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**Basic Study**  
**In silico evidence of Remdesivir action in the blood coagulation cascade modulation in the COVID-19 treatment**

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**Abstract**  
**BACKGROUND**
Coronavirus diseases 19 (COVID-19) has demonstrated several clinical manifestations which includes not only respiratory system issues, but also liver, kidney and other organ injuries. One of these abnormalities is coagulopathies, including thrombosis and disseminated intravascular coagulation (DIC). Because of this, the administration of low molecular weight heparin (LMWH) is required for patients that need to be hospitalized. In addition, Remdesivir is an antiviral that was used against MERS, EBOV, SARS-CoV and other diseases showing satisfactory results on recovery. Besides, there is evidence suggesting that this medication can provide a better prognosis for patients with COVID-19.

**AIM**
To investigate in silico the interaction between Remdesivir and clotting factors pursuing a possibility of using it as medicine.

**METHODS**
In this *in silico* study, the 3D structures of Angiotensin-Converting Enzyme 2 (ACE2), clotting Factor I-Fibrinogen, clotting Factor II-Prothrombin, clotting Factor III-Thromboplastin, clotting Factor V-Proaccelerin, clotting Factor VII-Proconvertin, clotting Factor VIII-Antihemophilic Factor A, clotting Factor IX-Antihemophilic Factor B, Stuart X-Factor clotting Factor and clotting Factor XI-Precursor of Thromboplastin (receptors) were selected from Protein Data Bank (PDB). The inhibitor structures (ligands) Remdesivir, Oseltamivir were selected from PubChem database, while Atazanavir was selected from ZINC database. The software AutoDock Tools (ADT) were used to prepare the receptors for molecular docking. Ions, peptides, water molecules and other ones were removed from each ligand, then, hydrogen atoms were added to the structures. The Grid Box was delimited and calculated using the same software ADT. A physiological environment with pH 7.4 is needed to ligands Interact with receptors, still the software Marvin sketch® (ChemAxon®) was used to forecast the protonation state. To perform molecular docking ADT and Vina software were connected. Using PyMol® software and Discovery studio® software from BIOVIA it was possible to analyze the amino acid residues from receptors that were involved in the interactions with the ligands. Ligands tortions, atoms that participated in the interactions, type, strength and duration of the interactions were also analyzed by those software.

RESULTS
Molecular docking analysis showed that Remdesivir and ACE2 had an affinity energy of -8.8 kcal/mol forming a complex with eight hydrogen bonds involving seven atoms of Remdesivir and five amino acid residues of ACE2. Remdesivir and Prothrombin had an interaction with six hydrogen bonds involving atoms of the drug and five amino acid residues of the clotting factor. Similar to that, Remdesivir and Thromboplastin presented interactions with seven hydrogen bonds involving five atoms of the drug and four residues of the clotting factor. While Remdesivir and clotting factor V established a complex with seven hydrogen bonds between, six antiviral atoms and six amino acid
residues from the factor and clotting factor VII connected with the drug by four hydrogen bonds, which involved three atoms of the drug and three residues of amino acids of the factor. The complex between Remdesivir and factor IX formed an interaction with 11 hydrophilic bonds with seven atoms of the drug and seven residues of the clotting factor, plus one electrostatic bond and three hydrophobic interactions. Clotting factor X and Remdesivir had an affinity energy of -9.6 kcal/mol, the complex presented 10 hydrogen bonds and 14 different hydrophobic interactions which involved nine atoms of the drug and 16 amino acid residues of the clotting factor. The interaction between Remdesivir and clotting factor XI formed five hydrogen bonds involving five amino acid residues of the clotting factor and five of the antiviral atoms.

CONCLUSION
Because of the in silico significant affinity, Remdesivir possibly could act in the SARS-CoV-2 infection blockade by interacting with ACE2 and concomitantly act in the modulation of the coagulation cascade preventing the hypercoagulable state.

