syndrome and severe acute respiratory syndrome (Clercq & Li, 2016; Huang et al., 2020; Liu & Wang, 2020).

As per the studies (Gralinski & Menachery, 2020; Paraskevis et al., 2020; Tipnis et al., 2000), the COVID-19 virus chooses Angiotensin-converting enzyme 2 (ACE2) of humans and from there, it gradually attacks the immune system. This enzyme is an integral casing of glycoprotein which lies in the essential issues of human beings. In this work, we used the Favipiravir/Dolutegravir drugs, which are crucial for the management of HIV. Further, the suppress activity of Favipiravir/Dolutegravir drugs on ACE2 is already proven (Tikellis & Thomas, 2012). In the present study, PDB6M03 pertinent to apo form of main protease apt to COVID-19 is the captivating drug prey for the remedy of COVID-19 pathologic process. As of late, given its positive outcomes in clinical preliminaries, Favipiravir was affirmed by the Food and Drug Administration to treat COVID-19 through emergency use authorization (Kandeel & Al-Nazawi, 2020). The structure and the source of the Protein/Drugs are shown in Table 1.

SARS-CoV-2 main protease (PDB6M03) as a drug target with certain drugs is available in the literature, but most of

Table 1. SARS-CoV-2 main protease in the apo form with Favipiravir/Dolutegravir drugs (ligand) used in the present study of molecular dynamics.

Protein/Drug	Structure	Source
SARS-CoV-2 (main protease)		https://www.rcsb.org/structure/6M03
Favipiravir drug		https://www.drugbank.ca/drugs/DB12466
Dolutegravir drug		https://www.drugbank.ca/drugs/DB08930

them used molecular docking rather than molecular dynamics (MD) with traditional force field (Chtita et al., 2021; Barros et al., 2020; Beck et al., 2020; Chellapandi & Saranya, 2020; Gurung et al., 2020; Khan & Htar, 2020; Kumar, Zhi, et al., 2020; Kumar, Singh, et al., 2020; Sanders et al., 2020; Shamsi et al., 2020; Ton et al., 2020). However, there is no proper theoretical exploration on checking the clinical suitability of a drug to SARS-CoV-2 until now.

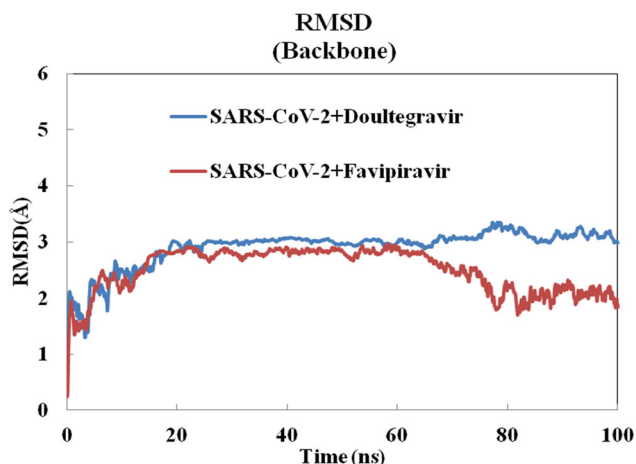
2. Methodology

The methodology we adopted in this article is based on the computation of the theoretical method to pick the best suitable drug for SARS-CoV-2 among Favipiravir/Dolutegravir. To the best of our knowledge, this is the archetypal study for the generation of trajectories from MD simulation for 100 ns using GROMACS with OPLS-AA force field between Favipiravir/Dolutegravir drugs and COVID-19 main protease (PDB6M03). As a part of methodology, the final result over the suitability of drug is derived on the successive explorations over generated trajectories through structural analysis, computation of biothermodynamics, interactions and entropy sign predictions. Further, this data related to interaction mechanisms of a Favipiravir/Dolutegravir with COVID-19 protein is needful to know their pharmacodynamics and

pharmacokinetics. The outcome of this work showed that Favipiravir/Dolutegravir is a valued invention suggested for assaultive COVID-19. As a minimum, we hope that this theoretical methodology can be accommodating for future design and improvement of more circumstantial activator for the treatment of the COVID-19 pathologic process.

