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In silico screening of drug inhibitors of SARS-CoV-2 RNA-dependent RNA polymerase target

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Abstract:

Objectives: the COVID-19 pandemic triggering acute respiratory syndrome has become a major global health concern. After one year into this pandemic, special therapies for COVID-19 remain an unprecedented challenge to mankind and finding drugs to treat this disease is extremely urgent. The SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) enzyme that regulates viral replication has been examined as a potential therapeutic target for the inhibition of SARS-CoV-2 infection. In this study, the authors evaluated the ability of RNA-dependent RNA polymerase drug inhibitors by using an *in silico* molecular docking model. Methods: the 3D structure of RdRp enzyme (PDB ID:6M71, resolution of 2.90 Å) was derived from the Protein Data Bank RCSB. The ligand structures were collected from DrugBank for the RdRp target. Molecular docking was done by AutoDock Vina software. Lipinski's rule of five is used to compare compounds with drug-like and non-drug-like properties. Pharmacokinetic parameters of potential compounds were evaluated using the pkCSM tool. Results: based on the DrugBank database, we collected 192 antiviral molecules and compared them to remdesivir, which has inhibitory activity with this protein target. Results showed that 26 out of 192 compounds have a higher ability to inhibit the SARS-CoV-2 RdRp enzyme than remdesivir. Next, 6 drugs were selected by visually inspecting the docking results with focus on the main interaction between crucial residues at the binding site of the SARS-CoV-2 RdRp enzyme. For the visual inspection, the existence of polar interactions with ASP760 and ASP761 were utilised as the preference criterion. Finally, Lipinski's rule of 5 criteria and absorption, distribution, metabolism, excretion and toxicity (ADMET) profile analysis suggested five drugs that have good pharmacokinetic properties. Conclusions: these drugs were dihydroergotamine, sofosbuvir, nilotinib, tipranavir, and darunavir and may be used as anti-SARS-CoV-2 agents.

Keywords: ***in silico*****, molecular docking, remdesivir, RNA-dependent RNA polymerase (RdRp), SARS-CoV-2.**

Classification number: **3.3**

Introduction

Since COVID-19 acute respiratory syndrome was first discovered in Wuhan city, Hubei province, China, the scientific community, as well as the entire human race, has come face-to-face with an unprecedented challenge to find treatments for this disease. As of October 28th, 2020, there have been 43,540,739 reported cases and 1,16,650 deaths globally (WHO 2020) as the virus continues to rapidly spread [1]. In Vietnam, 1,094 cases and 35 deaths have been reported. One of the biggest concerns of this disease is that its symptoms are often very diverse and manifest differently in each patient. Clinical symptoms are usually noticed 5-to-6 days after infection but the incubation period can be up to 14 days [2]. Fever, coughing, and fatigue are among the most common symptoms. There have been patients with no reported symptoms but suddenly deteriorate rapidly with severe hypoxia that can lead to other diseases and even death [3, 4].

SARS-CoV-2 has a 29.9 kb-size positive-sense RNA genome. It is composed of 14 open reading frames (ORFs), which encode a total of 27 proteins that are further divided into structural and non-structural proteins

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(NSPs) [5]. RNA-dependent RNA polymerase (RdRp) is an important enzyme to the viral RNA life cycle as it is involved in the transcription and translation of the SARS-CoV-2 genome. This enzyme is the cleavage product of polyproteins 1a and 1ab from ORF1a and ORF1ab [6]. Therefore, RdRp is considered to be a major target for antiviral inhibitors.

Molecular docking is a modelling technique that predicts the position and favourable configuration of a substrate molecule (ligand) binding to a protein molecule (target). This *in silico* method saves significant time and cost in the screening of compounds compared with experimental methods.

The rapid spread of COVID-19 has emphasised the need for the global development of coronavirus vaccines and therapies. Therefore, we investigated potential drugs to inhibit RNA-dependent RNA polymerase (RdRp) for COVID-19 treatment. Our research focused on antiviral compounds that were collected from DrugBank with keyword "antiviral". DrugBank is a pharmaceutical knowledge base that has enabled significant advancements in the field of data-driven medicine [7]. Remdesivir is an antiviral drug that has been approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 requiring hospitalisation [8]. Thus, to evaluate the ability of these compounds to inhibit SARS-CoV-2 RdRp, remdesivir was used as a positive control.

Materials and methods

Structure-based virtual screening (SBVS)

Virtual screening is presently a worthy solution to the discovery of new hits. The database of 192 antiviral chemical compounds, available from DrugBank, was chosen for SBVS studies. From this subset, molecular docking using AutoDock Vina was used to select the compounds based on binding energies lower than that of remdesivir. Next, the compounds were selected by visually inspecting the docking results with focus on the main interaction between crucial residues at the binding site of the SARS-CoV-2 RdRp enzymes. For the visual inspection, the existence of polar interactions with ASP760 and ASP761 were utilised as the preference criterion. Finally, the authors performed Lipinski's rule of five and the prediction of ADMET for hit compounds.

