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In Silico Identification of Potentially Effective Herbal Inhibitors of SARS-Cov-2 Main Protease by Virtual Screening Method

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ABSTRACT

Background: The COVID-19 pandemic is a global health emergency caused by SARS-CoV-2. Unfortunately, no effective drugs have been found to date. There is also a major need for new therapies to treat this disease. The main protease is an attractive drug target among coronaviruses due to its important role in the processing of viral RNA-translated polyproteins. Objective of This study was conducted to screen databases of herbal compounds for potential main protease inhibitors.

Material and Methods: Natural products from 3 database banks were first tested and filtered by ADME / toxicity, then their molecular energy was minimized, and finally, they were docked into the SARS-CoV-2 main protease and compared with indinavir.

Results: The binding energies of 6570 molecules from different herbal compounds comprising databases were tested and five of the molecules with the highest binding energies for SARS-CoV-2 main protease docking were selected and key interactions were studied.

Conclusion: In conclusion, five herbal compounds including Sodwanone B, Cyclomulberrin, and a glycosylated derivative of kaempferol had lower docking energy compared to indinavir and were suggested for further research.

INTRODUCTION

SARS-CoV-2 is a coronavirus related to the end of 2019 epidemiological outbreak. SARS-CoV-2 has many similarities with original SARS-CoV. SARS-CoV-2 proteases are attractive antiviral targets because of their essential roles in polyprotein processing and thus virus maturation [1, 2]. There is an urgent need to find an effective molecule to fight against this new, disastrous and resistant virus [3].

In this study, the potential efficacy of herbal compounds from various herbal compound databases was studied in the inhibition of COVID-19 main protease via virtual screening method.

MATERIAL AND METHODS

Preparation of screening library:

The library of chemical structures was constructed by combining SWEETLEAD Database [4], South African natural compound database (SANCDB) [5], and SymMap database [6], which is an integrative database of traditional Chinese medicine using Openbabel software [7]. FAF-Drugs4 web-based server was used to filter compounds based on ADME/toxicity predictions by an in house filter, Drug-Like Soft, designed by the server developers [8]. Finally, an energy minimization process was applied to the molecules using open babel software.

Screening method:

The crystal structures of COVID-19 main protease were obtained from Protein Data Bank (PDB code: 5R83). The center of the grid box for the crystal structures of COVID-19 main protease was set based on the location of Z44592329.

The structures were docked using AutoDock Vina software [9] and the top 5 molecules based on the score of docking were docked again on COVID-19 main protease with mere accurate settings. Finally, key interactions were investigated for the top molecule using BIOVIA Discovery Studio Visualizer v16.1.0.

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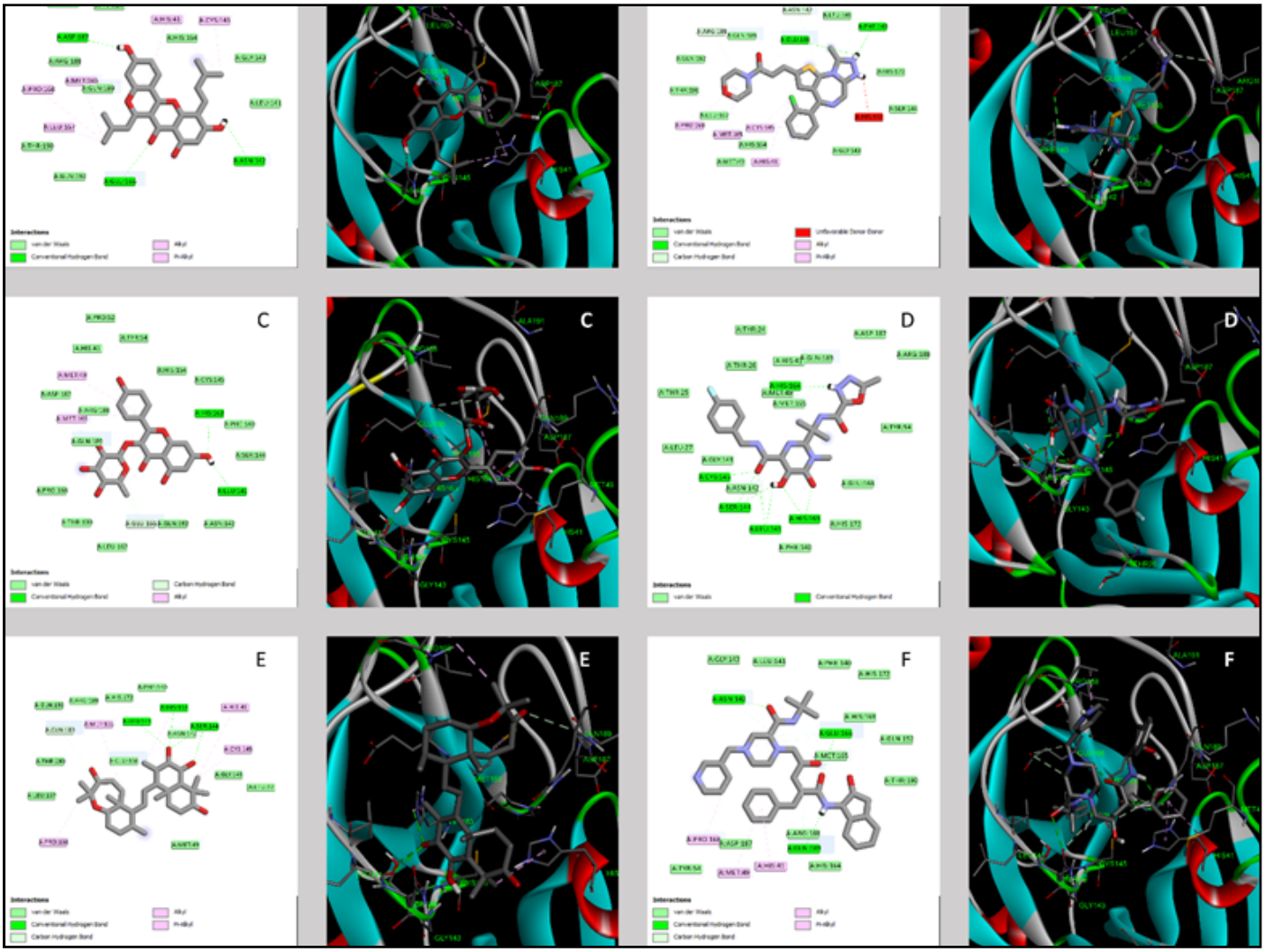