INTRODUCTION
Since the affinity energy value between two structures must be less than −6.0 kcal/mol for the interaction to be considered stable[37], it is possible to point out that Remdesivir was the only antiviral that presented itself within this premise. Remdesivir is a pro-drug, analogous to adenosine, which acts by inhibiting the viral replication of several viral families, among them, the Coronaviridae family. In its mechanism of action, it is observed that it competes with the endogenous ATP for incorporation at viral RNA through RNA polymerase RNA-dependent, triggering the termination of the chain[39].

The in silico analyses indicated that Remdesivir interacts with clotting factors, so in the investigation of the consequences of its use in patients with COVID-19 it is important to analyze the possible routes of action of the drug, as well as the related effects, since during infection by SARS-CoV-2 can occur from bleeding to thrombus formation[40], suggesting a broad spectrum of changes. Therefore, for the understanding
of the interference of Remdesivir in the coagulation it is essential to understand its physiological functioning.

It is important to highlight that the pathways generated by the cadence action of the different agents that are part of the hemostatic process are not fixed to a single series, occurring simultaneously and in ways not completely understood in vivo[41]. As described by an article of University Hospital of Wales (Cardiff, UK), hemostasis is triggered by endothelial damage, with collagen exposure and tissue factor, this process is accompanied by endothelial secretion that results in localized vasoconstriction reflex, reducing local blood flow[42].

Based on the results of molecular docking, it was possible to observe that in addition to the stable interaction with ACE2, Remdesivir also interacted, with significant affinity energy, with clotting factors of the intrinsic pathway, extrinsic and common pathway. It is emphasized that factors V (common pathway) and IX (intrinsic pathway) had less significant interactions (> -7 kcal/mol) with the drug in relation to the other clotting factors, which may result in a lower interference in the cascade from the inhibition of these two factors and, consequently, in anticoagulation.

However, there was significant interaction (-7.0 kcal/mol) between Remdesivir and factor VII, an initial factor of the cascade. Activated factor VII (factor VIIa) joins the tissue factor forming a complex that activates factor IX, leading to thrombin production; this same complex activates more factor VII molecules, so even with a low initial levels of this factor, its effectiveness is satisfactory due to the action of the factor factor/tissue factor complex[43]. In this respect, exclusively for the possible inhibition of factor VII by Remdesivir does not necessarily occur significant alteration in the cascade, because the release of tissue factor is an essential condition for the formation of the complex and occurs in case of endothelial damage, increased during the pro-inflammatory state of SARS-CoV-2[44]. In addition, low levels of factor VIIa are sufficient to feed back the track.

Between Remdesivir and factor X (common pathway) an interaction with affinity energy value of -9.6 kcal/mol was recorded, which is the most significant interaction
observed in this study, so this would be the most stable and most favorable interaction to occur in vivo and may be an important means of inhibiting the coagulation cascade. Secondary hemostasis is formed by extrinsic and intrinsic pathways, activated by different factors, which converge in the activation of factor X, resulting in a common pathway. inhibition of this factor has been shown to prevent the progression of the cascade in baboon models\textsuperscript{[45]}. In the common pathway, factor Xa associated with factor Va (activated by thrombin) cleaves prothrombin into thrombin. Thrombin (factor IIa), which potentiates secondary hemostasis, along with Ca2+ activates factor XIII and also cleaves fibrinogen into fibrin, forming polymers. Associated with factor XIIIa, fibrin polymers form cross-links. In the convergence of the two pathways, the activation of factor X allows the proteolytic cleavage of prothrombin into thrombin, which converts fibrinogen (soluble) into fibrin (insoluble); activates factor XIII, which establishes cross-links in the fibrin network; potentiates the coagulation cascade by catalyzing factors VIII and V; potentiates the coagulation cascade by catalyzing factors VIII and V and promotes platelet activation\textsuperscript{[46]}. Thus, additional anticoagulatory effects could occur due to the relevance of factor X in hemostasis and its interaction with Remdesivir.

