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Molecules against Covid-19: An *in silico* approach for drug development

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ABSTRACT

A large number of deaths have been caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) worldwide, turning it into a serious and momentous threat to public health. This study tends to contribute to the development of effective treatment strategies through a computational approach, investigating the mechanisms in relation to the binding and subsequent inhibition of SARS-CoV-2 ribonucleic acid (RNA)-dependent RNA polymerase (RdRp). Molecular docking was performed to screen six naturally occurring molecules with antineoplastic properties (Ellipticine, Ecteinascidin, Homoharringtonine, Dolastatin 10, Halichondrin, and Plicamycin). Absorption, distribution, metabolism, and excretion (ADME) investigation was also conducted to analyze the drug-like properties of these compounds. The docked results have clearly shown binding of ligands to the SARS-CoV-2 RdRp protein. Interestingly, all ligands were found to obey Lipinski's rule of five. These results provide a basis for repurposing and using molecules, derived from plants and animals, as a potential treatment for the coronavirus disease 2019 (COVID-19) infection as they could be effective therapeutics for the same.

1. Introduction

The world is currently in the paroxysm of the coronavirus infection pandemic called coronavirus disease 2019 (COVID-19) [1]. Reported by the World Health Organization (WHO), no effective treatment or vaccine against SARS-CoV-2 exists [2]. Cases of mortalities due to COVID-19 are reported to increase day by day at an alarming rate [2], highlighting that a potential cure is becoming the need of the hour.

Coronaviruses are a family of positive ribonucleic acid (RNA) viruses with the potential to infect several vertebrates, including humans, leading to severe acute respiratory syndrome (SARS) and a variety of other respiratory infections [3]. This virus group is known for its exceptionally large polycistronic genome of ~30 kb, which is a 5' capped and 3′ polyadenylated RNA [3]. COVID-19 is caused by a novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4].

In case of most prokaryotes, a single RNA polymerase species is present to transcribe all types of RNA [5]. The SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) is predicted to be the central enzyme, which, together with other viral and cellular proteins, constitutes a replication complex that is responsible for the replication of the viral RNA genome [6,7]. The RdRp protein is a good target to serve as the base of an antiviral therapeutic against the coronavirus, as RdRp is essential for replication [8]. Multiple drugs have been developed whose principal mechanism is to bind and act against an RNA polymerase protein. A well-founded example is the Zika

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virus whose drugs are potent inhibitors of the Zika virus RdRp or Hepatitis C virus, in case of which the drugs act on the nonstructural 5 protein [9]. This approach has been effective because this protein domain is vital in the life cycle of the virus, as it builds the new RNA strand from the complementary strand through the utilization of free nucleotides in the cytoplasm. Therefore targeting such a protein with inhibitors tends to stop the life cycle of the virus as well as eradicate the infection [9,10]. Based on previous successes obtained in case of polymerase inhibitors in the treatment of other viral infections, SARS-CoV-2 is an attractive target for *anti*-SARS agents.

As seen in other deadly diseases, more efficient drugs can often be designed based on the structure of natural compounds exhibiting the desired activity [11]. Indeed, half of all drugs approved between 1981 and 2014 were derived from or mimicked a natural compound [12]. There is a plethora of natural chemicals which possess potential biological benefits due to their chemical properties [13]. They exhibit antioxidant, anti-inflammatory, anticancer, antibacterial, antifungal, and antiviral activities. For example, curcumin, a component of turmeric was shown to have strong antiviral activity against a diverse range of viruses [14,15]. Phytochemicals, can therefore emerge as a rich source of effective and safer agents against SARS-CoV-2. Keeping this in mind, six naturally occurring drug-like molecules were screened to see whether they have any potential antiviral action against SARS-CoV-2.

