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FDA Approved Drugs and Herbal Based Inhibitors Target SARS CoV-2 RNA Dependent RNA Polymerase

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Abstract: The recent outburst of COVID-19 started as an epidemic in Wuhan city, China, in December 2019. It was declared a pandemic by World Health Organization on 30 January 2020. The rapid spread of the novel coronavirus leads to more deaths worldwide. Also, it has spared many lives in its second wave of disease in many countries. Although scientists had produced vaccines, it does not suit every human being, and they are getting infected again, which is due to a lack of extensive clinical trials. Also, drug repurposing is ineffective. There is a need for more research; using *in silico* methods may be the better option in the current situation to save the lives of virus-affected individuals. The drugs used for other diseases and herbal compounds might help target the coronavirus. In this study, a protein, RNA-dependent RNA polymerase (RdRp), was chosen as a target from the virus for molecular docking. It was docked against several drugs on the market and also several herbal compounds. This study will help further *in vitro* and *in vivo* studies with new lead compounds, new horizons for drugs in trials, and a new approach for *Insilco* analysis to treat COVID-19.

Keywords: COVID-19; drug repurposing; herbal compounds; RNA dependent RNA polymerase; molecular docking.

1. Introduction

Coronavirus, in general, belongs to the Coronaviridae family and the sub-family of Coronavirinae [1]. It is an enveloped RNA virus which is positively stranded. The name corona arrived due to the halo-like appearance, which is the spikes of glycoproteins protruding from the envelope on the surface [1]. The recently bloomed virus in December 2019 causes fever, cough, shortness of breath, and tiredness. It leads to death for people with medical complications and people who are immunocompetent. Also, the second wave of the disease is leading to inflammatory diseases in humans. It has been raised as a threat to global health.

SARS CoV-2 was officially named COVID-19 by the World Health Organization. The SARS CoV-2 is related to SARS and MERS. In 2003, there was an outbreak of SARS in Hong Kong [2], which also spared many lives.

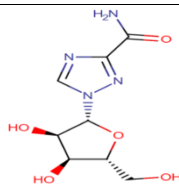
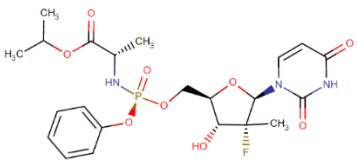
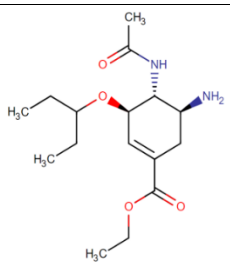
From the family of all known RNA viruses, the virus with a massive genome is the coronavirus. Its genome length is from 27-32 kilobase pairs [3], which is unknown in other RNA viruses. In this large genome, there are many proteins that help the virus inside the host, and also, there is much research carried out to inhibit it [4-6]. Still, a protein called RNA-dependent RNA polymerase acts as the main key that helps the viral genome for the transcription in not only SARS CoV-2 but also all the RNA viruses. Thus for this study, RNA-dependent RNA polymerase from SARS CoV-2 was chosen as a target. When this is being

inhibited, the further spread of the virus inside the human cell can be stopped leading to a cure for the disease.

There have been many antiviral drugs for many viral diseases found [7]. Also, some drugs like Remdesivir and Chloroquine were checked for their effectiveness against SARS-CoV-2 [8]. Remdesivir alone has proved its antiviral activity against many RNA viruses which has infected both humans and animals, such as Ebola, Nipah, SARS, and MERS [9]. Drugs and natural compounds from plants have shown their effectiveness against viral diseases [10-13]. Also, the natural compounds from plants have shown good responses against pneumonia-like infections [14]. And also, these herbal compounds can be made as nanocolloids [15-18] and nanoparticles for their even more effective application as a drug; these have been proved to be effective against various diseases in humans [19-22]. It is also less toxic in nosocomial infections[23,24]. Not only herbal compounds even nanoparticles from the fungal source have shown great applications in diseases [25-28]. For this study, nine drugs were selected for the docking purpose to inhibit the RdRp (Table 1). The selected drugs are FDA-approved. All these drugs have several activities and have been used to treat other viral infections. Apart from drugs, the compounds from herbs used in traditional Indian medicine were also selected. Eight compounds were selected to dock against the target (Table 2). These compounds also have many activities such as antiviral, anti-inflammatory, and also used for cancer.