Protein receptors preparation

The 3D structure of the RNA-dependent RNA polymerase (RdRp) enzyme (PDB ID: 6M71, resolution of 2.90 Å) was derived from the Protein Data Bank RCSB [9]. All water molecules and co-crystal were removed from the protein molecule using Discovery Studio Visualizer 4.0 software. After that, hydrogen atoms will be added to the protein before regenerating the active site using MGL AutoDock tools 1.5.6 software. Furthermore, the MOE SiteFinder algorithm was used to classify the RdRp binding pocket. The grid center for 6M71 was set as X=121, Y=120, and Z=125 (Angstrom), length 30 Å X 30 Å X 30 Å with the distance between grid cells is 1 Å [10]. The protein is then saved in PDBQT format to prepare for the docking program.

Ligands preparation

The ligand structures were collected from DrugBank for the RNA-dependent RNA polymerase enzyme (RdRp) target involved 192 antiviral compounds. The structures were downloaded from DrugBank in the simplified molecular-input line-entry system (SMILES) format and then converted into 3D structures in PDB format using MOE software [7]. After that, the ligands were optimised by Avogadro software using Conjugate Gradients and converted to PDBQT format using AutoDock tools software.

Performance of molecular docking

These collected compounds were docked into the active site using AutoDock Vina software. The ligand-protein interaction energy is calculated by the scoring function of AutoDock Vina.

Lipinski's rule of five

Lipinski's rule of five is used to compare drug-like and non-drug-like molecules [11]. It is widely employed to evaluate a potential molecule for use as a therapeutical drug. This rule acts as a filter that screens promising compounds with particular pharmacological characteristics. In this work, we used an online tool to evaluate Lipinski's rule of five [12]. The chemical structures were downloaded from the PubChem database and set at pH 7.0 [13].

Prediction of ADMET by computational analysis

In order to analyse the physiochemical efficiency of the five above-mentioned drugs to inhibit the target protein, we used *in silico* ADMET profiling. An ADMET profile involves five parameters: absorption, distribution, metabolism, excretion, and toxicity, which all play a significant role to demonstrate the likelihood of success of a drug. Drug absorption depends on factors including

membrane permeability, intestinal absorption, levels of skin permeability, and as a substrate or inhibitor of the P-glycoprotein. Drug distribution relies on factors like the blood-brain barrier (logBB), central nervous system (CNS) permeability, and volume of distribution (VDss). Based on the cytochrome (CYP) models for substrate or inhibition (CYP2D6, CYP3A4, CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4), metabolism is expected. Based on the total clearance model and the renal OCT2 substrate, excretion is expected. Based on salmonella typhimurium reverse mutation assay (AMES) toxicity, human ether-a-go-go-related gene (hERG) inhibition, hepatotoxicity, and skin sensitisation, the toxicity of drugs is expected. These criteria have been determined and their standard ranges have been tested for compliance. ADMET profiling was predicted using the pkCSM tool [14]. The canonical SMILES molecular structures of collected compounds were retrieved from the DrugBank database [7].

Results

Binding pocket

Using the MOE SiteFinder to find the RdRp binding pocket, we found these essential acid amines: ASP760, ASP761, ASP623, ASP452, TYR455, TYR456, ARG553, PRO620, ARG624, GLU811, TYR619, PRO620, LYS621, CYS622, ASP623, SER681, LYS798, GLU811, and SER814 were all involved at the active site. Fig. 1 illustrates the active site or binding pocket of RdRp in the yellow box.

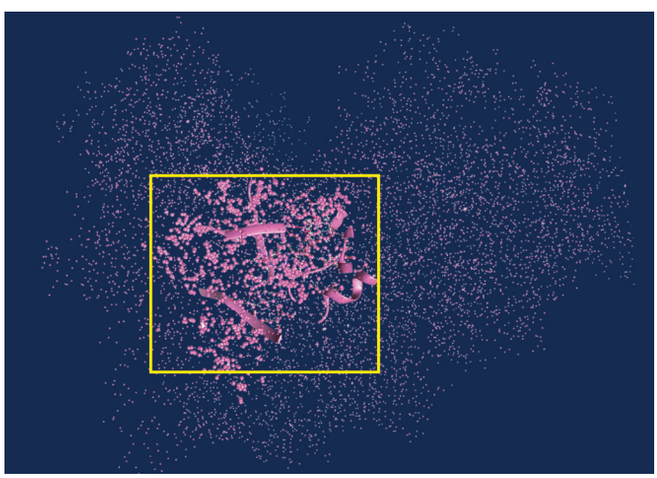

Fig. 1. The binding pocket of SARS-CoV-2 RdRp.

Binding energy

Figure 2 presents the SBVS workflow employed to find hits as SARS-CoV-2 RdRp enzyme inhibitors.

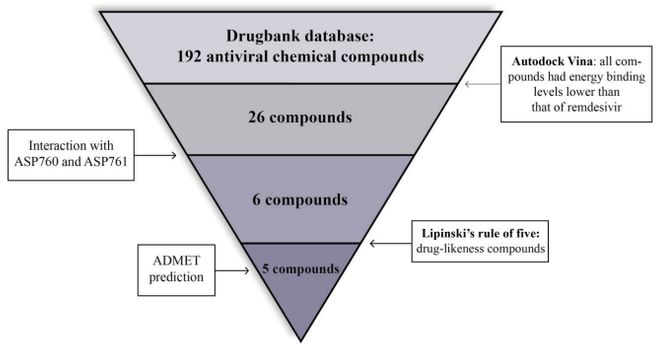

Fig. 2. The structure-based virtual screening workflow.