Meanwhile, factors I, II, III and XI also connected to Remdesivir with significant affinity energies (between -9.0 and -8.0 kcal/mol), so these factors would be possible sites of action of the drug in the coagulation cascade. Factor Xla in the presence of Ca2+ and, separately, factor VIIa activates factor IX, which, together with factor VIIIa activates factor X\textsuperscript{[47]}. Thus, combined with inhibition of factor X, all these possible interactions with the drug would result in anticoagulation effects, which would be additional to the main mechanism of action of Remdesivir, antiviral activity.

In view of the possibility of interaction of Remdesivir with components of hemostasis, it is necessary to discuss the possible pharmacodynamic interactions between this drug and anticoagulants that have been widely used for the treatment of patients with COVID-19, including Heparins, Warfarin and New Oral Anticoagulants (NOAC).
About the class of Heparins, represented by unfractionated Heparin (UFH), low molecular weight Heparin (LMWH) and Fondaparinux, it is contextualized that these compounds do not present intrinsic anticoagulant activity, binding to antithrombin, which triggers a higher rate of inhibition of coagulation proteases\textsuperscript{48}. Considering the 3 representatives, among the pharmacodynamic differences, the influence of variation on the number of chains of saccharides that make up the molecules stands out, in which the length of these molecules influences the binding and inactivation capacity of specific components of the coagulation cascade, conferring particularities to each molecule. For example, in the case of UFH, to potentiate thrombin inhibition (Factor IIa), chains composed of at least 18 units of saccharides (approximate molecular weight of 5,400 Da) are required. By presenting in their composition molecules with an average weight of 15,000 Da, virtually all UFH molecules are long enough for this function. On the other hand, LMWH, advantageously, have a greater capacity to potentiate the inhibition of factor Xa than thrombin, this results from the average molecular weight of its molecules being between 4,500 to 5,000 Da, resulting in the preference of inhibition of the factor Xa in relation to thrombin. In relation to Fondaparinux, it accelerates only the inhibition of factor Xa by antithrombin, and its length is insufficient to bind antithrombin to thrombin, which justifies the selectivity of action\textsuperscript{49}.

The NOAC, represented by the drugs Dabigatran, Rivaroxabana, Apixabana and Edoxabana, target the same clotting factors, the first being an active compound that binds competitively and reversibly to the active thrombin site (factor IIa) preventing procoagulant activity, while the others act as direct inhibitors of factor Xa.

Considering these particularities, it can be inferred that Remdesivir has the potential for synergistic interaction with the aforementioned drugs. In this sense, due to the stable affinity energy (-9.6 kcal/mol) of Remdesivir/Factor Xa complex, UFH, LMWH, Fondaparinux, Rivaroxaban, Apixaban and Edoxabana may have their effects pronounced when associated with the antiviral\textsuperscript{50}. Similarly, this effect can occur with Dabigatran and heparins, since they are connected to factor IIa, but with less emphasis
on LMWH. This results from the occurrence of a stable binding complex from Remdesivir to thrombin (-8.4 kcal/mol), resulting in a possible therapeutic contribution.

Regarding Warfarin, its mechanism of action involves the inhibition of coagulation cascade components, the factors: II, VII, IX, and X, which are dependent on vitamin K for its activation. Inhibition is the result of blocking the enzyme Vitamin K epoxide reductase (VKOR), Warfarin prevents the conversion of oxidized vitamin K epoxide to its reduced form, vitamin K hydroquinone. As a consequence, there is inhibition of vitamin K-dependent carboxylation, since the hydroquinone form would act as a cofactor for Gamma-glutamyl carboxylase, an enzyme responsible for the carboxylation process, dependent on vitamin K, of clotting factors$^{51,52}$. After carboxylation factors II, VII, IX and X are able to bind to Ca$^{2+}$ and interact with the anionic surface of phospholipids. With conversion blockage, there is no link between the factors and calcium, resulting in the absence of interaction with platelets, preventing the continuity of the cascade.

Considering the mechanism of action of Warfarin, possible synergistic drug interactions between warfarin and Remdesivir can be inferred. The possibility lies in the observation, in silico, of stable binding between Remdesivir and factors II, VII, IX and X, with energy of affinity values, respectively, of -8.4 kcal/mol, -7.0 kcal/mol, -6.5 kcal/mol and -9.6 kcal/mol.

