Sys Rev Pharm 2020; 11(5): 110 – 115
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453

The Promising Barrier: Theoretical Investigation

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Article History: *Submitted: 05.03.2020* *Revised: 09.04.2020* *Accepted: 10.05.2020*

ABSTRACT
Virus has become a global pandemic because of the rapid spread and imaginative numbers of cases and deaths. It becomes the most important issue that brings the attention of not only scientists but also the press, international and publishing houses, etc. All the countries involved all researches and centres efforts to find a vaccine or treatment to control it to no avail. This study not only investigates and explores the interaction between three types of medicine (Hydroxychloroquine, Favipiravir, and Remdesivir), and the angiotensin-converting enzyme (ACE2) receptors but also comparing the results with the interaction between the active part of the virus (Spike protein (**S1**)) and the cell. All interactions and properties of all molecules have been studied theoretically using theoretical calculations and computational methods based on the density functional theory.
The results indicate that one of the drugs, which is Remdesivir could be an effective barrier inhibits the bind of the S1 with the human cell. This result could be interpreted in terms of the binding energy, since the binding energy of the Remdesivir molecule with the ACE2 equals -8.564 eV, while the binding energy of S1 is -5.666 eV.
This research also founds that the electrons transfer from the drug to the ACE2 is 10.873 e, which is higher than that of S1 (5.155e). In addition, the results exhibit the Hydroxychloroquine does not have enough capability to inhibit the binding process between the virus and the cell since its binding energy (-2.948 eV) and the number of electrons transfer (0.7670) are the lowest. Finally, the Fermi energies values of Remdesivir (-3.5 eV) and ACE2 (-3.4 eV) molecules are convergent. In the context of the elastic transport, this predication is an important result since it interprets the large number of electrons that have been transferred from Remdesivir to ACE2 molecule, as shown in Figure 3 and Table 2, and this introduces the Remdesivir as a promising drug.

Keywords: Remdesivir, Binding Energy, Electrons transfer
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DOI: 10.31838/srp.2020.5.18

INTRODUCTION
After an outbreak, the World Health Organization (WHO), is considered an epidemic in terms of the number of registered deaths and cases in 192 countries1-3. Where Severe Acute Respiratory Syndrome (SARS) appeared in Guangdong Province, China in 2002[3-5]. The epidemic quickly spread around the world, reaching more than 26 countries in April[6]. Recently in December 2019, hen cases of pneumonia caused by a newly identified β-coronavirus in central China in the region of Wuhan the capital of Hubei province. COVID-19 has appeared in multiple countries around the world[7]. COVID-19 is utilized as a glycosylated spike (S) protein to allow entry into host cells. Functionally, the protein S is divided into two domains S1 and S2. The S1 region, located on the N-terminal side, allows recognition and binding to its cellular receptor[8]. The surface spike glycoprotein contains the receptor-binding domain (RBD) which is accountable for the interaction with the peptidase domain (PD) of Angiotensin converting enzyme 2 (ACE2) in the host cells[9]. While the S2 region is located on the C-terminal side and is implicated in the cell membranes as well as the virus fusion envelope, it is a class I fusion protein[10]. Also, ACE2 is a dicarboxypeptidase consisting of 805 amino acids containing the consensus zinc binding site of type HEXXH + E[11]. The ACE2 receptors present in the lower respiratory tract of humans are the entry point into human cells of certain coronaviruses. SARS-CoV and SARS-CoV2 use the angiotensin converting enzyme 2 (ACE2) to enter host cells[12-13].
Hydroxychloroquine (C18H26C1N3O) is considered as an analog of chloroquine. It takes fewer concerns of the interactions between drug and drug. Hydroxychloroquine is conceded as anti-SARS-CoV of SARS outbreak that was activity in vitro[14]. This suggests that hydroxychloroquine may be a potential pharmacological agent for the treatment of COVID-19 infection[15]. The molecular mechanism of action of chloroquine and hydroxychloroquine has not been fully elucidated[16]. Recently, the two well-known Remdesivir, Favipiravir (T-705) as well as (RDV, GS-5734) were utilized as antiviral drugs that are a clinical isolate in vitro for 2019-nCoV[17]. Remdesivir (GS-5734) is a nucleotide analog that may inhibit viral nucleotide synthesis, whereas Favipiravir (T-705) acts as a purine nucleoside that could lead to the synthesis of the inaccurate viral RNA[18].
In spite of the extensively studied by many of researchers[19-22] overall the world to obtain a deep understanding of the structure and properties of this virus and the right medications to inhibit the virus. Unfortunately, no appropriate treatment has been found yet, and all the drugs that have been tried, including Hydroxychloroquine, have shown a modest efficiency against the virus. In this investigation, theoretical calculations and computational methods were applied not only to reduce the gap of knowledge in this area, but also to obtain an insight of electrochemical properties of the interaction between three types of medicine Hydroxychloroquine, Favipiravir and Remdesivir, as well as the active part of the virus (COVID-19 Spike protein (S1)) with the human cell.