Figure 1. Docking pose and interactions of the top five molecules and COVID-19 main protease (PDB code: 5R83). A-F are 11742872, 23724810, 44258913, 71593514, 101675763, and Indinavir respectively.

RESULTS

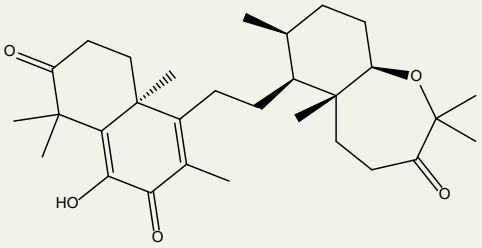
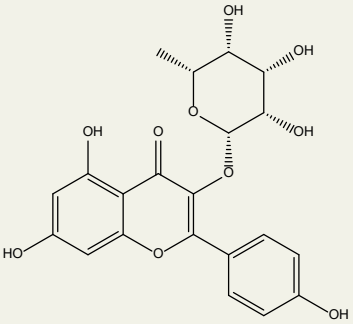
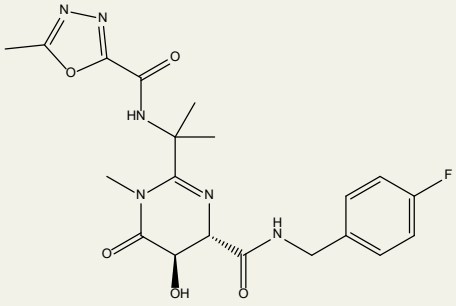
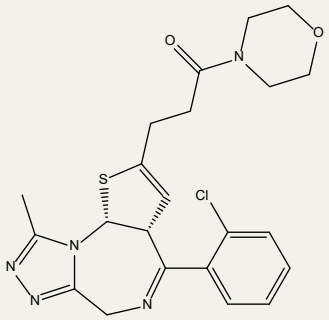
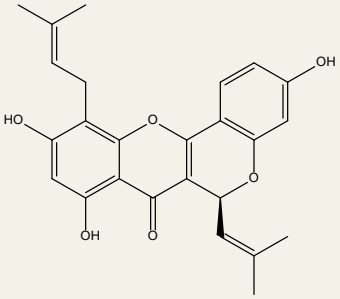
In this study, 13,145 molecules were reduced to 6570 molecules using ADME/toxicity filters, and then, the binding energies of these 6570 molecules were predicted using Autodock Vina software. As a result, the descriptions of five highest-ranked predicted binding energies for COVID-19 main protease are displayed in table 1. Also, docking results were compared with the external ligand of 5R83 and Indinavir which was reported as an inhibitor of COVID-19 main protease in previous studies [10].

Subsequently, the top five molecules were investigated for docking poses and interactions. Figures 1 demonstrate the interactions and docking pose for the top five compound and table 2 includes the interactions of molecules with protease. The key residues interacting via hydrogen bond are Leu:141, His:163, and Glu:166. Also, mere common non-hydrogen bond interacting residues are His:41, Met:165, Cys:145, and Pro:168.

Table 2. The key inactions of five highest ranked molecules. 674807 is the external ligand of 5R83 and 5362440 is another potentially inhibitor of COVID-19 main protease reported in literature.

