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# Computational and theoretical exploration for clinical suitability of Remdesivir drug to SARS-CoV-2

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ABSTRACT

A methodology for the exploration of clinical suitability of Remdesivir drug to SARS-CoV-2 main protease based on the computational, theoretical analysis pertinent to Gibb's free energy computed from the Molecular Dynamic simulations with OPLS-AA force field at 300 K/atmospheric pressure and the variation of thermodynamic potentials over the entire simulation run of 100 ns. This study emphasized the suitability of Remdesivir drug to SARS-CoV-2 protein and the same is emphasized by the results of global clinical trials. This methodology can be applied for future design, development of more specific repurposed inhibitors for the treatment of SARS-CoV-2 infection.

## 1. Introduction

Coronavirus disease (COVID-19) is an infection causing the severe acute respiratory syndrome. Coronavirus 2 (SARS-CoV-2), a recently revealed novel coronavirus is genetically different from viruses that trigger influenza. These are encased, single-stranded RNA viruses whose exterior is enclosed by a halo of protein spikes (corona). The SARS-CoV-2 fits in to the cysteine protease family and the fatality due to this has reached thousands and been mounting step by step, which is a major crisis in the world (Chen, 2020; Chen et al., 2020; Roberts et al., 2007). Since SARS-CoV-2 is rapidly spreading worldwide, World Health Organization (WHO) has declared it as a pandemic disease (Organization, 2020). Further, the devastation (de Wit et al., 2020; Xu et al., 2020) caused by this virus had raised high and critical interest to screen for expected medications through either sedate repurposing or novel medication advancement (Beck et al., 2020; Li and De Clercq, 2020; Lim et al., 2020; Novel, 2020; M. Wang et al., 2020). It is to be noted that the viruses need host-cell functional receptors in humans to accumulate and attack the immune system. As per the important studies (Cao et al., 2020; Gralinski and Menachery, 2020), the spike protein SARS-CoV-2 attacks the Angiotensin-converting enzyme 2 (ACE2) target protein on the surface of pulmonary epithelial cells of humans (Paraskevis et al., 2020; Tipnis et al., 2000). Consequently, the challenge to search for medicines to prevent novel COVID-19 is of immense concern for all scientists around the globe. In this connection, Governments and pharmaceutical companies are paying much attention on probing and developing the unambiguous vaccine or antiviral drug to avert or manage budding infection of SARS-CoV-2. However, drug repurposing permits to quickly examine medical management, at lower costs and with diminished danger of disappointment as the wellbeing profile of the medication is commonly entrenched.

As of late, in view of its positive outcomes in clinical preliminaries, Remdesivir was affirmed by Food and Drug Administration to treat COVID-19 through emergency use authorization. With regards to Remdesivir, it is a monophosphoramidate prodrug of an adenosine simple that has an expansive antiviral range including filoviruses, paramyxoviruses, pneumoviruses, and coronaviruses (Gralinski and Menachery, 2020; Lo et al., 2017). In vitro, Remdesivir represses all human and creature corona viruses tried to date, including SARS-CoV-1 &2, (MERS)-CoV and MERS infections (Brown et al., 2019; Sheahan et al., 2020, 2017; Warren et al., 2016). Furthermore, the inhibiting action of Remdesivir drug on Ebola (Chang et al., 2020; Warren et al., 2016) and on ACE2 is already proven (Zhang and Zhou, 2020). The principal prescription experience of the recuperated patients in the US