Theoretical calculations and computational methods
The electronic structures of molecules were firstly carried out at the B3LYP level of theory[23] with LANL2DZ[24] basis set used for metal atoms (Zn) and 6-31G** (all other atoms)[25] basis set to explore the charges distribution. All molecules were

optimized using the density functional theory methods SIESTA (is an acronym derived from the Spanish Initiative for Electronic Simulations with Thousands of Atoms)[26]. To obtain geometry, optimization and mulliken electrons transfer calculations were carried out using a generalized gradient approximation[26] and each molecule was relaxed until the forces on the atoms were less than 0.05 eVÅ^{-1}. Calculations were carried out using the PBE functional[27], a double ζ polarized basis set and a real-space grid with a plane wave cut-off energy of 250 Ry.

The employment of DFT to compute the ground state energy of various molecular junctions permits to calculate binding energies and optimal geometries. The counterpoise correction[28]. Assuming two molecular systems, denoted *a* and *b*, the energy of the interaction may be expressed by equation 1

$$\Delta E(ab) = E_{ab} - \left(E_a^{ab} + E_b^{ab}\right) \qquad (1)$$

The total energy of the combined *a* and *b* system is $\boldsymbol{E_{ab}}$, while the total energies of isolated systems *a* and *b* are E_a and E_b respectively with keeping identical basis sets for the three energies. $\Delta\boldsymbol{E}(\boldsymbol{ab})$ is the binding energy. The calculated binding energies are shown in figure 2.

RESULTS AND DISCUSSION

In seeking to explore the electronic properties of the molecules have been investigated by using DFT-based methods. Initial studies of the electronic structures were carried out at the B3LYP level for all atoms to explore the distribution and composition of the frontier molecular orbitals. Plots of the highest occupied molecular orbitals (HOMOs) and lowest unoccupied molecular orbitals (LUMO) are given in Figure 1.

Plots, composition and energies of molecular orbitals are shown in Figure 1 and given in Table 1 and provide a point for initial comparison of the electronic structures across the series. The HOMOs of Favipiravir, and Hydroxychloroquine molecules are mostly extended over the backbone. In contrast, the HOMOs of Remdesivir, ACE2 and S1 are presented a negligible weight on the backbone, and they are delocalized a special part of the molecule, which is may be responsible on the binding.

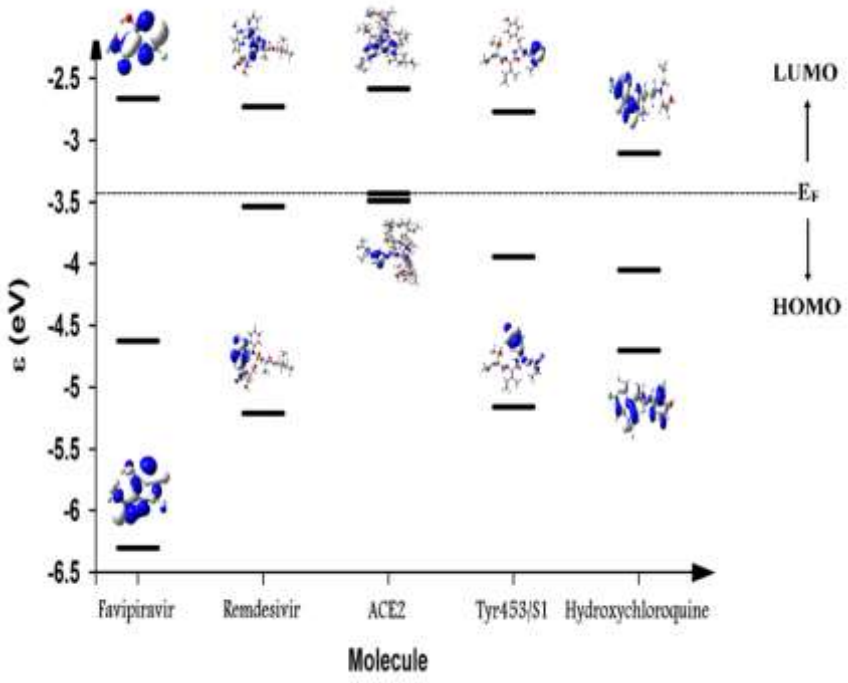

Figure 1: Plots, composition and energy (ε/eV) of frontier orbitals for all molecules. The dashed black line shows the Fermi energy of the ACE2 molecule.