After preparing the ligands, we docked the 192 antiviral drugs retrieved with RNA-dependent RNA polymerase enzyme to screen target inhibitory activity.

Remdesivir is an antiviral drug that has been approved by the FDA for the treatment of COVID-19 requiring hospitalisation [8]. As an RNA polymerase (RdRp) inhibitor, it can inhibit coronavirus replication in respiratory epithelial cells [15]. Therefore, in this study, we compared the docking scores of the ligands with remdesivir to evaluate the compounds' abilities to inhibit RNA-dependent RNA polymerase enzyme. Elfiky (2020a) [16] also reported that remdesivir has a binding energy with the SARS-CoV-2 RdRp target of -7.6 kcal/mol. Fig. 3 shows the interaction between remdesivir and the RdRp enzyme.

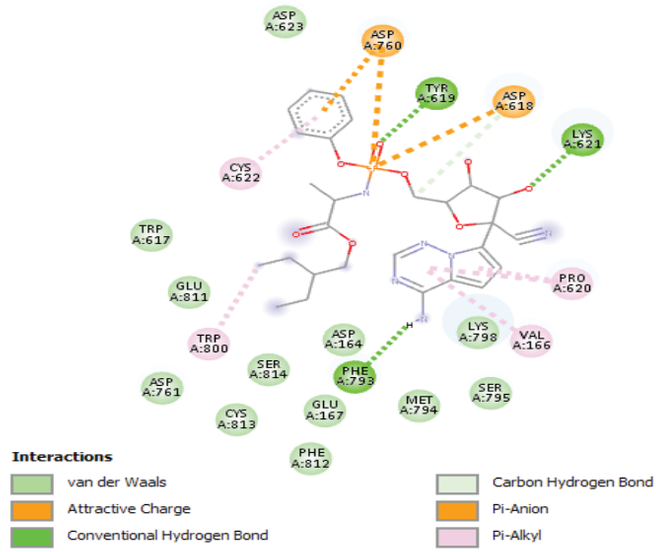

Fig. 3. Interaction between remdesivir and RdRp enzyme.

From the results of docking 192 drugs, we obtained 26 drugs with lower binding energy levels than remdesivir (-7.6 kcal/mol). Ligand-amino acid interactions of these 26 compounds are shown in Table 1.

Table 1. Ligand-amino acid interactions of 26 scoring antiviral drugs against the RdRp enzyme.

No	Name	Binding energy (kcal/mol)	Involved amino acids
1	Dihydroergotamine	-9.4	ASP760, ASP761, LYS621, ARG553, GLU811, LYS798, LYS551
2	Sofosbuvir	-9.4	ASP760, ASP761, ASO618, TYR619, CYS622, GLU811, TRP800, SER814, CYS813
3	Nilotinib	-8.8	ASP760, ASP761, LYS621, ARG553, ARG624, TYR455, TYR619, ASP623, SER814, PRO620
4	Inarigivir	-8.6	ASP760, ASP761, ARG553, ASP623, ALA554, ASP452, ARG624, SER814, CYS813, GLU811, TRP800
5	Tipranavir	-8.2	ASP760, ASP761, LYS621, ARG553, ARG624, ASP618, ASP452, TYR455, PRO620, GLU811, CYS622
6	Darunavir	-7.7	ASP760, ASP761, LYS621, ARG553, CYS622, TYR455, ARG624, ASP623, TYR619
7	Golvatinib	-9.3	ASP623 ARG624, LYS621, ARG553, THR680, TYR456, SER681, SER682
8	Beclabuvir	-9	ARG553, LYS621, CYS622, ASP164, ASN552
9	Nafamostat	-8.7	LYS621, VAL166, LYS798, TRP800, TRP617, GLY811
10	Bictegravir	-8.6	ARG624, ASP623, LYS621, ARG553, CYS 622, TYR619
11	Baloxavir marboxil	-8.2	ASP623, ASN691, CYS622, ASP760, ARG553,LYS621
12	Avatrombopag	-8.2	PRO620, VAL166, LYS521, TYR455, ARG553, ARG555, ARG836
13	Adarotene	-8.1	VAL166, PRO620, LYS621, ARG624
14	Delavirdine	-8	THR556, ARG553, LYS621, TYR619
15	Dolutegravir	-8	TYR619, ASP760, CYS622, LYS621, ARG553, ARG624, ASP623
16	Aplaviroc	-8	ARG553, LYS621, TYR455, GLU811, TRP617
17	Deferasirox	-8	ASP618, TYR619, CYS622, PRO620, LYS621, ARG553
18	Raltegravir	-7.9	ASN691, ALA688, THR556, ARG553, LYS621, TYR455, ASP623
19	Doravirine	-7.9	ARG553, ARG624, ASP623, TYR619, CYS622, ASN691, ASP760
20	Pritelivir	-7.9	LYS798, PRO620, LYS621, ASP623, ARG553, TYR455
21	Elsulfavirine	-7.9	ARG553, CYS622, ASP164, ASN552, THR556, ARG553, LYS621, TYR619
22	PF-232798	-7.9	ARG624, ASP623, LYS621, ASP761
23	Pranlukast	-7.8	ASP623, ARG555, ARG553, ARG624, ASP452, TYR455, LYS621
24	BMS-488043	-7.8	ASP623, CYS622, ASP761, GLU811, TRP617, TRP800, ALA762
25	Nelfinavir	-7.7	ARG553, TYR619, LYS621, PRO620, VAL166, SER795, PHE793
26	Benperidol	-7.7	VAL166, LYS798, PRO620, SER795, PHE793, LYS621, ARG553, ARG624

