International Invention of Scientific Journal
Online ISSN: 2457-0958
Available Online at http://www.iisj.in **Volume 8, Issue 02(April-May-June)|2024**|Page: 163-176
Original Research Paper-Basic Sciences

Validation of Interaction between Plant Compounds and Coronavirus Proteins Based on Virtual Screening and Molecular Docking Studies

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Article Received: 24-April-2024 Revised: 14-May-2024 Accepted: 04-June-2024

ABSTRACT:
Since the spread of the COVID-19 pandemic, researchers have tried to find a compound that can potentially inhibit the replication of the SARS-CoV-2 virus. The present study aimed to validate the reaction of plant compounds and proteins of coronavirus based on virtual screening and molecular docking studies. In the present study, 90 various plant compounds and 8 types of coronavirus types were studied. The Auto Dock Vina 1.5.6 was used for the evaluation of the molecular bond, the PvMol was used for validation, and the Biovia Discovery Studio 4.5 was used for analysis. The best protein-ligand complex was chosen through the determination of the docking score or the highest docking affinity (the most negative ΔG of Gibbs free energy of docking). Among the 720 dockings performed, 18 plant compounds with coronavirus receptors have an energy above -10 and a more favorable RMSD value. Regarding the docking mode, the values under 1 angstrom are acceptable. According to the obtained validation results, 18 compounds have been expressed among which 8 showed the best RMSD results which is indicative of the validity of the data.

Keywords: Coronavirus, SARS-CoV-2, plant compounds, molecular bond, Auto Dock Vina.

INTRODUCTION:

Although various medicines have been effective on the viruses from the same group, none have shown similar potentials for COVID-19 treatment. The main protease of coronavirus is an interesting objective to study antiviral drugs against SARS-CoV-2 and other coronavirus infections. Many plant bioactive compounds have shown antifungal, antibacterial, and antiviral activities. The plants and their derivatives have advantages over common treatment procedures such as simplicity, higher safety, less toxicity, lower costs, quicker response, and environmental friendliness. Among the various plant compounds, glycosidic, alkaloid, and terpenoid compounds which show many medicinal properties such as anti-cancer, anti-oxidant, anti-inflammatory, anti-viral, anti-bacterial properties and protect the immune system and liver have grabbed the attention of the researchers. They can also inhibit the virus replication and fight infections. The COVID-19 symptoms vary, however, they often include fever, cough, headache, fatigue, respiratory problems, and loss of smell and taste (1,2). This complex situation has led to the exploration of new treatments and rapid therapeutic measures to treat the disease and reduce its spread. As a result, understanding how this virus works and spreads is very important to produce a vaccine. Although various drugs have been effective against the viruses from the same group, none have shown similar potential to treat COVID-19 (3,4). The FDA approved malaria drugs, including hydroxychloroquine and hydroxychloroquine to fight COVID-19, but withdrew their approval after subsequent studies found the drugs to be ineffective (5). Accordingly, Ivermectin and Famotidine were also tested, however, they were also proved ineffective (6).

Tomilar et al. (2020) investigated the molecular bond in a study entitled “Potential of plant bioactive compounds as SARS-CoV-2 main protease (Mpro) and spike (S) glycoprotein inhibitors: a molecular docking study”. They asserted that Spike proteins, both in the closed (6VXX) and open (6VYB) states, have amino acid residue bonds in the form of van der Waals interactions, hydrogen bonds, and hydrophobic interactions. Their study showed that the natural compounds hesperidin, pectolinarin, epigallocatechin gallate, and rifulin have docking free energies of -13.51, -7.8, -7.8, and -8.2 kcal/mol with protein M pro, and -9.8, -8.8, -9.8 and -9.5 kcal/mol with SARS-CoV-2 S protein, respectively. Although the results of molecular docking of kaempferol, herbastin, eugenol,

and 6-shogaol are not as good, they have good availability and also have Ro5 criteria (7).

Vincent et al. (2020) investigated the antiviral effects of Kabasura Kudineer on SARS-CoV-2 3Clpro among 145 plant compounds of Kabasura Kudineer (KK). The results obtained from the molecular docking with the main protease 6LU7 showed that Acetoside (-153/06), Luteolin-7-rutinoside (-134/6), Rutin (-133/06), Chebulagic acid (-124/3), Sirigarcinol (-120/03), Acanthoside (-121/21) Andrographidine C (-101/8), Myristin (-9/96), Gingerone A (-93/9), Tinosporinone (-83/42), Geraniol (-62/87), Nootkatone (-62/4), Asarianin (-79.94) and gamma-sitosterol (-81.94) kJ are the main compounds from KK plants that may inhibit COVID-19 and provide a better energy score compared to synthetic drugs (8).