3. Theory

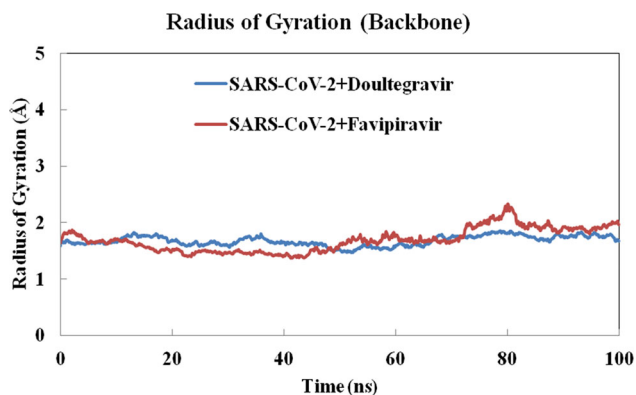
MD simulation is an *in silico* method based on atoms' movement in a molecular system with the aid of Newton equations of motions (Perozzo et al., 2004). The key in MD is the search for the drug which binds easily with coveted protein. This bind gives rise to negative Gibbs free energy between the combined system of the protein–ligand complex. Parametric quantity of mathematical relation depicts the potential energy of a system, called the force field, to simulate atoms and molecules (Jiayi et al., 2017; Ren et al., 2019). Optimize potential for liquid systems-all atom (OPLS-AA) is the highest degree force field used for biomolecules and is the amended force field over others when the effect of drugs has studied a protein (Robertson et al., 2015). Further, molecular mechanics (MM) is widely used in computer-aided drug design (CADD) (Sun et al., 2014). In this investigation, a MD study is performed with Gromacs-2020.1 on Ubuntu. The



Graph 1. RMSD graph for the backbone of (SARS-CoV-2 + Favipiravir) and (SARS-CoV-2 + Dolutegravir) systems.

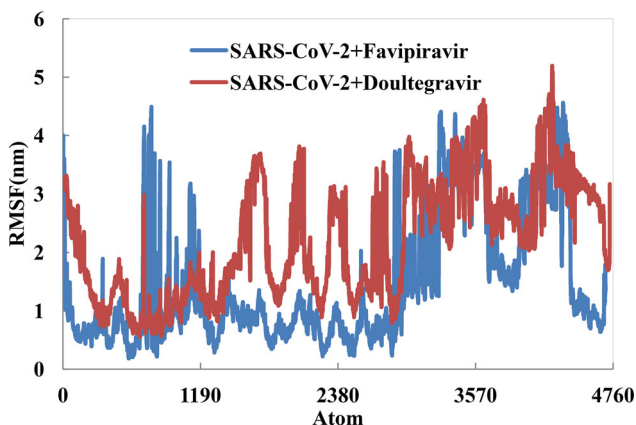
MM Poisson–Boltzmann surface region (MM/PBSA) strategy needs the trajectories created by GROMACS (g_mmpbsa) to figure the ΔG_{bind} between the SARS-CoV-2 receptor and Favipiravir/Dolutegravir drug. Preparation of (SARS-CoV-2 + Dolutegravir/Favipiravir) system for MD simulation methods through the OPLS-AA force field are as presented below:

Selected PDB6M03 protein of SARS-CoV-2 main protease from RCSB Protein Data Bank (Liu et al., 2020) and removed H₂O from it. Later at pH = 7.4, the PDB6M03 is optimized using Avagadro software. By GROMACS-2020.1, executable gro/topology files are created with OPLS-AA force field, and finally, its energy is minimized. The chemical structure of Dolutegravir (DB08930)/Favipiravir (DB12466) is taken from the drug bank (<https://www.drugbank.ca/>) database and is successively optimized with Avagadro software and converted to the executable OPLS-AA topology files (Dodda et al., 2017). Later, with the help of the GROMACS tool energy of the drugs is minimized. For simulation, in a dodecahedron box ($d = 3$ nm), the executable files of SARS-CoV-2 main protease with Favipiravir/Dolutegravir drug are combined, solvated and neutralized, respectively. The initial MD simulation is energy minimized by using steepest descent, immediately followed by the equilibration of the simulation box in the NVT ensemble. The temperature of the system is relaxed for 20 ns using a modified Berendsen thermostat with a relaxation time of 2 fs, and a reference temperature of 300 K. Temperature relaxation was followed by pressure relaxation of the simulation box in NPT ensemble for 40 ns. Pressure equilibration was achieved using Berendsen barostat. The relaxation time of 2 fs and reference pressure of 1 atm was used in pressure relaxation of the simulation box. Leapfrog algorithm was used during simulation to integrate the equation of motion. Long-range electrostatic interactions were accounted during for simulation by the Particle mesh Ewald method. During the simulation, a spherical cut-off of 1.2 nm was used for both electrostatic and van der Waals forces. Upon completion of NVT and NPT equilibrations, multiple final MD simulations have been carried out for 100 ns and a relaxation time of 2 fs with reference temperature at 300 K and pressure of 1 atm using



Graph 2. The radius of gyration graph for the backbone of (SARS-CoV-2 + Favipiravir) and (SARS-CoV-2 + Dolutegravir) systems.

RMSF



Graph 3. RMSF plot of SARS-CoV-2 main protease with different drugs.

modified Berendsen thermostat and Parrinello-Rahman barostat, respectively. All the bond lengths were limited by the LINCS algorithm. The electrostatic interactions were calculated using the Particle Mesh Ewald (PME) summation scheme (Essmann et al., 1995), and the conformations were stored every 20 ps. Further, three technical replication multi-simulations are performed to check the reproducibility in computational values.

4. Result analysis

4.1. Analysis of MD trajectories

The trajectories are examined using root mean square deviation (RMSD) and Radius of Gyration (Rg) using the GROMACS routines. The graphs of these two properties are widely used in predicting the structural activity of a macromolecule (Falsafi-Zadeh et al., 2012; Salsbury, 2010).

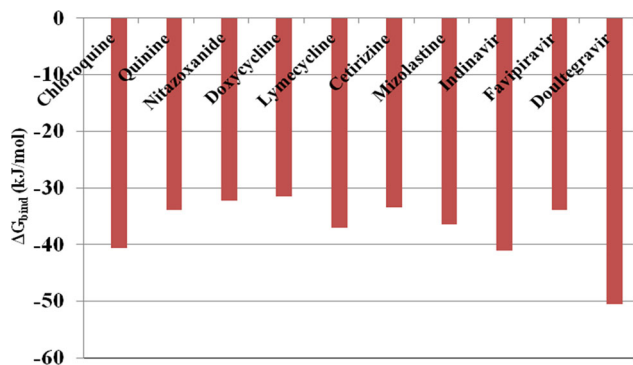
4.1.1. RMSD of the trajectory of the SARS-CoV-2 main protease backbone

The stabilities of the trajectories for (SARS-CoV-2 + Favipiravir) and (SARS-CoV-2 + Dolutegravir) are examined (Graph 1) using the

Table 2. ΔG_{bind} of Favipiravir/Dolutegravir drugs with the SARS-CoV-2 main protease calculated by the MM/PBSA method.

System	$\Delta \text{vdW} \pm \text{SEM}$	$\Delta \text{Elect} \pm \text{SEM}$	$\Delta \text{PS} \pm \text{SEM}$	$\Delta \text{SASA} \pm \text{SEM}$	$\Delta G_{\text{bind}} \pm \text{SEM}$
(kJ/mol)					
SARS-CoV-2+ Favipiravir;	-26.611 ± 0.643	-31.921 ± 1.156	27.325 ± 1.134	-3.221 ± 0.763	-34.428 ± 1.428
SARS-CoV-2+ Dolutegravir;	-83.221 ± 2.443	-16.337 ± 1.245	59.467 ± 1.777	-11.012 ± 0.478	-51.103 ± 1.433

Data are shown as mean \pm standard error of the mean (S.E.M.). ΔvdW = van der Waal energy, ΔElect = Electrostatic energy, ΔPS = Polar solvation energy, ΔSASA = Solvent Accessible Surface Area and ΔG_{bind} = Binding energy data of system in kJ/mol calculated by MM-PBSA.