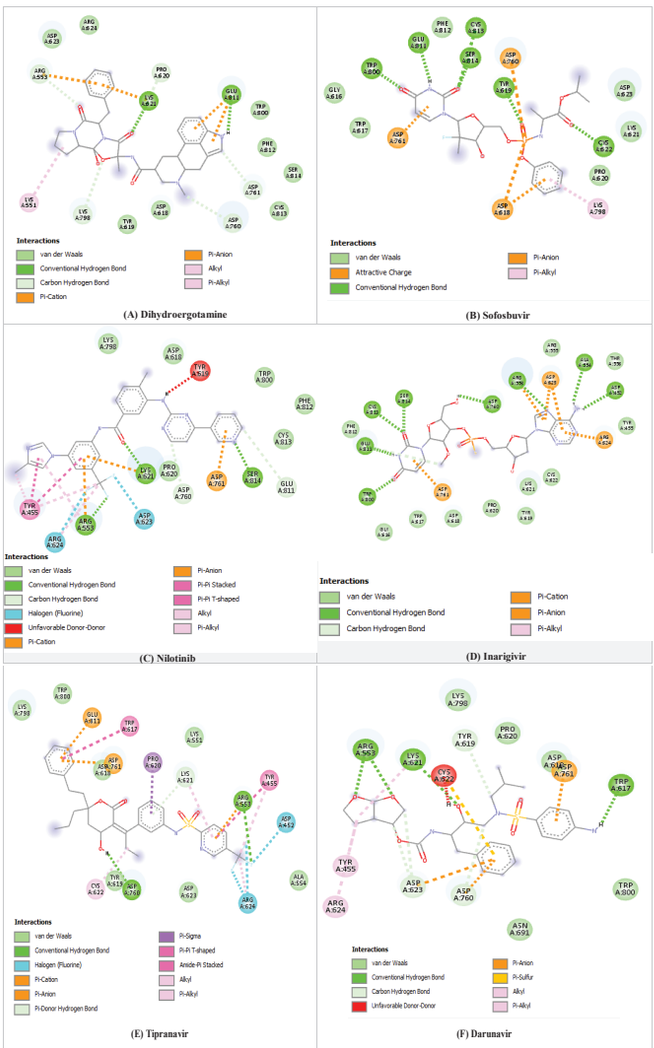

Fig. 4. Interactions between dihydroergotamine, sofosbuvir, nilotinib, inarigivir, tipranavir, and darunavir with the RdRp enzyme (A-F).

ASP760 and ASP761, two aspartate residues, are the main catalytic residues of RdRp [17, 18]. These two residues are exceptionally conserved in all coronaviruses. As a selection criterion, the presence of polar interactions with ASP760 and ASP761 was used. Six compounds were selected based on the main interaction between these essential residues at the binding site of SARS-CoV-2 RdRp enzyme. Fig. 4 shows the interaction between dihydroergotamine, sofosbuvir, nilotinib, inarigivir, tipranavir, darunavir, and the RdRp enzyme target.

Lipinski's rule of five

Lipinski's rule of five is used to distinguish between drug-like and non-drug-like molecules. It predicts high probabilities of drug-like effectiveness or failure for molecules complying with 2 or more of the following

rules: molecular mass (MW) below 500 Dalton; high lipophilicity (expressed as logP below 5); less than 5 donors of hydrogen bonds (HBD); less than 10 acceptors of hydrogen bonds (HBA1); and a molar refractivity (MR) between 40-130.

Table 2. The result of Lipinski's rule of five.

No	Drugs	Molecular weight	HBD	HBA1	logP	MR	Drug-likeness
1	Dihydroergotamine	583.0	3	9	1.498670	155.963348	Yes
2	Sofosbuvir	529.0	3.0	12.0	1.999300	123.152649	Yes
3	Nilotinib	529.0	2	7	6.356432	140.482941	Yes
4	Inarigivir	587.0	6	16	-0.876200	132.885513	No
5	Tipranavir	602	2.0	7.0	8.406303	152.331619	Yes
6	Darunavir	547.0	4	10	3.456099	141.639954	Yes

Among the 6 potential drugs, 5 of them satisfied more than 2 criteria, which we then suggest are potential candidates. These candidates are sofosbuvir, dihydroergotamine, nilotinib, tipranavir, and darunavir (Table 2). Then, we focus on analysing the pharmacokinetic properties including absorption, distribution, metabolism, excretion, and toxicity of these drugs.

Prediction of absorption, distribution, metabolism, excretion and toxicity (ADMET) profile

The prediction of absorption, distribution, metabolism, excretion, and toxicity profile of five selected drugs are shown in Table 3.

Discussion

Structure-based virtual screening and molecular docking

Comparing the interactions of the 5 drugs with remdesivir, we can see that their bonds to the RdRp enzyme have similarities with remdesivir. This is demonstrated by their association with several important amino acids such as LYS621, ASP761, ARG553, and especially the π-anion bond with ASP760. In addition, these drugs also bind to many other amino acids such as TYR619, PRO620, ASP618, CYS622, etc. In recent studies, they demonstrated the same residues to bind strongly within the active sites of RdRp [17, 19].