These orbitals are real functions and have a different distribution[29,30]. Crucially, the distribution of the HOMOs are of opposite to the LUMOs. This means that there is a significant difference in the electron transfer mechanism for each molecule. It is obvious that the transport mechanism is the HOMO-dominated electron transport for all molecules except the Remdesivir, since the Fermi energy position is very close to the HOMO. On the other hand, the Fermi energies values of Remdesivir (-3.5 eV) and ACE2 (-3.4 eV) molecules are convergent. In context of the elastic transport, this predication is an important result since it interprets the large number of electrons that have been transferred from Remdesivir to ACE2 molecule, as shown in Figure 3 and Table 2. Also, it is consistent with the binding energy results as shown in Figure 2. Finally, the position of Fermi energies for the Hydroxychloroquine and Favipiravir molecules is too far of the Fermi energy position of the cell, and this indicates that the Remdesivir may be the best choice for inhibiting the virus.

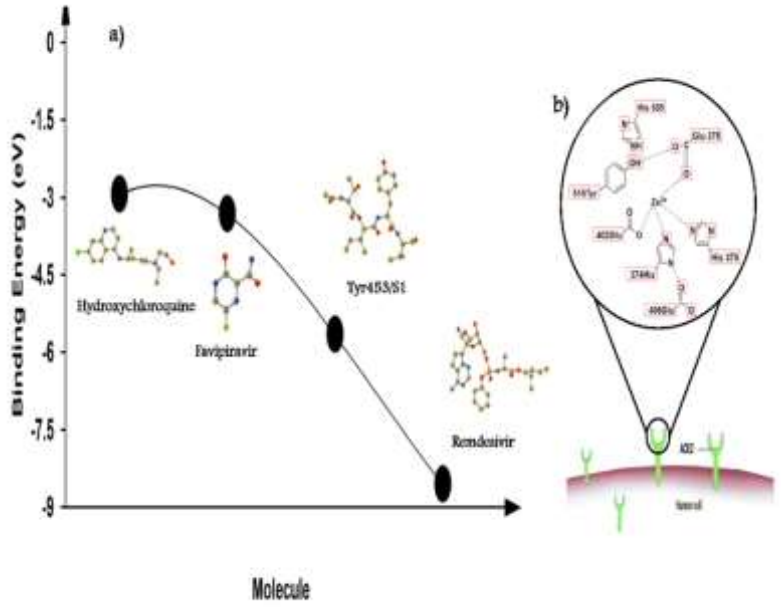

Figure 2: Plots illustrating the binding energies versus molecules. a) The binding energies of drugs Hydroxychloroquine, Favipiravir, and Remdesivir, and the COVID-19 Spike protein (S1). c) The structure of the ACE2.

Spike protein is an essential viral element that plays an important role in the contact and virus internalization to the host cell. A vast amount of host cell receptors are targets for viruses, including the cell surface ACE2. The main factor in the success of the contact process is the binding energy. Therefore, we calculated the binding energy between the cell and the virus, as well as between the different medications and the cell.

Calculated binding energies for four types of molecules are plotted in Figure 2, with two trends immediately apparent. The first one is the spike protein (S1) binds more strongly than the Hydroxychloroquine. Secondly, the binding energy of the Remdesivir molecule is the highest. This result in a fantastic consistent with frontier orbitals (HOMOs and LUMOs) results and previous studies[31,32], and it has been supported by the calculations of the Fermi energy as shown in Figure 1 and Table1.

For these molecules, the order of the binding energies is $B.E_{Remdesivir} > B.E_{Spike\ protein\ (S1)} > B.E_{Favipiravir} > B.E_{Hydroxychloroquine}$, which are broadly consistent with the electrons transfer results and iso-surfaces calculations (figures 1 and 3).

Table 1. The total number of electrons of the isolated molecule (Q_I), the total number of electrons of the molecule attached to the medicine or S1 (Q_{II}), the total number of electrons transferred from the molecule (Q). A is ACE2, H is Hydroxychloroquine, S1 is the active part of COVID-19 Spike protein, R is Remdesivir and F is Favipiravir. B.E is the binding energy.