**Graph 4.** Comparative free energies of SARS-CoV-2 main protease with different drugs.

RMSD for the backbone of the apo form of SARS-CoV-2 main protease. For (SARS-CoV-2 + Favipiravir) system, RMSD raised from 0 to 20 ns and attained a maximum RMSD value of 2.8 Å up to 65 ns. From 65 to 80 ns, RMSD decreased and later remained constant with approximately 1.9 Å up to 100 ns. Similarly, for (SARS-CoV-2 + Dolutegravir) system RMSD raised from 0 to 20 ns and attained a maximum of approximately 3.0 Å throughout the rest of the period. As per the statistical concept of RMSD (https://en.wikipedia.org/wiki/Root-mean-square_deviation), lesser deviation observed in (SARS-CoV-2 + Favipiravir) system suggests more stability over (SARS-CoV-2 + Dolutegravir) system.

4.1.2. Radius of gyration

The R_g of a system is defined as the distribution of atoms around its axis. Analysis of R_g provides us with an insight into the overall dimensions of the protein (SARS-CoV-2) main protease due to binding of the drug (Favipiravir/Dolutegravir). In other words, if a protein is stably folded, it will likely maintain a relatively steady value of the R_g . If a protein unfolds, its R_g will change over time. Thus, when a drug binds to the protein, there is a conformational change that alters the R_g (Daidone et al., 2003). The R_g for the systems are computed and drawn as Graph 2 against simulation time at 300 K. The higher R_g magnitude of Favipiravir from the graph revealed that the drug Favipiravir is creating more instability in SARS-CoV-2 main protease via binding than Dolutegravir.

4.1.3. Root mean square fluctuations

In general, higher variation in averaged root mean square fluctuations (RMSF) value shows more flexible movements whereas low variation in averaged RMSF value shows limited

movements during simulation in relation to its average position of atoms or residues.

From Graph 3, for SARS-CoV-2 + Dolutegravir, the RMSF range is found between 3.2 nm and 5.0 nm. The highest residual fluctuation in this protein structure can be noticed at residue number 4200 with the fluctuation of 5.0 nm. The RMSF range of the SARS-CoV-2 + Favipiravir structure is between 4.1 nm and 4.6 nm. High variation of fluctuation values in this structure can be seen throughout the simulation time period. The highest RMSF fluctuation is at residue number 750 with a fluctuation of 4.6 nm. From the RMSF Plot, we can clearly notice that there is an overall decrease in the variation of fluctuation of the SARS-CoV-2 + Dolutegravir residues when compared to the SARS-CoV-2 + Favipiravir structure. The terminal residues of both the structures show opposite fluctuations. The RMSF result shows that the SARS-CoV-2 + Dolutegravir structure is more stable than the SARS-CoV-2 + Favipiravir structure.

Thus, the action of Dolutegravir over SARS-CoV-2 main protease causes an overall comparative increase in stability when compared to the Favipiravir over SARS-CoV-2 main protein structure.

4.2. Exploration on binding energy ΔG_{bind}

The tool `g_mmpbsa` is developed using two widely used open-source software (GROMACS and APBS), and it has a similar user interface to other GROMACS tools. The tool consists of a script written in Python and calculates components of binding energy using MM-PBSA method for an energetic contribution of each residue to the binding using an energy decomposition scheme with a suitable command to the output file of GROMACS trajectories. The interaction between bonded and nonbonded for the entire framework (with dissolvable) under investigation is assessed with specific heads and lastly averaged to the binding energy in MM/PBSA. The ΔG_{bind} between (SARS-CoV-2 + Favipiravir/Dolutegravir) is evaluated with the MM/PBSA way for the entire 100 ns of multi-simulations. The technical replicate reproducibility relevant to ΔG_{bind} is found to be <1.7%. The MM/PBSA results are arranged in Table 2. In our work, the negative ΔG suggests a spontaneous interaction process and recommends the official use of Favipiravir/Dolutegravir for binding well to SARS-CoV-2 main protease primary protease.