Analysing the binding energy and interaction of the ligand-amino acid, we found that all five drugs had COVID-19 therapeutic potential. Dihydroergotamine and sofosbuvir, which had the lowest binding energy to SARS-CoV-2 RdRp (-9.4 kcal/mol), was docked into the active site of the enzyme in a similar manner to remdesivir. Dihydroergotamine was observed to interact via carbon hydrogen bonds to ASP760 and ASP761 along with π-anion electrostatic bonds to GLU811 and LYS621. On the other hand, sofosbuvir could bind

Table 3. The result of ADMET profile.

Properties	Dihydro-ergotamine	Sofosbuvir	Nilotinib	Tipranavir	Darunavir
Absorption					
Water solubility (log mol/l)	-2.941	0.953	-2.899	-5.181	-3.358
Caco-2 permeability (log Papp in 10^{-6} cm/s)	0.271	0.472	1.385	0.664	0.493
Intestinal absorption (human) (% absorbed)	64.091	64.308	99.538	98.275	75.477
Skin permeability (log Kp)	-2.735	-2.736	-2.735	-2.735	-2.739
P-glycoprotein substrate	Yes	Yes	Yes	Yes	Yes
P-glycoprotein I inhibitor	Yes	Yes	Yes	Yes	Yes
P-glycoprotein II inhibitor	Yes	No	Yes	Yes	No
Distribution					
VDss (human) (log l/kg)	1.301	-0.728	-0.547	-0.04	0.602
Fraction unbound (human) (Fu)	0.301	0.08	0.243	0	0.055
BBB permeability	-0.532	-1.873	-0.684	-1.368	-1.111
CNS permeability (log PS)	-2.693	-4.343	-2.052	-3.063	-3.519
Metabolism					
CYP2D6 substrate	No	No	No	No	No
CYP3A4 substrate	Yes	No	Yes	Yes	Yes
CYP1A2 inhibitor	No	No	No	No	No
CYP2C19 inhibitor	No	No	Yes	Yes	No
CYP2C9 inhibitor	Yes	No	Yes	Yes	No
CYP2D6 inhibitor	No	No	No	No	No
CYP3A4 inhibitor	Yes	No	Yes	Yes	Yes
Excretion					
Total clearance (log ml/min/kg)	0.67	-0.106	0.406	0.131	0.622
Renal OCT2 substrate (human)	No	No	Yes	No	No
Toxicity					
AMES toxicity	No	No	No	No	No
Max. tolerated dose (human) (log mg/kg/day)	0.135	1.049	0.199	-0.354	-0.763
HERG I inhibitor	No	No	No	No	No
HERG II inhibitor	Yes	No	Yes	Yes	No
Oral rat acute toxicity (LD_{50}) (mol/kg)	2.714	2.31	2.489	2.367	2.107
Oral rat chronic toxicity (LOAEL) (log mg/kg bw/day)	3.131	1.824	0.923	2.326	2.775
Hepatotoxicity	Yes	Yes	Yes	Yes	Yes
Skin sensitisation	No	No	No	No	No
T. Pyriformis toxicity (log ug/l)	0.285	0.283	0.285	0.286	0.289
Minnow toxicity (log mM)	1.74	1.023	1.301	-2.023	0.61

to the interface active pocket of the SARS-CoV-2 by conventional hydrogen bonding through TYR619, CYS622, and GLU811 as well as π-anion bonds through ASP760, ASP761, and ARG553. Nilotinib also interacted with SARS-CoV-2 RdRp by a conserved binding pattern. It was found that this compound had interacted with carbon hydrogen bonds to ASP760 and GLU811 along with π-anion bonds to ASP761, LYS621, and ARG553. Tipranavir and Darunavir had high binding energies to the viral RdRp through some of the same amino acids such as hydrogen bonds with ARG553, π-anion electrostatic bond with ASP761, and other interactions with ASP760, LYS621, and CYS622. For Tipranavir, hydrogen and π-anion bonds with ASP760 and ASP761, respectively, were observed with a docking score of -8.2 kcal/mol. The binding energy and the interaction of the ligand-amino acid between Darunavir and SARS-CoV-2 exhibited an inhibitory ability against COVID-19 of Darunavir. Both Tipranavir and Darunavir exhibited two π-anion interactions with ASP760 and ASP761 with docking score of -7.7 kcal/mol.