In these years, the role of bioinformatics has tremendously increased. It has joined hands with pharmacology in developing drugs quickly with almost low risk [33,34]. The present study will explain the best inhibition drug or herbal compound of SARS CoV-2 using molecular docking. Additionally, there has been no known analysis of certain drugs and compounds from herbs in this study. The findings from this study will give the researchers a good idea in developing a more effective drug to fight against COVID-19. Apart from helping treat the coronavirus, the herbal compounds may also help find a cure for other diseases as they have been proven to be effective [29-32] and in use from the past centuries.

Table 1. FDA-approved drugs used for docking against RdRp in SARS CoV-2.

No	Drug	Structure	Pharmacological function
1.	Ribavirin		Treatment of HSV and HCV
2.	Sofosbuvir		Treatment of Hepatitis C
3.	Oseltamivir		Treatment of Influenza A & B

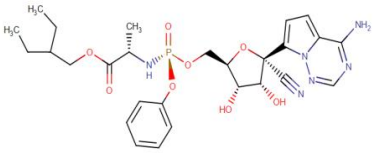
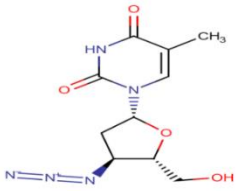
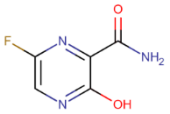
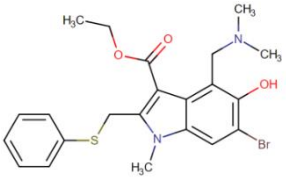
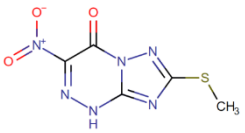
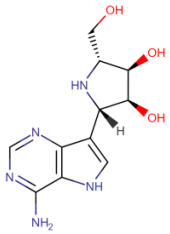
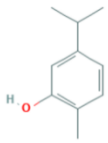
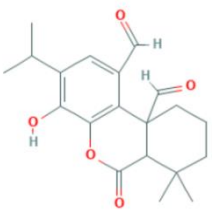
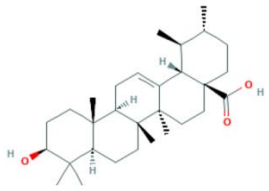
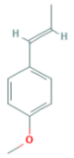
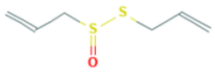
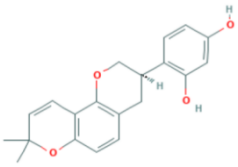
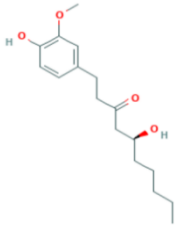
No	Drug	Structure	Pharmacological function
4.	Remdesivir		Treatment of EBOLA, Known to inhibit viral RNA polymerase
5.	Zindovudine		Treatment of HIV &AIDS
6.	Favipiravir		Treatment of influenza
7.	Umifenovir		Treatment of Influenza and other Respiratory infections
8.	Triazavirin		Treatment of Influenza A & B
9.	Galidesivir		Treatment of Zaire EBOLA virus

Table 2. Compounds from herbs used for docking against RdRp in SARS CoV-2.

No	Compound name	Structure	Known Function	Source	
				Common name	Scientific name
1.	Carvacrol		Anti-bacterial Anti-fungal Boost immune system	Oregano	*Origanumvulgare*
2.	Safficinocide		Anti-viral	Sage	*Salvia officinalis*

No	Compound name	Structure	Known Function	Source	
				Common name	Scientific name
3.	Ursolic acid		Anti-inflammatory	Holy basil	*Ocimumtenuiflorum*
4.	Trans anethole		Anti-inflammatory	Fennel	*Foeniculumvulgare*
5.	Allicin		Anti-bacterial Anti-fungal	Garlic	*Allium sativum*
6.	Glabridin		Anti plasmodial drug	Licorice	*Glycyrrhizaglabra*
7.	Gingerols		Antineoplastic agent	Ginger	*Zingiberofficinale*

2. Materials and Methods

2.1. Databases and software used.

Databases: Protein data bank, Drug Bank, PubChem.
Software: Auto dock 4, Biovia Discovery Studio, Open Babel, Pymol.