The importance of these drugs (Favipiravir/Dolutegravir) is evident in Graph 4. The obtained values of ΔG_{bind} (kJ/mol) for SARS-CoV-2 main protease with Favipiravir/Dolutegravir and other drugs (Tachoua & Kabrine, 2020) (where the authors used the molecular docking method with the SARS-CoV-2 main protease with different drugs for estimation of the binding energies) are compared in Graph 4. It is clear

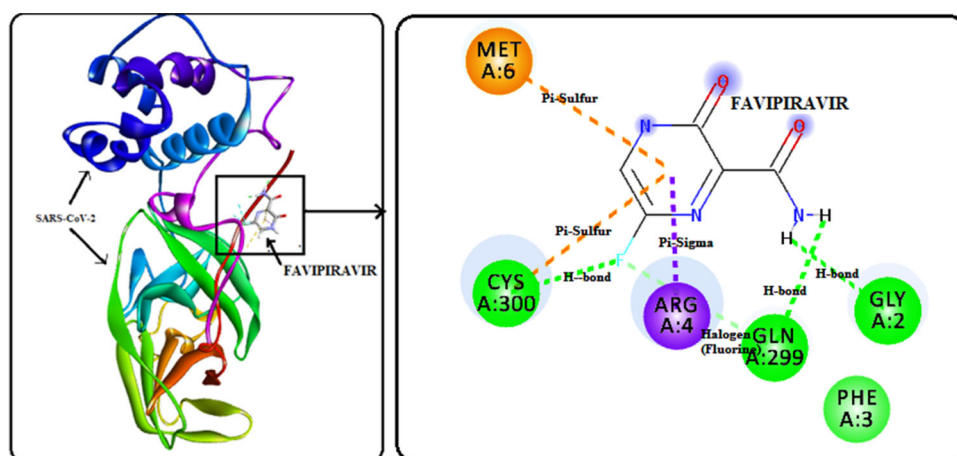


Figure 1. (SARS-CoV-2+ Favipiravir) interactions.

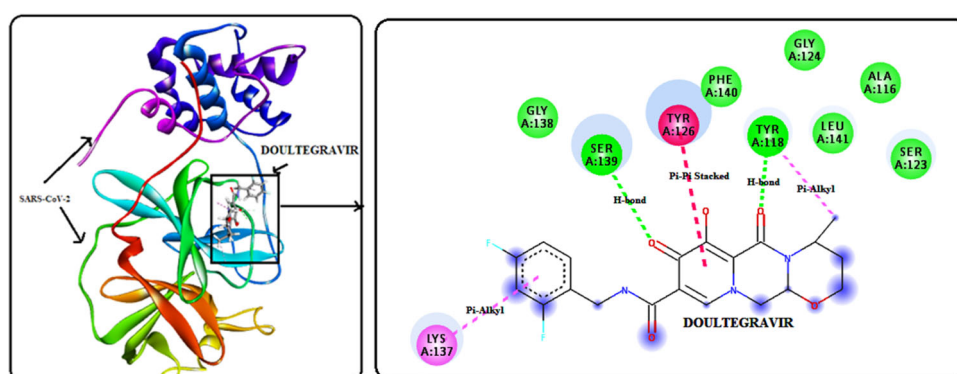


Figure 2. (SARS-CoV-2 + Dolutegravir) interaction.

from the graph that Dolutegravir has the highest value compared to other drugs.

4.3. Exploration of interactions

If the processed energy is negative, then, the nonbonded interactions overwhelm over unfavourable interactions and bonded terms. The bonded terms are, by definition, consistently favorable. Nonbonded interactions can be grouped principally into various classes, for example, π -effects, van der Waals, H-bonds and hydrophobic. These are basic interactions by which the three-dimensional structure of biomolecules is held together. Hence for the current study, we are limiting only to the nonbonded interactions (Atkins et al., 2018; Chang, 2005) between SARS-CoV-2+ Favipiravir/Dolutegravir and some of such interactions are shown at 20 ns in the figure as Figures 1 and 2, respectively (Biovia, 2017).