The molecules in the present study are known to be used as a cure for other maladies as well, as illustrated in Table 1. Ellipticine is an organic heterotetracyclic compound and a plant metabolite; it has a role as an antineoplastic agent [16–18]. Ecteinascidin is a marine tetrahydroisoquinoline alkaloid; it is a natural product derived from the Caribbean Sea squirt that possesses the anticancer activity and is used for the treatment of soft tissue sarcoma [19,20]. Homoharringtonine is a semisynthetic formulation of the cytotoxic plant alkaloid; it is isolated from Cephalotaxus [21] and was reported to have potential antiviral [22] and antineoplastic activities [21–23]. Dolastatins 10 and 15 are small peptides isolated from the marine sea hare Dolabella Auricularia with the ability to interact with tubulin; their growth-inhibitory properties were previously investigated through the involvement of human ovarian and colon-carcinoma cell lines [24–26]. Halichondrin is a synthetic macrocyclic ketone with a role in the treatment of a variety of solid tumors [27,28]. Plicamycin is an antibiotic isolated from the bacterium *Streptomyces plicatus*. Formerly known as Mithramycin, this compound is used as an anticancer agent in the therapy of testicular and germ cell cancers [29].

The listed natural molecules were chosen based on their ability to show the anticancer activity and potential antineoplastic roles. Hence, this study tries to focus on drug repurposing, the strategy of using existing drugs originally developed for one disease to treat another disease [30], to find a potential cure for SARS-CoV-2. There is rich literature available in association with the evidence of molecules which are successful examples of drug repurposing. For example, Thalidomide, a drug that was used for morning sickness during pregnancy but eventually withdrawn from the market, is now repurposed for the treatment of refractory multiple myeloma excluding pregnant women [30]. Another example is Exenatide, which was originally used for type II diabetes [31] and was subsequently repurposed, making its application possible in pharmacotherapy to treat non-diabetic obese patients, thus helping with the fight against the overweight epidemic [30–33]. Such drug repurposing promises faster access of drugs to patients while reducing costs in the long and difficult process of drug development [30,34].

Seeing its multiple benefits and successes in the medicinal field, the study outlined in this article tends to repurpose some of the anticancer drugs using computational tools for their action against SARS-CoV-2 RdRp.

Molecular docking has become an increasingly important tool for drug discovery [35]. This is a direct and rational drug discovery approach that has the advantage of the low-cost and effective screening. The molecular docking approach was used to model the interaction between these six small molecules (ligands) and a protein at the atomic level, allowing the characterization of the behavior of small molecules with respect to the target protein. Hence, this study focused on an *in silico* approach toward assessing the inhibitory effect of these six naturally occurring molecules on SARS-CoV-2. The docking software used in this investigation tends to provide us information on atomic contact energy, an estimate of the desolvation energy of the molecules in the protein-ligand complex state [36]. SARS-CoV-2 RdRp was used as a binding molecule for these ligands with the aim of identifying potential leads for the prevention and treatment of this worldwide problem of coronavirus.

Most virtual screening efforts employ docking as their principal screening technique [37]. This is followed by other relevant approaches being taken into consideration, which can provide information on drug likeliness, drug efficacy, and safety [38]. As a result, *in silico* absorption, distribution, metabolism, and excretion (ADME) studies were reported to be important in the early stages of drug discovery and development [38]. The earliest ADME filters involve simple rules of thumb derived from the distribution analysis of physicochemical properties of drugs having or lacking the desired behavior [39]. Lipinski's rule of five at Pfizer pioneered this kind of analysis. The "Lipinski's rule of five" is a mnemonic tool used for the rapid assessment of compounds during the drug discovery and optimization process [40]. The analysis of ADME profiles of the listed ligands is crucial for their clinical as well as the commercial success as potential SARS-CoV-2 drugs [41], hence the information about these molecules are also covered in this article.

This study, therefore, focuses on an *in silico* approach toward assessing and repurposing the effect of naturally occurring molecules

Table 1
Common pharmaceutical roles of selected inhibitors.

No.	Name of ligand	Common pharmaceutical roles
1	Ellipticine	Antineoplastic agent
2	Ecteinascidin	Anticancer activity·Treat soft tissue sarcoma
3	Homoharringtonine	Antineoplastic activity
4	Dolastatin	Employed in human ovarian and colon-carcinoma cell lines
5	Halichondrin	Treatment of a variety of solid tumors
6	Plicamycin	Antibiotic·Anticancer activity

derived from plants and animals in association with the SARS-CoV-2 protein to identify potential antiviral abilities for the prevention and treatment of the COVID-19 infection.