PubChem CID	Residues having H-bond	Residues having other types of interactions
101675763	Leu:141, Ser:144, His:163	His:41, Cys: 145, Met:165, Pro:168
44258913	Leu:141, His:163	Met:49, Met:165, Glu:166
71593514	Leu:141, Ser:144, His:163, His:164	
23724810	Phe:140, Glu:166	His:41, Cys: 145, Met:165, Pro:168
11742872	Asn:142, Glu:166, Asp:187	His:41, Cys: 145, Met:165, Leu:167, Pro:168
674807	Cys:145, Glu:166	His:41, Met:49, Met:165, Leu:141
5362440	Asn:142, Glu:166, Gln:189	His:41, Met:49, Pro:168

Table 1. The 5 highest ranked predicted binding energy from screening a combined library of SWEETLEAD, SANCDB, and SymMap databases. Z44592329 is the external ligand of 5R83 and Indinavir is another potentially inhibitor of COVID-19 main protease reported in literature.

Source	Structure	Name	PubChem CID	Docking score
SANCDB		Sodwanone B	101675763	-9.4
SymMap		(4As)-5-[2-[(5aR,6S,7S,9aR)-2,2,5a,7-tetramethyl-3-oxo-5,6,7,8,9,9a-hexahydro-4H-benzo[b]oxepin-6-yl] ethyl]-8-hydroxy-1,1,4a,6-tetramethyl-3,4-dihydronaphthalene-2,7-dione	44258913	-8.7
SWEETLEAD		N-[2-[4-[(4-Fluorophenyl) methylcarbamoyl]-5-hydroxy-1-methyl-6-oxo-4,5-dihydropyrimidin-2-yl] propan-2-yl]-5-methyl-1,3,4-oxadiazole-2-carboxamide	71593514	-8.6
SWEETLEAD		3-[7-(2-Chlorophenyl)-13-methyl-3-thia-1,8,11,12-tetrazatricyclo[8.3.0.02,6] trideca-4,7,10,12-tetraen-4-yl]-1-morpholin-4-ylpropan-1-one	23724810	-8.5
SymMap		Cyclomulberrin	11742872	-8.4
Z44592329		1-Phenyl-3-pyridin-3-ylurea	674807	-6.1
		Indinavir	5362440	-8

DISCUSSION

In this work, we investigated the potential efficacy of herbal compounds against COVID-19 by screening a library of these compounds using an in Silico approach. The results of this study predict two flavonoids and one triterpenoid molecule to be effective against COVID-19. From the literature, sodwanone B is a triterpenoid obtained from South African Species of the marine sponge Axinella sp. The solvent extraction of Axinella sp. using CH2Cl2: MeOH (1:1) contains different Sodwanone and Yardenone Triterpenes. A previous study showed sodwanone B has potential anti-cancer activity through inhibition of Hypoxia-Inducible Factor-1 (HIF-1) Activation [11]. On the other hand, 44258913 is a glycosylated derivative of kaempferol which has a glycoside substitution at position 3'. Kaempferol glycosides have demonstrated depigmenting, anti-inflammatory, antioxidant, anti-microbial and aldose reductase inhibitory properties [12, 13]. Kaempferol is a natural bioactive tetrahydroxyflavone which is found to be a potential therapeutic agent for variety of diseases, including cancer, diabetes, osteoporosis, and cardiovascular diseases. Based on previous preclinical studies. These various pharmacological effects can be explained by the ability of kaempferol to modulate different intracellular and extracellular pathways [14, 15]. Also, a recent study declared that flavonoids, including kaempferol, have inhibitory effect against SARS-CoV 3C-like protease [16]. Kaempferol and its derivatives are present in many plant-based edibles (cabbage, broccoli, tomato, beans, grapes, etc.) and medicinal plants (Ginkgo biloba, Tilia spp, Acacia nilotica). There are different methods for extraction of kaempferol, such as solvent extraction (using methanol, ethanol, acetone or water), microwave or ultrasound assisted extraction and super critical fluid extraction [17]. Also, from this study, Cyclomulberrin is a prenylated flavonoid obtained from different parts of Morus alba L plants along with other prenylflavonoids. It is mainly isolated from MeOH extract of Morus plants root barks (Mori Cortex). Mori cortex has been applied as a traditional Chinese medicine since 500 B. C. for the treatment of various health conditions such as cough, edema, lung heat, pulmonary diseases, bronchitis, nephritis, oliguria, etc [18, 19]. Cyclomulberrin has exhibited diverse pharmacological effects in preclinical studies. For instance: antiplatelet activity [20], cytotoxic and antitumor effects [21, 22] and protecting human neural cells against nitric oxide-induced death [23].

CONFLICT OF INTERESTS

The authors state that there is no conflict of interest in this study and in the written manuscript.

AUTHORS' CONTRIBUTIONS

All authors (A.D.B., D.H, S.A, S.A.Z., and M.R.) have read and approved the final manuscript.

A.D.B., D.H, and S.A performed the research. S.A.Z, designed the research study. M.R. A.D.B., and S.A.Z., wrote the paper.

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