2.2. COVID-19 RdRp structure.

The RNA-dependent RNA polymerase was selected as a target from the virus. The protein 3-dimensional structure was downloaded from the Research Collaboratory for Structural Bioinformatics website (RCSB) https://www.rcsb.org/. The protein was downloaded in PDB format for docking purposes.

2.3. Drug as ligand preparation.

In this study, the drugs already approved by the FDA and the drugs currently in the study were taken. The 3-dimensional structure for the ligand was downloaded from the Drug bank website https://www.drugbank.ca/. The drugs were downloaded in PDB format.

2.4. Compounds from herbs as ligand preparation.

The main component from herbal plants used in early Indian and Chinese medicine was selected. The compounds were downloaded from the PubChem website https://pubchem.ncbi.nlm.nih.gov/. The compounds were downloaded in SDF format. It was then converted to PDB format by using the Open Babel software http://openbabel.org/wiki/Main_Page.

2.5. Molecular docking.

The ligands were docked against the protein to find out the best inhibitor for RdRp in SARS CoV-2. The docking procedure was carried out by using Auto dock 4 software http://autodock.scripps.edu/.

2.6. Analyzing the result.

The analysis of the docking was done in Discovery studio software https://discover.3ds.com/. The interacting amino acids with the target protein were all found. The binding energy was also found to find the best inhibiting molecule. The docking pose of the best inhibiting molecule for drug and the herbal compound was done using Pymol software https://pymol.org/2/.

3. Results and Discussion

The currently emerged virus is creating a catastrophic situation for the whole world. This will be stopped only when a cure is found. Finding a vaccine or drug can be more time-consuming; thus bioinformatics method of analysis will be of great use for not only fully eradicating but can be stopped to an extent. As soon as the virus rose up in China, researchers worldwide started to sequence the virus's genome. The protein RdRp was first made online Protein Data Bank website in April 2020. The discovery of this protein structure in the virus provided a good opportunity to identify drugs and compounds, especially for *Insilico* analysis to combat the virus.

Already it is evident that herbal compounds showed good efforts in treating viral diseases in humans [35,36]. Many drugs have also exhibited good antiviral efforts in humans [7,8]. Today's world of research has grown to greater heights; it has successfully served mankind curing a wide range of diseases, including deadly cancer and neuro diseases [37-40]. In this study, using molecular docking studies, nine drugs in which some have been approved and seven herbal compounds were explored for their inhibitory effect on RdRp in COVID-19.

The docking result for the ligand and protein was determined by the binding energy produced. Their molecular formula, binding energy, and interacting amino acid are shown (Table 3). All the herbal compounds used their molecular formula, herbal source, binding energy, and interacting amino acid are shown (Table 4).

Table 3. Molecular docking of drugs against RdRp in COVID-19.

Ligands name	Ribavirin	Sofosbuvir	Oseltamivir	Remdesivir	Zindovudine	Favipiravir	Umifenovir	Triazavirin	Galidesivir
Molecular formula	$C_8H_{12}N_4O_5$	$C_{22}H_{29}FN_3O_9P$	$C_{16}H_{28}N_2O_4$	$C_{27}H_{35}N_6O_8P$	$C_{10}H_{13}N_5O_4$	$C_5H_4FN_3O_2$	$C_{22}H_{25}BrN_2O_3S$	$C_5H_4N_6O_3S$	$C_{11}H_{15}N_5O_3$
Binding energy	**-5.99**	**-5.72**	**-5.47**	**-8.33**	**-6.22**	**-4.58**	**-6.75**	**-5.85**	**-6.22**
Interacting amino acid	SER681, THR680,ARG624,SER682, THR687,ASP623,ASN691,ALA688,THR556,ARG555,ARG553,SER759,ASP760.	ASP452, SER682, THR687,THR556,THR680, TYR455,ARG624,LYS545, ARG555,ALA554,ARG553, ASN691,CYS622,LYS621, ASP760.	ARG624,ASP623, TYR455,CYS622,LYS621,ARG553,PRO620,TYR619, ASP618.	VAL557,THR556,LYS545,ARG555,ARG553,SER682,ARG624,ASP623, CYS622,LYS621,ASP760, TYR619,PRO620.	ASP452, TYR455,THR556,ALA554,ARG555, ARG553,ARG624,ASP623, LYS621,CYS622, PRO620,TYR619,ASP760	THR556,LYS545,ARG555,ALA554,ARG553,ASP623, ARG624,SER682,ASP452.	ASP452, TYR455,THR556,LYS545,ALA554,ARG555, ARG553,ARG624,ASP623, LYS621,CYS622, PRO620,ASP760, TYR619,ASP618	ASP618,ASP760, TYR619,PRO620,CYS622,LYS621,ASP623, ARG624,TYR455,ASP452, THR556,ALA554,ARG555,ARG553,LYS545	SER682, THR556,ASP623,ARG624,ASP452, TYR455,LYS621, LYS545,ARG555,ALA554,ARG553