2. Material and methods

2.1. Ligand and protein structure

The electron microscopy structure of the SARS-CoV-2 RNA-dependent RNA polymerase (Protein Data Bank [PDB] ID: 6M71) was obtained from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank. The structure of all ligands (Ellipticine, Ecteinascidin, Homoharringtonine, Dolastatin 10, Halichondrin, and Plicamycin) was also downloaded from the PubChem database and saved in the.sdf format. These structures from the.sdf file were subsequently converted to the.pdb format using the OpenBabel software, which is free software that presents a solution for conversion between multiple chemical file formats [42].

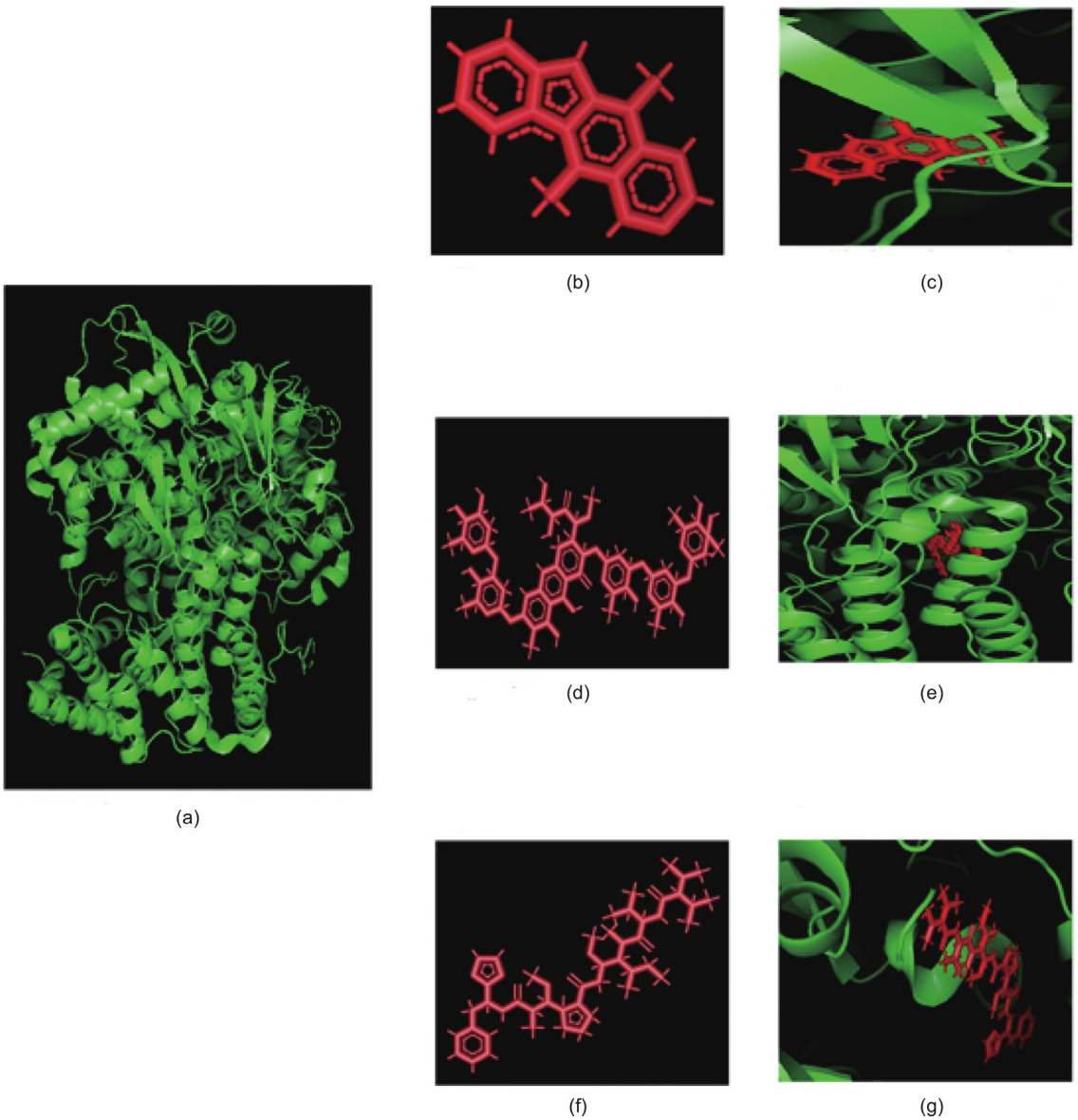


Fig. 1. Three-dimensional (3D) structure and putative binding site: (a) 3D ribbon structure of the SARS-CoV-2 RdRp protein (receptor), (b) 3D structure of Ellipticine (ligand), (c) putative binding site of Ellipticine on the SARS-CoV-2 RdRp protein (Ellipticine interaction with SARS-CoV-2 RdRp), (d) 3D structure of Plicamycin (ligand), (e) putative binding site of Plicamycin on the SARS-CoV-2 RdRp protein (Plicamycin interaction with SARS-CoV-2 RdRp), (f) 3D structure of Dolastatin, and (g) putative binding site of Dolastatin on the SARS-CoV-2 RdRp protein (Dolastatin interaction with SARS-CoV-2 RdRp).

2.2. Molecular docking

PatchDock, online docking software, was used to dock the ligands with the SARS-CoV-2 RNA-dependent RNA polymerase protein. It was also used to perform structure prediction for protein-small molecule complexes. Moreover, it is a geometry-based molecular docking algorithm and the servers of this software are very efficient, the main reason behind which is its fast transformational search driven by local feature matching [40].

The.pdb structures of each ligand as well as the protein were submitted on the online portal of PatchDock, which provided the docked result in a few minutes. The structure with the top score was downloaded and analyzed.

PyMOL was used to visualize the resultant docked structures; it is a user-sponsored molecular visualization system often used for molecular visualization by crystallographic and molecular dynamics simulation. All the docked structures were provided in figures [43].

2.3. Prediction of Lipinski's rule of five properties

Lipinski's rule of five is a rule of thumb that helps with distinguishing between drug-like and non-drug molecules. Lipinski's rule of five includes the following rules: i) Molecular mass should be less than 500 Da (Da), ii) high lipophilicity, iii) less than 5 hydrogen bond