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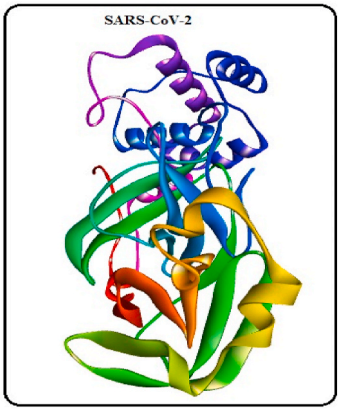
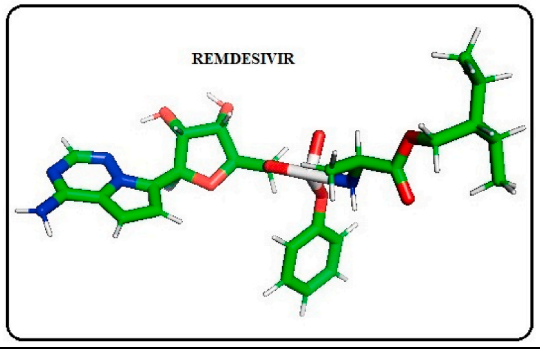
has driven Remdesivir to be the "specific drug" (De Clercq and Li, 2016; Huang et al., 2020; Liu and Wang, 2020; McKee et al., 2020). However, there is no theoretical exploration on its suitability to SARS-CoV-2. To the best of our knowledge, this is the first report of computational approach of the Remdesivir drug on the main protease (PDB6M03) of SARS-CoV-2 using molecular dynamic simulations by Gromacs with the latest OPLS-AA force field at 300 K/1 atmospheric pressure.

It is our hope that as a minimum, this theoretical work is not only helpful for assessing the suitability of Remdesivir drug to SARS-CoV-2 but also for future design and development of more specific inhibitors for the treatment of SARS-CoV-2 infection. The sources from which SARS-CoV-2 main protease in apo form and drug of Remdesivir taken for this non-financial project are given in Table 1.

## 2. Literature review about the use of Remdesivir for SARS-CoV-2

A brief literature review about the studies of Remdesivir that are available as preclinical and clinical study to SARS-CoV-2 is worth noting. The repurposing therapeutic drugs are classified in to two types, 1) drugs directly target the virus replication cycle, and 2) Immunotherapy based approach (Tu et al., 2020). In pre-clinical models, Remdesivir has demonstrated potent antiviral activity against numerous human and animal disease β-coronaviruses, including SARS-CoV-2. In numerous clinical trials, efficaciousness of Remdesivir (GS-5734) against Ebola virus has been incontestable. Moreover, Remdesivir could also be an efficient medical aid in vitro and in animal models infected by SARS and MERS coronaviruses. Hence, the drug could also be in theory, effective against SARS-CoV-2. This drug is a phosphoramidate prodrug of associate nucleoside C-nucleoside (Gordon et al., 2020). From clinical trials on animals, it was confirmed that Remdesivir inhibits SARS-CoV-2 replication, reduces infectious agent load, and exerts protecting effects in SARS-CoV-2 infected animals. Remdesivir conjointly reduces the organic process, alleviates delicate symptoms, and improves pneumonic lesions in SARS-CoV-2-infecetd animals (Frediansyah et al., 2020). In mice infected with the chimeral virus, therapeutic Remdesivir administration diminishes lung infectious agent load and improves pulmonary function compared with vehicle-treated animals. This information demonstrates that Remdesivir is powerfully active against SARS-CoV-2 in vitro and in vivo, supporting its additional clinical testing for treatment of COVID-19. On human trials it was confirmed that Remdesivir powerfully inhibits Covid-19 replication in human respiratory lung cells and primary human airway epithelial cultures. Weaker activity was determined in Vero E6 cells as a result of their low capability to metabolize Remdesivir (Pruijssers et al., 2020). By entrance into respiratory epithelial cells in humans, the prodrug is metabolized to an active nucleoside triphosphate type. This nucleoside analog inhibits the infectious agent's RNA-dependent RNA enzyme (RdRp) by contending with the counterpart adenosine triphosphate (ATP). The nucleoside analog is incorporated into the generating RNA strand and causes a delayed stop within the infectious agent's replication method (Hashemian et al., 2020). Based on the current progress in COVID-19 clinical trials, it was confirmed from the structural features of Remdesivir that the high concentrations of the active triphosphate metabolite allow intracellularly causing it to evade and inhibit virus RNA synthesis (Jorgensen et al., 2020). Having incontestable potent antiviral activity against coronaviruses in preclinical investigations, Clinical test analysis of Remdesivir now yielded promising results. In May 2020, Taiwan accepted the employment of Remdesivir in patients with severe COVID-19. This was followed by the European Union, Canada, USA, Japan and the remaining countries also gave their special approval for emergency use successively (Lamb, 2020; Poduri et al., 2020). A large-scale investigation suggested that the clinical efficaciousness of Remdesivir suggested a dose of 200 mg on day one, followed by a 100 mg once daily in conjunction with avoiding the prescription of non-steroidal anti-inflammatory drugs, ACE inhibitors, or angiotensin II type I receptor blockers is also advised for COVID-19 patients (Jean