Our docking findings revealed that dihydroergotamine (DHE) is a semi-synthetic ergot alkaloid that exhibits high affinities against RdRp with docking binding energies of -9.4 kcal/mol, which is similar to the research result of Gul, et al. (2020) [20]. Previous studies using *in silico* models have also shown the SAR-CoV-2 inhibitory potential of DHE due to interactions within the binding pocket through a good number of hydrogen bonds and hydrophobic interactions [20, 21]. In the research of Gupta, et al. (2020) [22] using molecular mechanics Poisson-Boltzmann surface area (MM/PBSA), DHE had the lowest binding free energy of -17.9 kcal/mol among the final set of surveyed drugs. Thus, it is suggested that a strong interaction between SARS-CoV-2 and DHE exists. Sofosbuvir is a virus inhibitor of great interest among direct-acting antivirals currently in development [23]. Sofosbuvir was also shown to have an ability to bind to the SARS-CoV-2 RNA-dependent RNA polymerase and inhibit enzyme activity [24]. Previous studies reported that sofosbuvir may be a possible candidate in the treatment of COVID-19 based on the similarity of HCV and coronavirus replication systems [25-28]. Nilotinib is another potential compound that showed strong binding energy towards SAR-CoV-2 RdRp. A recent study by Ruan, et al. (2020) [24] showed the binding energy between nilotinib and the active site of the SARS-CoV-2 RdRp enzyme to be -8.4 kcal/mol, which is similar to our result of -8.8 kcal/mol. Noticeably, nilotinib should be able to inhibit SARS-CoV-2 replication in *in vitro*, both in Vero-E6 and in Calu-3 cells, with a half maximal effective concentration (EC_{50}) evaluated at 1.44 and 3.06 μM, respectively [29]. Also, some recent publications demonstrated that Tipranavir could serve as a potential COVID-19 medicinal product, with additional validation studies, because of interactions with the main protease and RNA-dependent RNA polymerase of SARS-CoV-2 [30, 31]. Finally, darunavir exhibited inhibitory ability against COVID-19 in our research. This drug has been carried out in many studies and shows signs of improvement in COVID-19 treatment [32-34].

All five drugs mentioned have been approved by the FDA for antiviral treatment. Due to the COVID-19 pandemic, the option of these FDA-approved drugs is a wise decision in this current emergency because they have already been tested prior to FDA approval.

Each of the five drugs have been shown to treat many diseases as well as inhibit viruses. Dihydroergotamine is a semi-synthetic ergot alkaloid that has been widely used in the treatment of migraines [35]. Sofosbuvir is a hepatitis C virus inhibitor of great interest among direct-acting antivirals currently in development [23]. Nilotinib is a tyrosine kinase inhibitor used to treat chronic myelogenous leukemia [36]. Tipranavir is a new protease inhibitor that, by blocking HIV-1 and HIV-2 proteases, is highly selective for therapeutic intervention in the viral life cycle [37, 38]. As darunavir's high genetic barrier and potency, it is a protease inhibitor for the successful treatment of HIV-1 infection in both naive and experienced subjects [39, 40]. Thus, these medications propose their reuse for new health complications. The benefits associated with repurposed drugs include safety for human use, no escalating cost, and a reduced timeline for its development [41].

ADMET prediction

The absorption of drugs is predicted based on membrane permeability, intestinal absorption, skin permeability levels, and P-glycoprotein substrate or inhibitor. When the Papp coefficient is $>8\times10^{-6}$, the predicted value is >0.90. Hence, the compound has high Caco-2 permeability and is simple to absorb [42]. Nilotinib was predicted to have high Caco-2 permeability. The intestinal absorption (human) percentage of all mentioned compounds is comparatively high: sofosbuvir (67.308%), dihydroergotamine (64.091%), nilotinib (99.538%), tipranavir (98.275%), and darunavir (75.477%). Concerning skin permeability, a compound with log Kp>-2.5 is understood as having very poor skin permeability [42]. However, none of the drugs were considered to have low skin permeability. P-glycoprotein is a member of the superfamily of ABC transporters that can excrete drugs or other exogenous chemicals from cells. The results suggest that sofosbuvir, dihydroergotamine, and nilotinib may be actively exuded from cells by P-glycoprotein. Dihydroergotamine, tipranavir, and nilotinib were predicted to be a P-glycoprotein inhibitor.

The distribution of medication depends on factors that consist of the blood-brain barrier (logBB), CNS permeability, and the volume of distribution (VDss). The distribution extent is a parameter to signify the distribution of medication in numerous tissues *in vivo*. VDss is considered low if it is below 0.71 l/kg (log VDss<-0.15) and high if it is above 2.81 l/kg (log VDss>0.45) [43]. The results confirmed that the distribution volume of dihydroergotamine and darunavir were high whereas the VDss of sofosbuvir and nilotinib were -0.728 and -0.547, respectively, and lower than -0.15. For a given drug, a log BB <-1 is considered to poorly cross the blood-brain barrier [43]. Sofosbuvir, tipranavir, and darunavir were predicted to have difficulty crossing the blood-brain barrier. For CNS permeability, sofosbuvir, tipranavir, and darunavir were predicted to be unable to penetrate the central nervous system (CNS) (logPS is <-3) while dihydroergotamine and nilotinib may penetrate the CNS.

Metabolism is anticipated based on the CYP fashions for substrate or inhibition (CYP2D6, CYP3A4, CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4). A significant detoxification enzyme in the body, primarily found in the liver, is cytochrome P450. The two main isoforms of cytochrome P450 that are responsible for drug metabolism are CYP2D6 and CYP3A4 [44]. The results confirm that sofosbuvir is not a substrate for the two subtypes. However, all four remaining compounds were substrates for CYP3A4. This suggests that nilotinib, dihydroergotamine, darunavir, and tipranavir may be metabolised in the liver. The prediction demonstrates that the total clearance of dihydroergotamine is the best observed by means sofosbuvir, tipranavir, nilotinib, and darunavir.