4.3.1. Hydrogen bond

In (SARS-CoV-2 + Favipiravir) system, h-bonds are observed between the residue CYS (300) and Fluorine of Favipiravir; GLY (2) and H of Favipiravir; GLN (299) and H of Favipiravir. For the case of (SARS-CoV-2 + Dolutegravir), h-bonds are observed between the residue SER-139 and Oxygen of Dolutegravir; TYR (118) and Oxygen of Dolutegravir.

H bonds play a vital role in molecular recognition and the overall stability of the protein structure. However, the dominance of electrostatic energy (Table 2) over other type of

energies with the Favipiravir to SARS-CoV-2 main protease is making the lesser value of binding energy Dolutegravir.

4.3.2. Hydrophobic interactions

According to Schauerl (Schauerl et al., 2016), hydrophobic interactions lead to positive free energy change, and hydrophilic interactions give rise to negative free energy change. The van der Waals pi-sulphur/ π - sigma/pi-alkyl/pi-pi stacked interactions arise due to the interaction of pi-electron cloud over an aromatic group and lone pair of electron cloud of sulphur/sigma electron/electron group of an alkyl group/pi-electron cloud of aromatic, respectively, pertinent to both protein and ligand.

(i) π - sulphur type interactions: In (SARS-CoV-2 + Favipiravir), such interactions are observed between the face of the π -system of Favipiravir with protein residue MET (6) and residue CYS (300), respectively.

(ii) π - sigma interaction: This interaction is observed between the face of the π -system of Favipiravir with ARG (4) residue of SARS-CoV-2 main protease.

(iii) π - alkyl interaction: This type is observed for Dolutegravir with LYS (137) and TYR (118), respectively.

(iv) π - π stacked interaction: This type is observed for TYR (126) and Dolutegravir.

4.3.3. Electrostatic interactions

Electrostatic halogen interaction is observed between the Fluorine of Favipiravir and SARS-CoV-2 main protease residue GLN (299).

From Table 2, electrostatic interaction energy for (SARS-CoV-2 + Favipiravir) ~ 2 times of (SARS-CoV-2 + Dolutegravir) and vander Waals energy for (SARS-CoV-2 + Dolutegravir) > 3 times of (SARS-CoV-2 + Favipiravir) causing the observed binding energy in the systems.

4.4. Exploration on thermodynamical potentials

The significant thermodynamic potential relation is given by

$$\Delta G_{\text{bind}} = \Delta H - T \cdot \Delta S \quad (1)$$

where ΔG_{bind} = Change in Gibb's binding energy; ΔH = Change in the total energy of the system (Enthalpy); T = absolute temperature (here, 300 K) and ΔS = Change in entropy;

If $\Delta G_{\text{bind}} = -ve \Rightarrow$ Equation (1) suggests the existence of two possibilities as follows

$$(i) \Delta H = -ve \ \& \ \Delta S = -ve \quad (2)$$

$$(ii) \Delta H = -ve \ \& \ \Delta S = +ve \quad (3)$$

Here, we are restricted on entropy (ΔS) term only since $\Delta H = -ve$ exists in both the Equations (2) and (3). Further, the entropy (ΔS) is a measure of disorder or randomness in atoms and molecules in a system and since positive/negative entropy change implies that the overall increase/decrease in degrees of freedom of the system suggest the instability (disorder)/stability (order) of SARS-CoV-2 main protease with the binding of drug, respectively.