**Table 1**
Target SARS-CoV-2 main protease in apo form with Remdesivir drug used in study.

| Protein/Drug | Structure | Source |
|---|---|---|
| SARS-CoV-2 (main protease in apo form) |   | https://www.rcsb.org/structure/6M03 |
| Remdesivir drug[$C_{27}H_{35}N_6O_8P$] |   | https://www.drugbank.ca/drugs/DB14761 |

et al., 2020). More literature about the clinical study of Remdesivir to SARS-CoV-2 is available (Brown et al., 2019; Chang et al., 2016; Choy et al., 2020; Gordon et al., 2020; Hillaker et al., 2020; Jorgensen et al., 2020; Kiser et al., 2015; Kujawski et al., 2020; Shannon et al., 2020; Sheahan et al., 2020; M. Wang et al., 2020; Y. Wang et al., 2020; Warren et al., 2016).

## 3. Theory

Molecular dynamics (MD) simulation is a computational method that enables us to calculate movements of atoms in a molecular system by numerically solving Newton equations of motions (Perozzo et al., 2004). In MD, one usually looks for a drug which can bind easily with the desired protein leading to the highest negative Gibbs Free Energy. Parameters of mathematical functions describing the potential energy of a system, termed the force field, are set to simulate the movements of atoms and molecules (Jiayi et al., 2017; Ren et al., 2020). OPLS-AA (Optimize Potential for Liquid systems-all atom) is the most widely used biomolecular force field and is the better force fields over others when drugs are to be included (Robertson et al., 2015). Preparation of (SARS-CoV-2 + Remdesivir) system for MD simulation through OPLS-AA force field is supplied in **Supplementary file**.

The method of fabrication in understanding of binding energies between protein-drug interactions with the aid of thermodynamics was recently used to assist in the discovery, development of antiviral drug (Sun et al., 2014) and computer-aided design of drug molecules (CADD).$\Delta G_{bind}$ In the present context, Molecular Dynamics study is performed with Gromacs-2020.1 on Ubuntu platform. The molecular mechanics Poisson-Boltzmann surface area (MM/PBSA) method needs the trajectories generated by GROMACS (g_mmpbsa) (Sharp and Honig, 1990; Tsui and Case, 2000) to calculate the $\Delta G_{bind}$ between the SARS-CoV-2 receptor and Remdesivir. The mathematical theory of Bio thermodynamics pertinent to MM/PBSA is incorporated in **Supplementary file.**

## 4. Result analysis

### 4.1. On interaction energies

The information concerning interaction mechanisms of Remdesivir with SARS-CoV-2 main protease is the requisite to know the drug's pharmacodynamics and pharmacokinetics (Cui et al., 2008). The susceptibility of drug in study towards the SARS-CoV-2 protein is estimated using the MM/PBSA approach to the whole 100 ns for multiple simulations and the reproducibility pertinent to $\Delta G_{bind}$ is found to be <1.7%. For the present case, Gibbs free energy is negative indicating the dominance of favorable non-bonded interactions over unfavorable bonded interactions, thus non-bonded interactions > bonded terms. These non-bonded interactions stabilize the three-dimensional structure of protein-ligand complex by means of electrostatic, π-effects, van der Waals forces, H-bonds and hydrophobic effects (Schauperl et al., 2016). Here, we restrict to the non-bonded interactions (Atkins et al., 2018; Chang, 2005) between SARS-CoV-2+Remdesivir only. Since, our aim is to explore the interactions between SARS-CoV-2+Remdesivir system in study, the observed non-bonded interactions at 22 ns are listed and plotted in Fig(1) (BIOVIA, 2017; Wallace et al., 1995). These non-bonded interaction energies which give rise to average $\Delta G_{bind}$ of computed MM/PBSA is tabulated in Table 2. From Table 2, the computed energies follow the order: Electrostatic interaction energy (ΔElect) > van der Waals (ΔvdW) interaction energy > ΔSASA energy. Mathematically, the value of Electrostatic interaction energy (ΔElect) ~ 3.5 times of van der Waals (ΔvdW) interaction energy and Electrostatic interaction energy (ΔElect) ~ 18 times of ΔSASA energy. However, the positive polar solvation energy (ΔPS) finally made the requisite binding energy of (SARS-CoV-2+ Remdesivir) system to -(167.095 ± 1.446) kJ/mol. The negative $\Delta G_{bind}$ implies a spontaneous interaction process.