The toxicity profile of these compounds were also analysed. The toxicities of these drugs are expected based on their AMES toxicities, hERG inhibition, hepatotoxicities, and skin sensitization. Almost all of these compounds were observed to inhibit the human ether-a-go-go-related gene II (hERG II) except for sofosbuvir and darunavir. The toxicity prediction from the AMES test (*Salmonella typhimurium* reverse mutation assay) indicated that all the compounds could be considered as non-mutagenic agents. High toxicities were shown for all the compounds in *Tetrahymena pyriformis*. All the compounds may not affect skin sensitisation.

Although these above-mentioned drugs were approved by the FDA, we used ADMET prediction to re-evaluate their structural alerts of toxicity. Nilotinib, tipranavir, and dihydroergotamine were observed to be hERG II inhibitors, which is the principal cause for the development of acquired long QT syndrome leading to fatal ventricular arrhythmia. All five drugs are the substrates of P-glycoprotein, which are easily transported in the body but may have hepatotoxicity.

Conclusions

Our research is to screen existing approved drugs by the FDA and suggest their reuse for new medical complications. This current research screened 192 antiviral drugs from the DrugBank database for inhibition of the SARS-CoV-2 virus. We showed that five FDA-approved drugs found after virtual screening showed stable interaction with key residues of the RdRp enzyme including dihydroergotamine, sofosbuvir, nilotinib, tipranavir, and darunavir, which inhibited viral proliferation. ADMET predictions demonstrated some structural alerts of toxicity in these drugs. In conclusion, based on our findings, we suggest that these five promising drugs should be further studied *in vitro*, *in vivo,* and in clinical trials to combat this widespread infection.

COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

REFERENCES

[1] Ministry of Health (2020), *Information on Acute Respiratory Infections COVID-19*, https://ncov.moh.gov.vn (in Vietnamese).

[2] N. Chams, et al. (2020), "COVID-19: a multidisciplinary review", *Frontiers in Public Health*, DOI: 10.3389/fpubh.2020.00383.

[3] M. Cevik, et al. (2020), "COVID-19 pandemic - a focused review for clinicians", *Clin. Microbiol. Infect.*, **26(7)**, pp.842-847.

[4] J.F-W. Chan, et al. (2020), "A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster", *The Lancet*, **395(10223)**, pp.514-523.

[5] A. Wu, et al. (2020), "Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China", *Cell Host & Microbe*, **27(3)**, pp.325-328.

[6] Y. Gao, et al. (2020a), "Structure of the RNA-dependent RNA polymerase from COVID-19 virus", *Science,* **368(6492)**, pp.779-782.

[7] D.S. Wishart, et al. (2018), "DrugBank 5.0: a major update to the DrugBank database for 2018", *Nucleic Acids Res.*, **46(D1)**, pp.1074-1082.

[8] D. Rubin, et al. (2020), "FDA approval of remdesivir - a step in the right direction", *The New England Journal of Medicine*, **383(27)**, pp.2598-2600.

[9] Y. Gao, et al. (2020b), "SARS-Cov-2 RNA-dependent RNA polymerase in complex with cofactors", *RCSB Protein Data Bank*, DOI: 10.2210/pdb6M71/pdb.

[10] S. Singh, et al. (2020), "Plant-derived natural polyphenols as potential antiviral drugs against SARS-CoV-2 via RNA-dependent RNA polymerase (RdRp) inhibition: an *in-silico* analysis", *Journal of Biomolecular Structure and Dynamics*, DOI: 10.1080/07391102.2020.1796810.

[11] C.A. Lipinski (2004), "Lead- and drug-like compounds: the

rule-of-five revolution", *Drug Discovery Today: Technologies*, **1(4)**, pp.337-341.

[12] B. Jayaram, et al. (2012), "*Sanjeevini*: a freely accessible web-server for target directed lead molecule discovery", *BMC Bioinformatics*, **13**, DOI: 10.1186/1471-2105-13-S17-S7.

[13] E.E. Bolton, et al. (2011), "PubChem3D: a new resource for scientists", *Journal of Cheminformatics*, **3**, DOI: 10.1186/1758-2946-3-32.

[14] D.E. Pires, et al. (2015), "pkCSM: predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures", *J. Med. Chem.*, **58(9)**, pp.4066-4072.

[15] C.J. Gordon, et al. (2020), "The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus", *J. Biol. Chem.*, **295(15)**, pp.4773-4779.

[16] A.A. Elfiky (2020a), "Ribavirin, remdesivir, sofosbuvir, galidesivir, and tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): a molecular docking study", *Life Sciences*, **253**, DOI: 10.1016/j.lfs.2020.117592.

[17] S.O. Aftab, et al. (2020), "Analysis of SARS-CoV-2 RNA-dependent RNA polymerase as a potential therapeutic drug target using a computational approach", *Journal of Translational Medicine*, **18**, DOI: 10.1186/s12967-020-02439-0.

[18] X. Xu, et al. (2003), "Molecular model of SARS coronavirus polymerase: implications for biochemical functions and drug design", *Nucleic Acids Research*, **31(24)**, pp.7117-7130.

[19] J. Ahmad, et al. (2020), "SARS-CoV-2 RNA dependent RNA polymerase (RdRp) - a drug repurposing study", *Heliyon*, **6(7)**, DOI: 10.1016/j.heliyon.2020.e04502.

[20] S. Gul, et al. (2020), "*In silico* identification of widely used and well-tolerated drugs as potential SARS-CoV-2 3C-like protease and viral RNA-dependent RNA polymerase inhibitors for direct use in clinical trials", *Journal of Biomolecular Structure & Dynamics*, DOI: 10.1080/07391102.2020.1802346.