Shaikh et al. (2020), in a study titled "The revelation of various compounds found in Nigella sativa L.(Black Cumin) and their possibility to inhibit COVID-19 infection based on the molecular docking and physical properties", found that Dithymoquinone, thymohydroquinone, thymol, thymoquinone with docking energies of 7.19 and 4.89 and 4.46 and 4.98 kcal/mol found in this medicinal plant may inhibit the infection of Covid-19 based on the results of molecular docking of protein 2AJF. Compared to Chloroquine, these compounds have equal or better energy scores. The black seed powder or oil is preferable because Ayurveda/Hellenic medicine does not have any side effects. These results encourage further in vitro and in vivo research and also justify the traditional preventive use of black seed (9).

Alrasheid et al. (2021), in a study entitled "Evaluation of certain medicinal plants compounds as new potential inhibitors of novel coronavirus (COVID-19) using molecular docking analysis", expressed that the analysis of the docking revealed that the protease 6LU7 of COVID-19 may be inhibited by some plant compounds. Based on the energy score obtained by MOE-DOCK (10) ranged from -8.20 to -17.45. we suggest that compounds such as naringin, Quercetin, Capsaicin, Psychotrine, and Gallic acid can be tested and used to produce antiviral drugs against corona. These molecules can be used for further innovation and development of antiviral compounds against coronavirus. Still, further research is required to investigate the potential applications of medicinal plants with these ingredients (11).

Shree et al. (2022) studied the molecular docking by targeting COVID-19 (SARS-CoV-2) main protease through active phytochemicals of ayurvedic medicinal plants–Withania somnifera (Ashwagandha), Tinospora cordifolia (Giloy) and Ocimum sanctum (Tulsi), and concluded that two probable inhibitors against SARS-CoV-2 Mpro (main protease) were Withanoside V with docking energy of -10.32 kcal/mol and Somniferine with docking energy of -9.62 kcal/mol. According to this study, it can be suggested that active Phytochemicals of medicinal plants can potentially inhibit SARS-CoV-2 and improve the management strategy against the global spread of COVID-19 (12).

Plants are a source of medicinal bioactive compounds widely used for treatment of the diseases (13,14). Many reported bioactive plant compounds show antifungal, antibacterial, and antiviral properties (15). Today, to reduce the costs and time of drug production, bioinformatic procedures have been much focused in the pre-studies. In this method, the use of bioinformatics tools and calculation methods that predict the effectiveness of the medicinal compounds and their toxicity with a great confidence level has become the center of attention in recent years (16). Molecular docking, simulation, determination of the target point, and investigation of chemical stability are among the most important bioinformatic methods in drug production. Meanwhile, the molecular docking is special. In this technique, the interaction between molecules can be investigated considering different modes of intended molecules in a 3-dimensional space and estimation of the interaction between the protein (receptor) and bioactive compounds (ligand), and determine the factors effective in more stable interaction that are important in terms of drug recognition (17). The computational docking approach using various molecular docking software such as Auto Dock (18) has provided the opportunity to identify and evaluate the dockings and efficiency of various inhibitors of natural and synthetic sources. After evaluating efficient inhibitors, the suitability of the drug can be determined through analysis of the medicinal properties. Although probable therapeutic agents can only be validated by experimental tests, computational docking can open the door towards faster development of effective drugs against diseases such as COVID-19.

The results obtained from the present study can be very helpful as a preliminary screening to candidate the potential medicinal compounds and conduct in vitro and in vivo tests on animal and human models. In this regard, the present study aimed to validate the interaction between the plant compounds and coronavirus proteins based on virtual screening and molecular docking studies.

METHODOLOGY:

The molecular docking was done based on the following stages. The 3-D structure of the protein was extracted from the Protein Data Bank (PDB) (47) (Figure 1). To prepare the protein for docking, first, the water and ligand (if present) were removed from the protein, using the Biovia Discovery Studio 4.5. Now, each of these proteins was optimized in Auto Dock Tools 1.5.6 and saved in Pdbqt format (20).