Therefore, high magnitude with negative $\Delta G_{bind}$ for the system shows that Remdesivir binds well to SARS-CoV-2 protein. Thus, this result is one of the first theoretical preliminary step which pave a way for checking the usage of the drug (Remdesivir) as a clinical trial on (SARS-CoV-2) protein.

### 4.2. Analysis on thermodynamical potentials

The important thermodynamic potential relation is given by

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

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

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

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

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

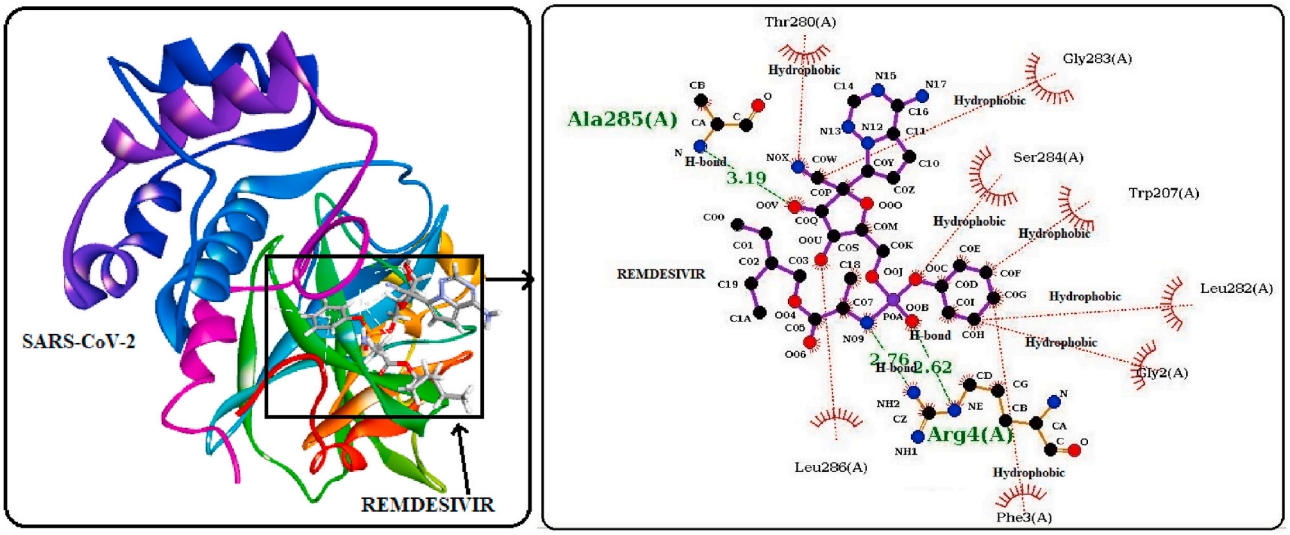



**Fig. 1.** (SARS-CoV-2+ Remdesivir) interactions.

**Table 2**
$\Delta G_{bind}$ of Dexamethasone and Umifenovir drugs with the SARS-CoV-2 protein calculated by the MM/PBSA method. Data are shown as mean ± standard error of mean (SEM). ΔvdW = van der Waal energy, ΔElect = Electrostatic energy, ΔPS = Polar solvation energy, ΔSASA = Solvant Accessible Surface Area and $\Delta G_{bind}$ = Binding energy data of system in kJ/mol calculated by MM-PBSA.

| System | ΔvdW ±SEM | ΔElect ±SEM | ΔPS ±SEM | ΔSASA±SEM | $\Delta G_{bind}$ ± SEM |
|---|---|---|---|---|---|
| | | | (kJ/mol) | | |
| SARS-CoV-2+ Remdesivir; | −71.571 ± 0.714 | −243.223 ± 2.033 | 161.276 ± 1.005 | −13.593 ± 0.076 | −167.095 ± 1.446 |