Similar to the in silico data, case reports were observed in the medical literature, despite the low level of evidence, these studies strengthen the hypothesis of a drug interaction between Remdesivir and Warfarin, due to the performance of both in the coagulation cascade. In a first observation of changes in the international normalized ratio (INR) - a marker used for analysis of extrinsic and common pathways, resulting from a possible interaction between the two drugs, a case report describes an INR that increased 2 days after the start of Remdesivir administration. The laboratory parameter remained elevated during remdesivir therapy and began to decrease after completion of treatment. Being reached the therapeutic target of 2-3 after 5 days of the last dose of Remdesivir. In addition, the authors mentioned that the probability score calculated on
the Naranjo scale was 6, suggesting that the increase in INR observed was secondary to a probable drug interaction between Warfarin and Remdesivir\textsuperscript{[53]}. In addition, Landayan and colleagues reported a potential unwell-understood interaction between Warfarin and Remdesivir with Dexamethasone. The application of the Drug Interaction Probability Scale to this case resulted in a score of 5, highlighting a potential drug interaction. According to the authors, this probable interaction is demonstrated by marked increases of INR within 24 to 48 h after the beginning of the combination (Remdesivir plus Dexamethasone) in 2 cases with patients with a history of stable INR\textsuperscript{[54]}. In another case report, Yao and colleagues described an increase in INR after the onset of Remdesivir administration to treat pneumonia due to COVID-19 in a patient on stable chronic warfarin therapy. The INR remained supratherapeutic after discontinuation of Remdesivir and returned to therapeutic levels approximately eight days after discontinuation. The Naranjo Drug Adverse Reaction Probability Scale was 4, indicating a possible adverse reaction to the drug\textsuperscript{[55]}.

**MATERIALS AND METHODS**

Among the complexes formed between protein and antiviral drugs, the most stable ones were selected, according to the affinity energy value. Simulations between Atazanavir, Remdesivir and Oseltamivir with ACE2, clotting factors I (Fibrinogen) and II (Protrombin) indicated significantly greater stability between the three proteins and Remdesivir (Table 1). Due to the most promising data of Remdesivir, the analyses followed with this drug. Molecular docking was performed between Remdesivir and other clotting factors and the drug interacted with all tested factors in silico (Table 2). Remdesivir and ACE2 formed a complex through eight hydrogen bonds involving seven atoms of Remdesivir and five amino acid residues of ACE2 (Table 1); affinity energy was -8.8 kcal/mol. In molecular docking simulations, Remdesivir was used in its protonation state at pH 7.4, in which the amount of the drug is 99.85% protonated.
The association between Remdesivir and Prothrombin occurred through six hydrogen bonds involving atoms of the drug and five amino acid residues of the clotting factor (Table 3); similarly, Remdesivir/Thromboplastin complex was stabilized by seven hydrogen bonds involving five atoms of the drug and four residues of the clotting factor.

Clotting factor V and Remdesivir formed a complex through seven hydrogen bonds between six antiviral atoms and six amino acid residues from the factor. Four hydrogen bonds were observed between Remdesivir and clotting factor VII. These bonds involved three atoms of the drug and three residues of amino acids of the protein (Table 3). The Remdesivir/Factor IX complex was stabilized by 11 hydrophilic bonds (hydrogen bonds) involving seven atoms of the drug and seven residues of the clotting factor, one electrostatic bond and three hydrophobic interactions.

Clotting Factor X and Remdesivir were associated with an energy of affinity equal to -9.6 kcal/mol. The complex was established and maintained by hydrogen bonds (10) and hydrophobic interactions (14) of varied types involving nine atoms of the drug and 16 amino acid residues of the clotting factor. (Table 4). Remdesivir and clotting factor XI formed a complex by the interaction between five amino acid residues of the clotting factor and five antiviral atoms by means of five hydrogen bonds. Complexes with significant affinity energy, whose physiological behavior is relevant to explain the supposed action of Remdesivir as a treatment of symptoms resulting from COVID-19, are shown in Figure 1.