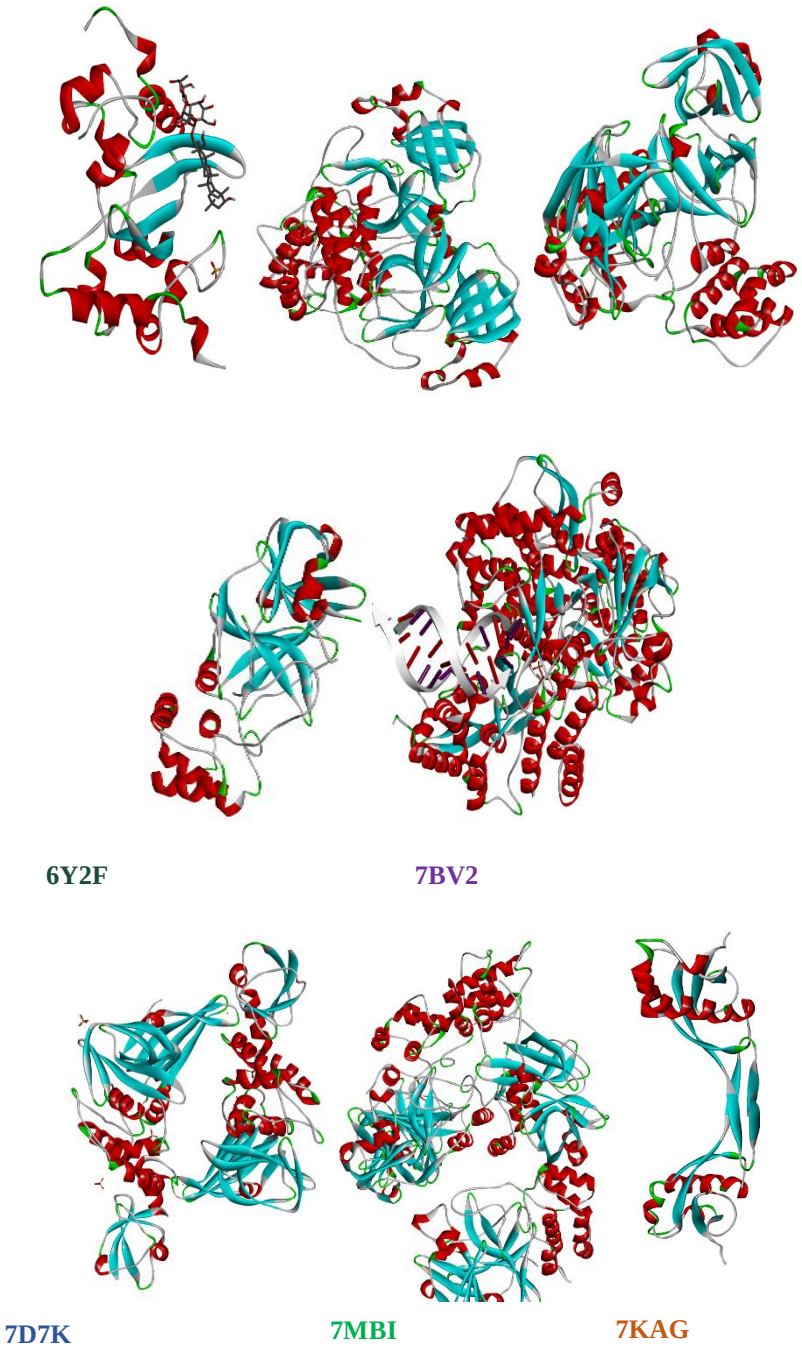

Figure 1: 2-D images of proteins studied in the present study

Among 29 proteins of SARS-CoV-2 proteins, 8 proteins were chosen in the present study for docking (Table 1).

Table 1: Receptors studied in the present study

Receptor name	Specifications
2GIB	Crystal structure of Nucleocapsid protein dimerization domain
3VB3	Crystal structure of SARS-CoV 3C-like protease
6XHL	Covalent complex of SARS-CoV major protease with N-[(2S)-1-({(2S,3S)-3,4-dihydroxy-1-[(3S)-2-oxopyrrolidin-3-yl]butan-2- (yl}250amino)-4-methyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide
6Y2F	The crystal structure (monoclinic form) of the complex resulting from the reaction between the main protease of SARS-CoV-2 (2019-nCoV) and tert-butyl (1-((S)-1-(((S)-4-(benzylamino))-3 4-dioxo-1-((S)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-2-oxo-1 2-di Hydropyridine-3-yl carbamate (alpha-ketoamide 13b)
7BV2	The nsp12-nsp7-nsp8 complex binds to the RNA template-primer and

	Remdesivir Triphosphate Form (RTP).
7D7K	Crystal structure of papain-like protease of SARS-CoV-2
7KAG	Crystal structure of ubiquitin-like domain 1 (Ubl1) of Nsp3 from SARS-CoV-2
7MBI	Structure of SARS-CoV2 3CL protease covalently bound to peptidomimetic inhibitor.

Grid Box:

One of the vital parameters for ligand docking is the size of the exploration space used to identify the low-energy docking positions of drug candidates. In docking-based medicine development and screening, there are two general approaches namely the blind and targeted docking. In blind docking, the entire protein is paced at the center of the box since we do not have precise information on amino acids that have much higher potential to react with the ligand. However, in the targeted docking, all the information of these amino acids is available, and according to the information of the desired amino acids, we set the range of the grid box to the same amino acids (21). To define a dedicated grid box, the Autodock Tools software is used.