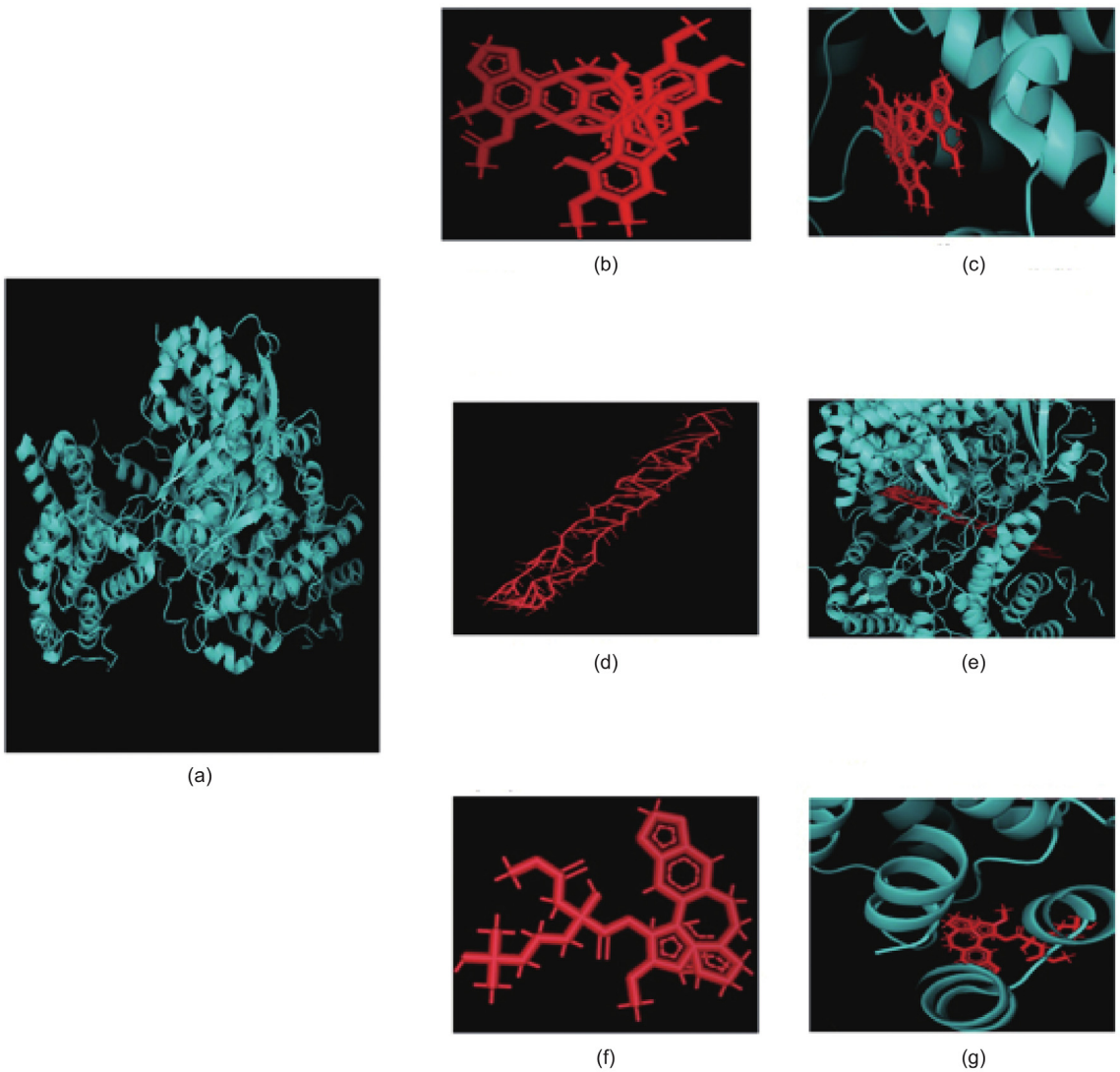


Fig. 2. 3D structure and putative binding site: (a) 3D ribbon structure of the SARS-CoV-2 RdRp protein (receptor), (b) 3D structure of Ecteinascidin, (c) putative binding site of Ecteinascidin on the SARS-CoV-2 RdRp protein (Ecteinascidin interaction with SARS-CoV-2 RdRp), (d) 3D structure of Halichondrin, (e) putative binding site of Halichondrin on the SARS-CoV-2 RdRp protein (Halichondrin interaction with SARS-CoV-2 RdRp), (f) 3D structure of Homoharringtonine, (f) putative binding site of Homoharringtonine on the SARS-CoV-2 RdRp protein (Homoharringtonine interaction with SARS-CoV-2 RdRp).

donors, iv) less than 10 hydrogen bond acceptors, and v) molar refractivity should be between 40 and 130. Drug likeness is seen when a molecule complies with two or more of these rules, helping with screening for tested ligands with drug-like properties.

All ligand profiling through Lipinski's rule of five was performed at pH 7 using online software tools.

3. Results and discussion

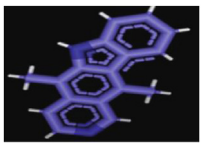
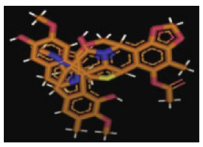
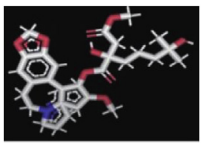
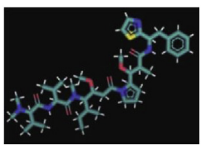
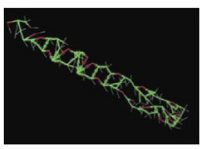
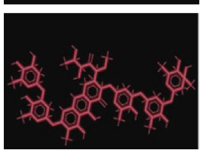
SARS-CoV-2 RNA-dependent RNA polymerase is a viral protein with a total weight of 161.22 kDa. It is a heterotetramer with an 8541 atom count [44]. This protein was put under investigation and exposed to molecular docking to derive valuable results.