RESULTS

Preparation of receptors and ligands

The three-dimensional structures of the human proteins were obtained from the Protein Data Bank (PDB) (rcsb.org/pdb): Angiotensin-Converting Enzyme 2 (ACE2) (PDB:6VW1), clotting factor I-Fibrinogen (PDB:3GHG), clotting factor II-Prothrombin (PDB:3U69), clotting factor III-Thromboplastin (PDB:5W06), clotting factor V-Proaccelerin (PDB:1CZT), clotting factor VII-Proconvertin (PDB:1KLJ), clotting factor
VIII-Antihemophilic factor A (PDB:2R7E), clotting factor IX-Antihemophilic factor B (PDB:6MV4), Stuart X-Factor clotting factor (PDB:4Y71) and clotting factor XI-Thromboplastin precursor (PDB:5Q7U). These structures, technically called receptors, were prepared for molecular docking using the AutoDock Tools 4 (ADT) software (autodock.scripps.edu). Any ions, peptides and molecules previously attached to the receptor, as well as water molecules derived from the crystallization technique for resolution of the structure by X-ray diffraction were removed at this stage. Subsequently, missing hydrogen atoms were added to the receptors, and the location and dimensions of the Gridbox were determined. The Gridbox features x, y, and z coordinates, being built with grid spacing of 1.0 Å using the AutoGrid component of the ADT software. Gridbox data and coordinates were used in molecular fitting.

The three-dimensional structures of the ligands (drugs) were obtained from two different sources. In the PubChem database (pubchem.ncbi.nlm.nih.gov) three-dimensional antiviral structures Remdesivir (PubChem 121304016) and Oseltamivir (PubChem 65028) were obtained. Oseltamivir was administered with good results in patients with COVID-19 without hypoxia[35].

In the ZINC database (zinc12.docking.org) the three-dimensional structure of the antiviral Atazanavir (ZINC 3941496) was obtained. The ligands interact with their receptors in a physiological environment with pH 7.4, so, to reliably simulate their interaction, a calculation was performed to predict the protonation state using Marvin sketch® software (ChemAxon®). Protonated ligands were prepared for molecular docking using ADT software which detects the torsion points of the inhibitors and calculates their torsion angle.

**Molecular docking**

Molecular docking simulations were performed using ADT software connected to AutoDock Vina v.1.2.0. software[36]. This software associates two components - a search algorithm and a scoring function. The algorithm is responsible for searching for possible combinations in the bindings, exploring the degrees of rotational, translational and
conformational freedom of the ligand, as well as proteins. Then the scoring function is used to choose the best binding modes. These functions are obtained according to the strength fields of molecular mechanics and empirical parameters from free energy calculations, so an affinity energy is calculated. The cutoff point for stable interactions is considered an affinity energy < -6.0 kcal/mol[37]. The results are based on the first conformer of the ligands with reference Root-Mean-Square Deviation of atomic position (RMSD) equal zero[38]. The analyses of amino acid residues of the receptors involved in the interactions with the ligands, as well as the ligand torsions, atoms involved in the interactions, type, strength and duration of the interactions were performed using the PyMol® (Schrödinger, Inc.) and BIOVIA Discovery studio® (Dassault Systemes) software.

**DISCUSSION**

At the end of 2019 the health system of Wuhan - China reported an alarming growth in the number of patients with severe acute respiratory syndrome (SARS) triggered by a new coronavirus SARS-CoV-2[1-3]. A highly contagious disease, COVID-19 spread across several countries[4] in the following months, culminating in the decree of a pandemic by the World Health Organization (WHO) on March 11, 2020[1]. Due to the high transmissibility of the disease and the increase in the number of deaths, several governments imposed measures to use face masks, isolation of new cases and social distancing, restriction of circulation, with the closure of schools and universities, prohibition of agglomerations, as well as decreeing the paralyzing of non-essential activities in an attempt to slow down the spread of the disease[2].