Molecule	Q_I	Q_{II}				Q	B.E (eV)
S1	206.000	200.845				5.155	-5.666
H	126.000	125.233				0.767	-2.948
R	226.000	215.127				10.873	-8.564
F	58.000	54.55				3.450	-3.322
ACE2	486.000	$Q_{II(AS1)}$	$Q_{II(AH)}$	$Q_{II(AR)}$	$Q_{II(AF)}$	0	
		491.155	486.767	496.873	489.45		

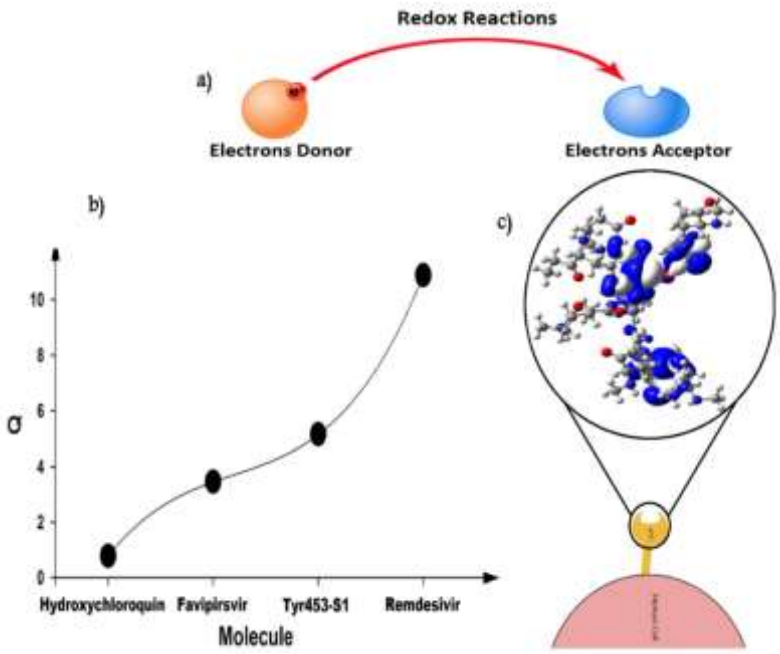

Figure 3: The number of electrons (Q) transferred from each molecule to the ACE2. a) The redox reaction. b) The number of electrons (Q) transferred from drugs (Hydroxychloroquine, Favipiravir, and Remdesivir), and the COVID-19 Spike protein (S1). c) The charges distribution over the structure of the ACE2.

Charges transfer between molecules critically depends on the chemical identity of active parts of the compound[33,34]. Our results show that the number of electrons that have been transferred from Remdesivir molecule to the ACE2 molecule is 10.873e, which is increased by more than one order of magnitude than that of the of the S1. Figures 3 and 2 report that the calculated bulk charges transport of the contacted compounds from Remdesivir is likely to be associated with the largest binding energy (B.E) between ACE2 connected to Remdesivir, as shown in Figure 2 and Table 1. Further, DFT based charges transfer calculations reveal that the significant low number of the transferred electrons is exhibited via Hydroxychloroquine molecule, and that is another fact makes the Remdesivir is a strong candidate to inhibit the virus.

Table 2: The energy (ε/eV) of frontier orbitals (HOMO and LUMO) and the Fermi energies. S1 is the active part of COVID-19 Spike protein, R is Remdesivir and F is Favipiravir. E_F is the Fermi energy.

Molecule	HOMO (eV)	LUMO (eV)	E_F (eV)
S1	-5.16	-2.77	-3.94
H	-4.69	-3.1	-4.05
R	-5.21	-2.72	-3.53
F	-4.57	-3.40	-3.43

CONCLUSIONS

In conclusion, we have carried out a theoretical study of electronic properties (the binding energy, electrons transfer and energy (ε/eV) of frontier orbitals) of some of the medications and their interaction with the human cell (angiotensin-converting enzyme (ACE2)) receptors. Also, we have investigated the interaction between the active part of the virus (COVID-19 Spike protein (S1)) and the cell. This work predicted that the drug (Remdesivir) could play an important role in determining not only the inhabitation process aspects of the virus but also these results provide a considerable body of information concerning the design and select appropriate drugs that can eliminate the virus. Overall, our work provides key insight into the development of a new chemist for treatment the global pandemic (COVID-19).

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