Ligand binding to a macromolecule at a specific site is considered a key step in enzymatic reactions and thus can be involved in their inhibition [45]. Therefore, a detailed understanding of the interactions between small molecules and proteins may form the basis of a rational drug design strategy for SARS-CoV-2. Docking, which was originally developed to support the understanding of the mechanisms of molecular recognition between small and large molecules has growing significance in drug discovery [46]. Existing literature has witnessed multiple successes about the same. With this aim, ligands were docked to a SARS-CoV-2 protein, and features like specific amino acid residues involved in binding, atomic contact energy, and the potential of listed ligands to be a drug were studied.

In this study, six naturally occurring molecules with different chemical properties and sources for repurposing have been investigated. Their binding is shown with the SARS-CoV-2 protein in Fig. 1 and Fig. 2. This docking can be an important tool to support the understanding of the way these chemical compounds interact with specific amino acid residues. The atomic contact energy can also be determined, which is a score that can be considered as an estimate of the change in the desolvation energy of the molecule during its transition from the unbound state to the complex state. It is important to note that a lower atomic contact energy (ACE) value implies lower (and hence more favorable) desolvation free energy [36].

The docking study thus revealed that the interaction of Ellipticine with Leucine 631, Serine 681, and Glycine 682 residues was characterized as the polar interaction, showing the ACE value of −51.16 (Fig. 1 (b) and (c)), whereas Plicamycin was observed to make polar interactions with the Glycine 681 and Threonine 686 residues of the SARS-CoV RdRp and was measured to have an ACE value of 62.26 (Fig. 1 (d) and (e)). Moreover, Dolastatin showed the most negative ACE value at −375.73 and the lack of polar interactions (Fig. 1

Table 2
Docking analysis used for different ligands.

No.	Name of ligand	Structure	Atomic contact energy
1	Ellipticine		−51.16
2	Ecteinascidin		150.75
3	Homoharringtonine		−71.30
4	Dolastatin		−375.73
5	Halichondrin		−193.14
6	Plicamycin		62.26

(f) and (g)). Contrarily, Ecteinascidin displayed the polar interaction with the Lysine 477 and Cysteine 496 of the protein as well as showed the maximum positive ACE value of 150.75 (Fig. 2 (b) and (c)). The ligand Halichondrin was found to interact with Isoleucine 778, Lysine 620, and Proline 619, and have the ACE value of −193.14 (Fig. 2 (d) and (e)). Lastly, Homoharringtonine was perceived to interact with Lysine 42 with the ACE value of −71.30 (Fig. 2 (f) and (g)). The 3D structure and atomic energy of each ligand is illustrated in Table 2. The binding of these ligands can be essential in terms of blocking several biochemical pathways related to the SARS-CoV-2 RdRp, therefore these docking results indicate that future research should be focused on the antiviral property of these ligands in the corona virus treatment.

Polar interactions between a ligand and a protein can be considered as a significant type of inter-linkage with the potential to cause inhibition. Abundant literature is available with examples pointing toward the same. For instance, ligands were reported to show polar interactions with specific amino acid in Rho-associated kinases (ROCKs), which has been regarded as a promising drug target mechanism for the treatment of cardiovascular diseases, nervous system diseases, and a variety of cancers [47]. On the other hand, tetrahydrocurcumin, a metabolite of curcumin was found to exhibit the inhibitory action against Ebola virus proteins through polar interactions [14]. Another such example was given by Sarno et al., highlighting how polar interactions between 8-hydroxy-4-methyl-9--nitrobenzo(g)chromen2-one (NBC) as well as surrounding residues in the maize protein kinase (maize CK2a) lead to the inhibition of the protein and can be used to develop a potential cure [48]. A similar type of interaction was found to be evident in our study between the ligands and SARS-CoV-2 RdRp, pointing toward the fact that these chemicals may have an inhibitory effect on SARS-CoV-2 RdRp.