[21] A.B. Gurung, et al. (2020), "*In silico* screening of FDA approved drugs reveals ergotamine and dihydroergotamine as potential coronavirus main protease enzyme inhibitors", *Saudi J. Biol. Sci.*, **27(10)**, pp.2674-2682.

[22] A. Gupta, et al. (2020), "Profiling SARS-CoV-2 main protease (M(PRO)) binding to repurposed drugs using molecular dynamics simulations in classical and neural network-trained force fields", *ACS Combinatorial Science*, **22(12)**, pp.826-832.

[23] M. Bourlière, et al. (2017), "Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection", *N. Engl. J. Med.*, **376(22)**, pp.2134-2146.

[24] Z. Ruan, et al. (2020), "SARS-CoV-2 and SARS-CoV: virtual screening of potential inhibitors targeting RNA-dependent RNA polymerase activity (NSP12)", *Journal of Medical Virology*, DOI: 10.1002/jmv.26222.

[25] A. Nourian, et al. (2020), "Sofosbuvir as a potential option for the treatment of COVID-19", *Acta Biomed.*, **91(2)**, pp.236-238.

[26] R. Gupta, et al. (2020), "Sofosbuvir for COVID-19 infection: a potential candidate", *Indian J. Pharmacol.*, **52(3)**, pp.232-233.

[27] A.A. Elfiky (2020b), "Anti-HCV, nucleotide inhibitors, repurposing against COVID-19", *Life Sciences*, **248**, DOI: 10.1016/j.lfs.2020.117477.

[28] B. Sayad, et al. (2020), "Sofosbuvir as repurposed antiviral drug against COVID-19: why were we convinced to evaluate the drug in a registered/approved clinical trial?", *Arch. Med. Res.*, **51(6)**, pp.577-581.

[29] V. Cagno, et al. (2020), "The tyrosine kinase inhibitor nilotinib inhibits SARS-CoV-2 *in vitro*", *Basic & Clinical Pharmacology & Toxicology*, DOI: 10.1111/bcpt.13537.

[30] P. Indu, et al. (2020), "Raltegravir, indinavir, tipranavir, dolutegravir, and etravirine against main protease and RNA-dependent RNA polymerase of SARS-CoV-2: a molecular docking and drug repurposing approach", *J. Infect. Public Health*, **13(12)**, pp.1856-1861.

[31] Y. Kumar, et al. (2020), "*In silico* prediction of potential inhibitors for the main protease of SARS-CoV-2 using molecular docking and dynamics simulation based drug-repurposing", *J. Infect. Public Health*, **13(9)**, pp.1210-1223.

[32] E.J. Kim, et al. (2020), "Use of darunavir-cobicistat as a treatment option for critically ill patients with SARS-CoV-2 infection", *Yonsei Med. J.*, **61(9)**, pp.826-830.

[33] T.U. Singh, et al. (2020), "Drug repurposing approach to fight COVID-19", *Pharmacol. Rep.*, **72(6)**, pp.1479-1508.

[34] E. Meriglier, et al. (2021), "Safety of hydroxychloroquine and darunavir or lopinavir in COVID-19 infection", *J. Antimicrob. Chemother*, **76(2)**, pp.482-486.

[35] J.R. Saper, et al. (2006), "Pharmacology of dihydroergotamine and evidence for efficacy and safety in migraine", *Headache*, DOI: 10.1111/j.1526-4610.2006.00601.x.

[36] E. Jabbour, et al. (2010), "Nilotinib for the treatment of chronic myeloid leukemia: an evidence-based review", *Core Evidence*, **4**, pp.207-213.

[37] S. Thaisrivongs, et al. (1999), "Structure-based discovery of tipranavir disodium (PNU-140690E): a potent, orally bioavailable, nonpeptidic HIV protease inhibitor", *Biopolymers*, **51(1)**, pp.51-58.

[38] Z. Temesgen, et al. (2005), "Tipranavir", *Drugs Today (Barc)*, **41(11)**, pp.711-720.

[39] V. Spagnuolo, et al. (2018), "Darunavir for the treatment of HIV infection", *Expert Opin. Pharmacother.*, **19(10)**, pp.1149-1163.

[40] E.D. Deeks (2014), "Darunavir: a review of its use in the management of HIV-1 infection", *Drugs*, **74(1)**, pp.99-125.

[41] S. Pushpakom, et al. (2019), "Drug repurposing: progress, challenges and recommendations", *Nat. Rev. Drug Discov.*, **18(1)**, pp.41-58.

[42] Y. Han, et al. (2019), "*In silico* ADME and toxicity prediction of ceftazidime and its impurities", *Front. Pharmacol.*, DOI: 10.3389/fphar.2019.00434.

[43] D.E.V. Pires, et al. (2015), "pkCSM: predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures", *Journal of Medicinal Chemistry*, **58(9)**, pp.4066-4072.

[44] C. Prakash, et al. (2000), "Identification of the major human liver cytochrome P450 isoform(s) responsible for the formation of the primary metabolites of ziprasidone and prediction of possible drug interactions", *British Journal of Clinical Pharmacology*, **49** Suppl.1, pp.35S-42S, DOI: 10.1046/j.1365-2125.2000.00151.x.