The most widespread form of contagion of SARS-CoV-2 is through the contact with droplets of oropharynx secretions from an infected person. In addition, the transmission of the virus is aggravated by its incubation time - which varies from 3 to 14 days, and by the probability of asymptomatic people or those with mild symptoms transmitting the disease[5]. COVID-19 may not manifest symptoms (asymptomatic patients), manifest mild, moderate or severe symptoms, and may progress to severe
pneumonia and death\textsuperscript{[6,7]}. In addition to the respiratory system, other organs and systems may also present injury from viral infection, such as the liver, kidneys, heart and neural system\textsuperscript{[8]}. Thus, although respiratory failure is the main factor leading to death, causes linked to organ failure, thrombosis and disseminated intravascular coagulation (DIC), accompanied by intense inflammatory response, are also responsible for a great decline in the health status of patients\textsuperscript{[9]}. Of the COVID-19 positive patients who had DIC, only 0.6\% survived, which demonstrates the high lethality at this stage of the disease\textsuperscript{[10,11]}.

The immune response to SARS-CoV-2 infection is associated with the prevalence of coagulation pathway activation and the large increase in the production of pro-inflammatory cytokines, TNF-alpha and IFN-gamma, a condition called "cytokine storm". In addition to acting in the conversion reaction of Fibrinogen into Fibrin to form the clot, Thrombin can also act in increasing inflammation, since these inflammatory events are related to high concentrations of this enzyme and low concentrations of Proteinase Activated Receptors (PAR-1), Antithrombin III and Protein C\textsuperscript{[12]}. Although the coagulopathies observed in these patients are reminiscent of DIC and other thrombotic events, they have characteristics inherent to COVID-19\textsuperscript{[9]}. D-dimer, a product of Fibrin degradation, when elevated, has been associated with a higher mortality rate\textsuperscript{[13]}. Some studies have reported that the increase in D-dimer and Fibrinogen in the bloodstream are poor prognosis to monitor the occurrence of thrombotic events\textsuperscript{[14,15]}. At other times, these parameters are not consistent with the severity of pathological conditions\textsuperscript{[9,10,16]}. In any case, the severity of COVID-19 promotes the imbalance of coagulation and anticoagulation factors, in addition to precipitating the formation of thrombosis, DIC, respiratory deterioration and multiple organ failure\textsuperscript{[11]}.

The International Society of Thrombosis and Hemostasis (ISTH) recommends that low molecular weight heparin (LMWH) be administered in patients in need of hospitalization, in severe or unconditioned or not, prophylactic doses of LMWH should be administered and that D-dimer, prothrombin, activated partial thromboplastin and
Fibrinogen levels be performed daily\textsuperscript{[17]}. The adoption of LMWH was recommended since the tests in patients treated with prophylactic doses had better prognoses and reduction of mortality when compared to the untreated ones\textsuperscript{[18]}.

Near the end of 2020, studies were underway for the development of prophylactic vaccines against COVID-19. Currently, several vaccines are available to the world population, with different vaccination strategies in relation to the number of doses. As for the present time, the epidemic is controlled and vaccine prophylaxis contributed to this scenario. However, the situation of the COVID-19 pandemic is still unpredictable. There is no effective vaccine in fact, given reinfections, or specific antiviral drugs to treat patients with severe COVID-19\textsuperscript{[19]}.

The treatment of severe cases, accompanied by DIC, represents a challenge in the therapeutic process of safeguarding the lives of patients. Although there are studies on experimental drugs considered promising, the lack of proven and effective treatment for severe cases of COVID-19 raises the possibility of reconducting drugs i.e., the reuse of existing drugs, in order to optimize time in controlling disease progression and reduce the cost spent by health systems\textsuperscript{[20,21]}.