As per Kamps and Moradi et al. (Kamps et al., 2015; Moradi et al., 2018), case (i) leads to the dominance of van der Waals interactions along with the hydrogen bonds and case (ii) leads to the dominance of electrostatic interactions in the system respectively. For the present study, Table 2 states that the magnitude of electrostatic interaction [Linh et al., 2020] is highest and hence is dominating over other non-bonded type interactions. This suggests that the second case is most favorable among the system in study over the entire simulation time of 100 ns. Here, we are limited to concentrate on entropy term only since ΔH = -ve exists in both the cases. We know that entropy is a measure of disorder or randomness in atoms and molecules in a system and since ΔS = +ve, implies that the overall increase in degree of the freedom of the system suggest the destruction [Moradi et al., 2018] (disorder) of SARS-CoV-2 (apo form of min protease) with the binding of Remdesivir (ligand).

Thus, this computational, theoretical analysis pertinent to Gibb's free energy computed from the Molecular Dynamic simulations and the variation of thermodynamic potentials jointly emphasized the theoretical suitability of Remdesivir drug to SARS-CoV-2 protein.

The obtained values of $\Delta G_{bind}$ for SARS-CoV-2 main protease with Remdesivir and other drugs (Wafa and Mohamed, 2020) are compared in Graph 1. It is clear from the graph that the Remdesivir has the highest value of ΔGbind when compared to other drugs emphasize the presence of strong interactions between (SARS-CoV-2+Remdesivir). Thus, it is concluded from the computation exploration that Remdesivir is one of the best clinically suitable drug to SARS-CoV-2 protein.

The clinical results of Remdesivir drug for the treatment of SARS-CoV-2 suggest the supremacy of Remdesivir over the other repurposed drugs and they emphasize our theoretical conclusion of clinical suitability of Remdesivir to SARS-CoV-2 infection in humans.

## 5. Conclusion

This study proposes a potential theoretical approach to the use of Remdesivir, to tackle the current pandemic SARS-CoV-2. Very high magnitude with negative sign of $\Delta G_{bind}$ = -(167.095 ± 1.446) kJ/mol opens the door towards the use of Remdesivir to prevent and treat SARS-CoV-2 infection in humans. This supremacy of Remdesivir is well supported by the results of global clinical trials and Covid-19 therapeutic approved management guidelines of all countries. Furthermore, the obtained results not only demonstrated how repurposed anti-HIV drugs could be used to combat SARS-CoV-2 main protease, but the fundamental knowledge at the atomic level could also be helpful for further design or development of more specific inhibitors in treating human SARS-CoV-2 infection.

## CRediT authorship contribution statement

**Shaik Mahammad Nayeem:** Conceptualization, Methodology, Supervision. **Ershad Mohammed Sohail:** Writing - review & editing. **Gajjela Priyanka Sudhir:** Data curation, Writing - original draft. **Munnangi Srinivasa Reddy:** Visualization, Investigation, Software, Validation.

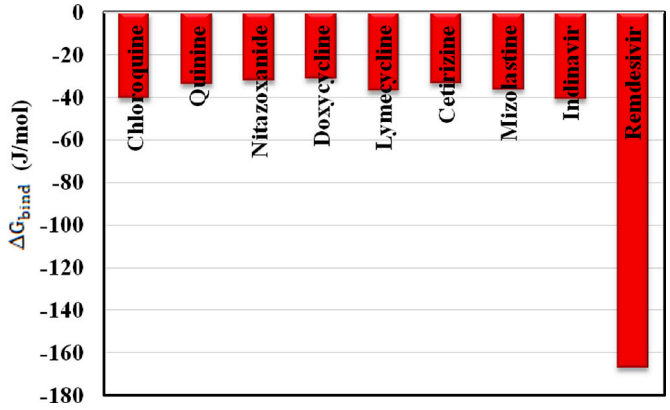



**Fig. 2.** Comparative free energies of SARS-CoV-2 main protease with different drugs.

## Declaration of competing interest

The authors declare that they have no conflict of interest.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejphar.2020.173642.

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