The result based on the binding energy value for the drugs as ligands docked were Remdesivir>Umifenovir>Zindovudine>Galidesivir>Ribavirin>Triazavirin>Sofosbuvir>Oseltamivir>Favipiravir. The binding energies were -8.33, -6.75, -6.22, -6.22, -5.99, -5.85, -5.72, -5.47 and -4.58 respectively. The results for the herbal compounds as ligands docked were Ursolic acid>Glabridin>Safficinolide>Allicin>Carvacrol>Trans anethole>Gingerols. The binding energies were -10.88, -7.78, -7.39, -5.67, -5.15, -4.63, -4.56 respectively. The docking pose of all the ligands with the RdRp protein is shown (Figure 1).

Table 4. Molecular docking result of herbal compounds against RdRp in COVID-19.

Ligand Name	Carvacrol	Safficinolide	Ursolic acid	Trans anethole	Allicin	Glabridin	Gingerols
Molecular formula	$C_{10}H_{14}O$	$C_{20}H_{24}O_5$	$C_{30}H_{48}O_3$	$C_{10}H_{12}O$	$C_6H_{10}OS_2$	$C_{20}H_{20}O_4$	$C_{17}H_{26}O_4$
Herbal source	Oregano	Sage	Holy Basil	Fennel	Garlic	Licorice	Ginger
Binding energy	**-5.15**	**-7.39**	**-10.88**	**-4.63**	**-5.67**	**-7.78**	**-4.56**
Interacting Amino Acid	SER681, THR680, ARG624, ASP623, SER682, THR556, ALA558, MET542, TYR456, LYS676.	ARG624, ASP623, CYS622, LYS621, ASP760, TYR619, ARG553.	TYR455, ASP452, THR556, ARG62, ASP623, LYS621, CYS622, PRO620, TYR619, ALA554, ARG55.	LYS676, TYR456, MET54, ARG62, THR680, SER681, ASP623, ALA55, THR556, SER682.	PRO461, MET463, THR462, THR246, LEU460, ASN791, LEU247, PRO243, TYR788.	ARG624, ASP623, TYR455, SER682, VAL557, ASP452, THR556, ARG555, LYS545, ARG553.	LYS676, TYR456, THR680, ARG624, ASP623, SER681, SER682, ALA558, MET542, VAL557, THR556, ARG555, LYS545, ARFG553

The information mentioned above shows us that in the case of drugs as a cure for COVID-19, the drugs Remdesivir, Umifenovir, Zidovudine, and Galidesivir showed good binding energy and were found to be very effective against RdRp. And in the case of herbal compounds Ursolicacid, Glabridin, and Safficinolide, binding energies depict the very good interaction with the target protein RdRp. According to this study, the docking pose of the best-docked drug and herbal compound to protein is also shown (Figure 2). From this study, it is recommended to use Remdesivir as a drug and as Ursolic acid-containing Holy Basil as a dietary supplement.

Table 4 shows the molecular docking result of herbal compounds with their molecular formula, herbal source, binding energy, and interacting amino acid. The binding energy indicated in red color shows the highest energy, and the green color shows the lowest.