Remdesivir (GS-5734) is a broad-spectrum antiviral that has been shown to be effective in containing the replication of pathogens that cause Middle East Acute Respiratory Syndrome (MERS), Acute Respiratory Syndrome (SARS-CoV), Ebola (EBOV) and other infectious agents\textsuperscript{[22-24]}. This drug is a prodrug of adenosine and its metabolic product, the active triphosphate GS-443902, is analogous to ATP and inhibits by competition the enzyme RNA-dependent RNA polymerase (RdRp)\textsuperscript{[25-28]}. Studies conducted with COVID-19-positive patients, who were treated with Remdesivir, showed satisfactory results of faster recovery when compared to patients not treated or those who received placebo\textsuperscript{[29-32]}. In addition, a report validated results of patients with severe COVID-19 hospitalized who were treated with Remdesivir, suggesting that the drug can prevent the progression of the severity of infection, since in the treated group there was less evolution of cases\textsuperscript{[30]}. 
The analysis of data and hypotheses about the action and effectiveness of drugs, such as Remdesivir, can be aided by bioinformatics tools that can act as a method of understanding and predicting the molecular interactions of the drug with possible molecules that may be involved in the process of viral infection or in the development of symptoms and pathological conditions. In this context, some in silico studies have proposed candidate drugs against some target structures of SARS-CoV-2 that have been deposited in the databases until then\(^{[33,34]}\). Based on the hypothesis that Remdesivir acts in symptomatic events of COVID-19 and according to the premises that patients' coagulopathies are of great severity and that Remdesivir is a drug of approved and useful use in the treatment of patients affected by COVID-19, this study aims to verify by molecular docking the interaction of Remdesivir with coagulation cascade factors seeking to contribute to the best understanding of its action and application of covid-19 pharmacological therapy.

**CONCLUSION**

*In silico* analyses indicate that Remdesivir behaves as an antiviral by interacting with ACE2 with considerable affinity, and thus competing with the virus and hindering cellular infection. At the same time this drug is able to bind with affinity and stability to several clotting factors, which would prevent the activation of the blood coagulation cascade. In cases of severe COVID-19 with the possibility of DIC, Remdesivir could act synergistically with anticoagulants to modulate hypercoagulation states and prevent further harm to patients.

**ARTICLE HIGHLIGHTS**

*Research background*

The need for a treatment for COVID-19 has prompted some commercial drugs to be tested off label. The emergence in the evaluation of off-label drugs has provided incomplete information about their efficacy and gaps about long-term and chronic adverse effects. Remdesivir is an example of an off-label drug that showed promising
results in the treatment of COVID-19, but may have other benefits that have not been explored and could be studied in silico.

Research motivation
+ADw-html+AD4APA-p+AD4-The motivation for this study arose from the need to provide data that could help inform studies on Remdesivir, since this drug has not been evaluated through standard clinical trials for COVID-19. Remdesivir has met clinical trials for the treatment of another viral disease, and when used for the treatment of a different disease, both benefits and side effects can arise. Since our team observed the affinity of this antiviral for clotting factors in silico, we hypothesized that it might have benefits not only for preventing SARS-CoV-2 infection, but also for treating symptoms of severe COVID-19, such as disseminated intravascular coagulation.

Research objectives
The aim of the research was to evaluate whether Remdesivir had interaction affinity with clotting factors and to compare these interactions with the interaction made key receptors in SARS-CoV-2 infection to infer possible pharmacological activities.

Research methods
The study was performed in a computational environment using molecular docking and bioinformatics tools that allow to mimic the rational behavior of Remdesivir based on its chemical characteristics. The affinity energy and chemical bonds of Remdesivir with target molecules were analyzed and used to extrapolate in silico information to the human physiological environment.

Research results
The in silico results on the activity of Remdesivir in the coagulation cascade are promising when considering severe cases of COVID-19, but they need to be evaluated
in vivo. In silico data show that Remdesivir can bind to various clotting factors with different affinities; this suggests that this drug can prevent coagulation by acting at several distinct points of the cascade, which increases its effectiveness when disseminated intravascular coagulation is triggered by viral infection.

**Research conclusions**

Our research team suggests that Remdesivir may be an off-label drug used as an antiviral for the treatment of COVID-19, but it can also be used to treat severe symptoms of the disease; however, this needs to be confirmed by in vivo testing.

**Research perspectives**

The research perspective is to evaluate, in silico, other off-label drugs suggested for the treatment of COVID-19.
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