It is a well-known fact that the changes in thermodynamic potentials can be anticipated from the fundamental interactions between a protein and a ligand (Kamps et al., 2015). The changes in enthalpy and entropy are denoted by ΔH and ΔS , respectively. For $\Delta H > 0$ and $\Delta S > 0$, the primary overwhelming association forces are hydrophobic; a blend of $\Delta H < 0$ and $\Delta S < 0$ infers the presence and predominance of van der Waals cooperations and hydrogen bonds; and $\Delta H < 0$ and $\Delta S > 0$ demonstrates the dominance of electrostatic interactions (Md Nayeem et al., 2021). Table 2 shows that for (SARS-CoV-2 + Dolutegravir), the strength of van der Waals interactions is high, recommends the presence of $\Delta H < 0$ and $\Delta S < 0$ between the apo form of SARS-CoV-2 main protease with Dolutegravir drug. For (SARS-CoV-2 + Favipiravir), electrostatic energy is the highest contributor to the negative binding energy with the apo form of SARS-CoV-2 main protease with Favipiravir. This suggests the case of $\Delta H < 0$ and $\Delta S > 0$ between SARS-CoV-2 and Favipiravir drug.

Therefore, for (SARS-CoV-2 + Dolutegravir) system, negative entropy change suggests the overall decrease in the degrees of freedom of the system suggesting the stability (order) of SARS-CoV-2 main protease with the binding of Dolutegravir (ligand) drug. For (SARS-CoV-2 + Favipiravir) system, positive entropy change implies that the overall increase in the degrees of freedom of the system suggests the instability (disorder) of SARS-CoV-2 main protease with the binding of Favipiravir (ligand) drug. This fact is well supported by the conclusion of variation in averaged RMSF. According to Moradi, destruction (Moradi et al., 2018) of

SARS-CoV-2 main protease with the binding of Favipiravir (ligand) drug will happen due to positive entropy. Similar conclusion was arrived from the dominance of electrostatic interaction over other types between SARS-CoV-2 main protease and the drug Remdesivir with OPLS-AA force field (Nayeem et al., 2021). Thus, the result of thermodynamic entropy also supports the conclusions arrived from RMSD/Rg/RMSF and observed interaction energies of Table 2.

Thus, we can conclude from this theoretical investigation that the Favipiravir drug is more clinically suitable to treat SARS-CoV-2 main protease than Dolutegravir.

The results of clinical trials of Favipiravir/Dolutegravir drugs for SARS-CoV-2 main protease (Cai et al., 2020; Chen et al., 2020; Coomes & Haghighbayan, 2020; Jomah et al., 2020; Khan et al., 2020; Shannon et al., 2020; Tu et al., 2020; Yanai, 2020; Yavuz & Unal, 2020) suggest the efficacy of Favipiravir, and this emphasizes our theoretical conclusion of more clinical suitability of Favipiravir over Dolutegravir on SARS-CoV-2 infection in humans. Furthermore, the Drug Controller General of India (DCGI) has approved the manufacturing and marketing of an antiviral drug named Favipiravir for treating patients with SARS-CoV-2 main protease. The dosage has been recommended to be set at 1800 mg twice daily on day 1, followed by 800 mg twice daily up to day 14. Russia, Saudi Arabia, Japan, Bangladesh, Italy and China have also included it in their COVID-19 therapeutic management guidelines.

5. Conclusion

In this article, a unique theoretical methodology for the selection of suitable drugs among Favipiravir/Dolutegravir to SARS-CoV-2 main protease is devised and applied. This approach is based on the exploration of structural analysis, computation of biothermodynamics, interactions and entropy sign predictions via MD. The analysis of these parameters not only suggested the presence of strong interactions between (SARS-CoV-2 + Favipiravir/Dolutegravir) but also emphasized the clinical suitability of Favipiravir over Dolutegravir to treat SARS-CoV-2 main protease. The same conclusion of clinical suitability of Favipiravir over Dolutegravir drug is well supported by the results of global clinical trials. Furthermore, the obtained results demonstrated how repurposed anti-HIV drugs could be used to combat SARS-CoV-2 main protease and that the fundamental knowledge at the atomic level could be helpful for further design or development of more specific inhibitors in treating human SARS-CoV-2 infection.

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Disclosure statement

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Ethical approval

This article does not contain any studies with human or animal participants performed by any of the authors.

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