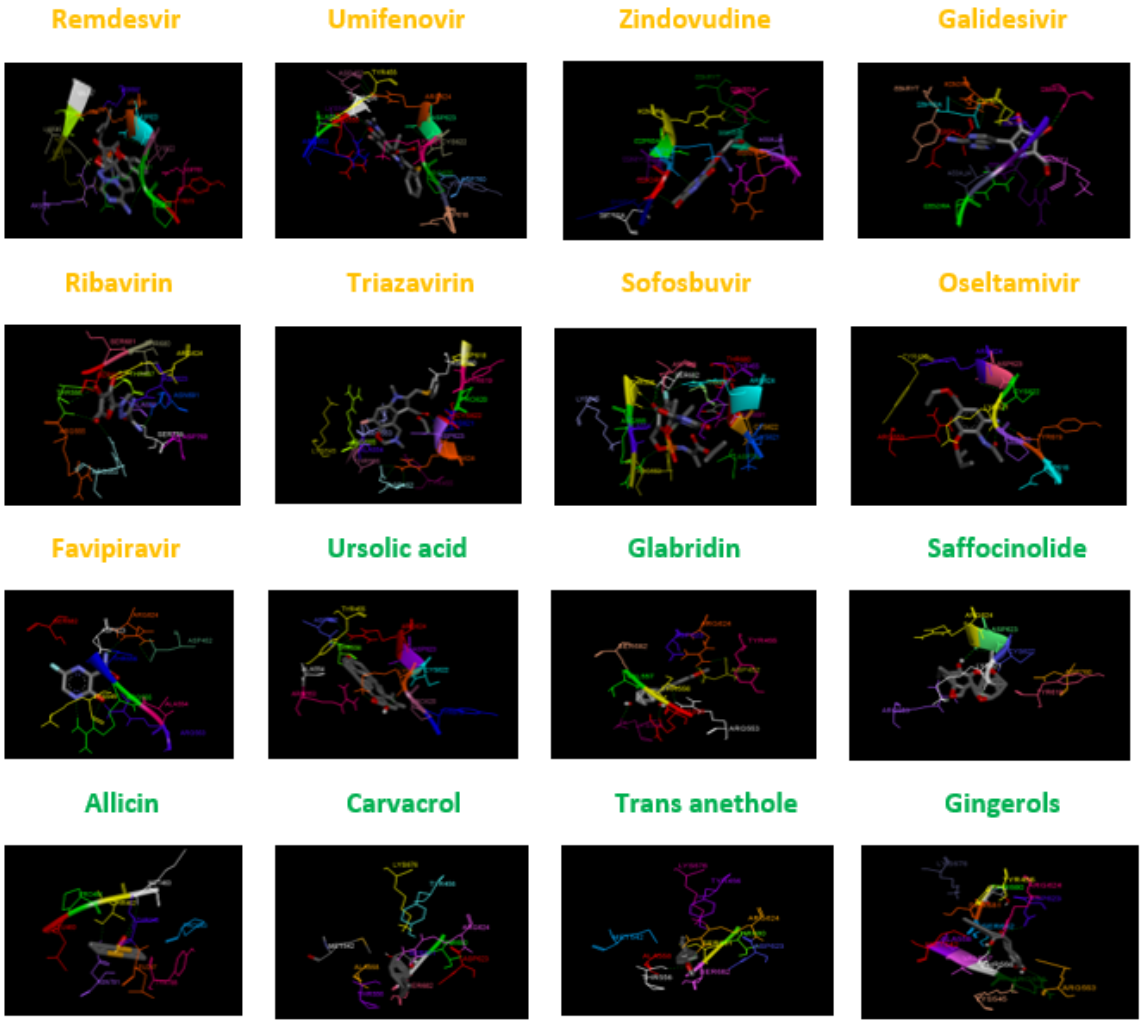
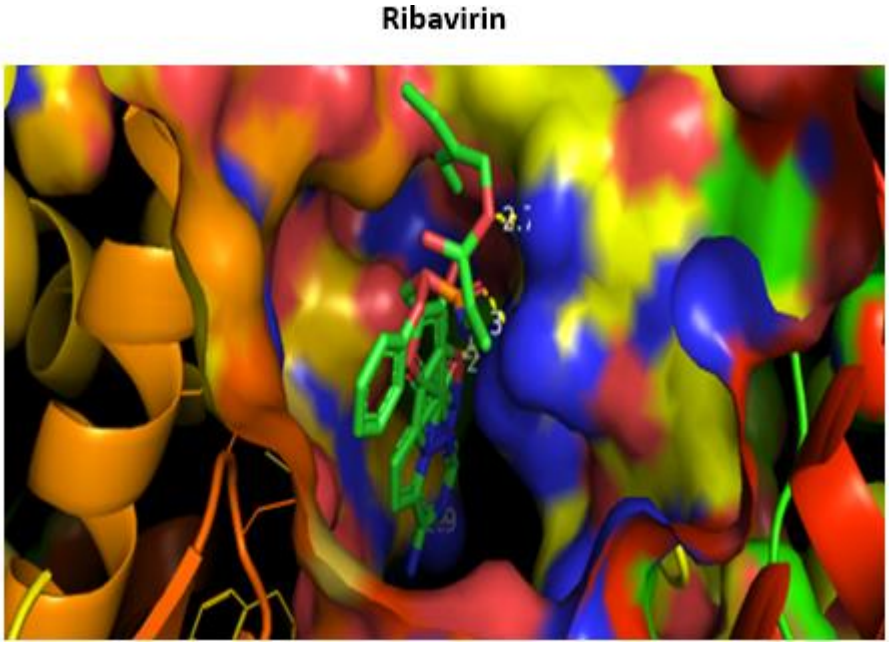