Like many other drugs available on the market, drugs, such as Galantarnine, Donepezil, Tacrine, Ibuprofen, and Metrifonate that are used to treat Alzheimer's disease, are known to follow Lipinski's rule of five [49]. Therefore it is a reliable approach for predicting the druglikeness of molecules. This rule can be used to filter libraries and select molecules with predicted, rich, drug-like properties. Moreover, it helps to determine whether a biologically active chemical is likely to have the necessary physicochemical properties to be orally bioavailable as well as whether the compound holds the potential to form a viable drug. If there is any violation of these conditions, it is predicted that the molecule is a non-orally available drug [39,50]. The ligands in this study showed that all the six molecules under investigation pass the criteria for Lipinski's rule of five as shown in Table 3. It is important to note that even though Homoharringtonine had two violations, it still passed three criteria of Lipinski's rule of five. These molecules were further suggested to have the ability to become a bioavailable drug.

These versatile chemical molecules may serve as the basis of new medication for the treatment of coronavirus infection as this study opens avenues for the consideration of natural chemicals as therapeutic antiviral agents. Further experimental (*in vitro* and *in vivo*) studies in association with our selected group of potential chemicals are necessary to strengthen our perspective of natural products based therapeutic interventions that are in need currently to deal with this worldwide problem.

The insights provided in this *in silico* study are therefore anticipated to be regarded as valuable toward the development of an antiviral agent against SARS-CoV-2 after the proper experimental drug verification of these natural chemicals.

4. Conclusion

WHO has declared COVID-19 a public health emergency of international concern. CoVs belong to the Orthocoronavirinae subfamily in the Coronaviridae family and Nidovirales order, where SARS-CoV-2 is the seventh member of the family of CoVs that infect humans. Therefore, the better understanding of SARS-CoV-2 is essential for the exploration of effective vaccines and drugs [2]. For the discovery of an effective drug against SARS-CoV-2, this *in silico* study was conducted.

The *in silico* approaches, such as docking, can be regarded as well-established and experimentally validated for the prediction of novel drug-target associations. Docking is also notably well-suited for either drug-based or target-based drug repurposing [51]. The various discoveries made through computational tools possess significance in regard of deducing a potential drug, as the success of the derived molecules is evident, which is shown by the drugs currently in use and new ones reaching the market [52].

It is suggested by the proposed study that the repurposing and the use of naturally occurring chemicals could serve as effective therapeutics for the treatment of COVID-19.

In this computational study, for the prediction of potential drug-like naturally occurring molecules against SARS-CoV-2, six molecules were selected out of the whole pool to be investigated using multiple computational tools. The identified six molecules were seen to be capable of binding to the SARS-CoV-2 RdRp protein. Therefore, these versatile natural molecules show the potential of an inhibitor-like character and serving as a novel medication for restraining and treating COVID-19.

Therefore, our findings through the applied structural bioinformatics approach suggest that all of these compounds may have the

Table 3
ADME Properties of selected inhibitors against SARS-CoV-2 RdRp.

No.	Name of ligand	Mass (Dalton)	Hydrogen bond donor	Hydrogen bond acceptor	Logp (denotes lipophilicity)	Molar refractivity	Drug likeliness
1	Ellipticine	246.000000	1	1	2.581889	70.061699	Yes
2	Ecteinascidin	312.000000	5	6	−0.053101	77.145782	Yes
3	Homoharringtonine	545.000000	1	9	5.153130	144.267776	Yes (only 2 violations)
4	Dolastatin	312.000000	5	6	−0.053101	77.145782	Yes
5	Halichondrin	312.000000	5	6	−0.053101	77.145782	Yes
6	Plicamycin	312.000000	5	6	−0.053101	77.145782	Yes

potential to be used against SARS- CoV-2 and should be explored further as preventive therapeutics for COVID-19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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