Figure 1. Docking pose of all the ligands with the protein using Biovia Discovery Studio.

This figure shows the docking pose of all the ligands with the protein using Biovia discovery studio. In figure 1, yellow-colored inlet captions depict the drugs, and green colored inlet captions depict the herbal compounds.



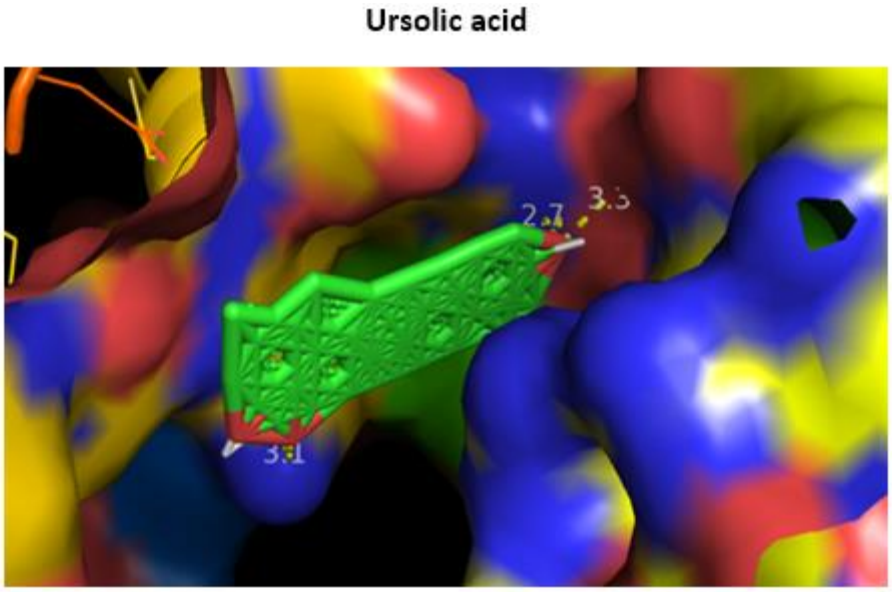


Figure 2. Docking pose of best-docked ligands (Ribavirin and UrsolicAcid) using Pymol.

This figure shows the best-docked ligand with the protein Ribavirin and Ursolic Acid.

4. Conclusions

Currently, the coronavirus has become a great health topic due to its worst ongoing second wave worldwide. Many covid infections have created life threats causing the deaths of lakhs of human beings. This worsening COVID pandemic has raised the development of effective antiviral agents from herbal sources to prevent further losses. Herbal compounds have played a great role in developing a drug against this pandemic, causing COVID and other diseases. Also, repurposing of drugs available had been more helpful to save patients diagnosed with early infection leading to a reduction in the death rate of affected people. This study's main aim was to identify herbal compounds and repurposing drugs to combat the COVID-19. And from this study, it was found that Ursolic acid is effective against COVID 19 through targeting RdRp. This study will provide a platform for the researchers to find a cure through drug development and eradicate the virus out from this world.

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Conflicts of Interest

The authors declare no conflict of interest.

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