Table 2: Dimensions and size of spatial position of studied proteins

	center_x	center_y	center_z	size_x	size_y	size_z
2GIB	46.029	25.006	9.484	126	126	124
3VB3	11.132	0.362	23.235	126	126	126
6XHL	46.026	36.536	47.42	126	126	126
6Y2F	-4.73	-2.885	12.052	126	126	126
7BV2	97.263	98.282	99.732	126	126	126
7D7K	67.865	-36.447	2.418	126	126	126
7KAG	45.438	74.038	-0.003	118	126	126
7MBI	31.451	43.615	47.754	126	126	126

Ligand Preparation:

In the present study, 90 plant compounds that have antiviral, antitussive, anti-inflammatory, anti-blood clotting effects, etc., based on their research and experimental background, were selected from the TCMSP database (22). Then, their 3-D structure were extracted from the PubChem and ChemSpider databases and were studied (Table 3).

These 3-D structures which were in Pdb and Mol formats in the aforementioned databases were converted to pdbqt using the Open Babel software. In ligand selection, Lipinski's rule of five is also better to be followed. Lipinski's rule of five helps with better differentiation of drugs from placebo.

Table 3: Specifications of ligands studied in the present study

	Compound Name	Molecular Formula	CID	MW
1	Arachis hypogaea	Soyasaponin I	$C_{48}H_{78}O_{18}$	108898*	943.1
2	Water lily	Nupharin A	$C_{41}H_{30}O_{26}$	8709251*	938.7
3	Green tea	4-coumaroyl-CoA	$C_{30}H_{42}N_7O_{18}P_3S$	4944344*	913.7
4	Periwinkle	vinblastine	$C_{46}H_{58}N_4O_9$	12773*	811.0
5	Lady's glove	Digoxin	$C_{41}H_{64}O_{14}$	2006532*	780.9
6	Cissampelos	Warifteine	$C_{36}H_{38}Cl_2N_2O_6$	170074	665.6
7	Forsythiae fructus	Forsythiaside A	$C_{29}H_{36}O_{15}$	5281773	624.6
8	Mint	Hesperidin	$C_{28}H_{34}O_{15}$	10621	610.6

9	Water pepper	Rutoside	$C_{27}H_{30}O_{16}$	5280805	610.5
10	Ginsen radix	Panasenoside	$C_{27}H_{30}O_{16}$	9986191	610.5
11	Ziziphi Spinosae Semen	Spinosin	$C_{28}H_{32}O_{15}$	155692	608.6
12	Stephania cephalantha	Cepharanthine	$C_{37}H_{38}N_2O_6$	10206	606.7
13	Mint	Eriocitrin	$C_{27}H_{32}O_{15}$	83489	596.5
14	Eriobotryae folium	-	$C_{27}H_{32}O_{14}$	10507459	580.5
15	Citrus reticulata	Naringin	$C_{27}H_{32}O_{14}$	442428	580.5
16	Chrysantbemi flos	Isorhoifolin	$C_{27}H_{30}O_{14}$	9851181	578.5
17	Spinach	Lutein	$C_{40}H_{56}O_2$	5281243	568.9
18	Boldo	-	$C_{18}H_{16}N_8O_7S_3^{-2}$	2656	552.6
19	Pheasant's eye	Adonitoxin	$C_{29}H_{42}O_{10}$	441838	550.6
20	Ganoderma	Ganoderic acid C2	$C_{30}H_{46}O_7$	57396771	518.7
21	Rose	LNK754	$C_{29}H_{22}ClN_3O_2$	9805146	480.0
22	Perforate St John's-wort	-	$C_{24}H_{25}F_3N_2O_5$	5449447	478.5
23	Hedysarum multijugum	-	$C_{23}H_{24}O_{11}$	46899140	476.4
24	Azadirachta indica	Hyperoside	$C_{21}H_{20}O_{12}$	5281643	464.4
25	Impatiens semen	Isoquercitrin	$C_{21}H_{20}O_{12}$	5280804	464.4
26	Chrysanthemi flos	Thermopsoside	$C_{22}H_{22}O_{11}$	11294177	462.4
27	Carthami Flos	Lignan	$C_{25}H_{30}O_8$	261166	458.5
28	Currant	-	$C_{22}H_{18}O_{11}$	65064	458.4
29	Illicium Difengpi KLB Et KIM	Betulinic Acid	$C_{30}H_{48}O_3$	64971	456.7
30	Perilla Frutescens	Ursolic Acid	$C_{30}H_{48}O_3$	64945	456.7
31	Ganoderma	-	$C_{30}H_{46}O_3$	21635716	454.7
32	Spinach	Vitamin K	$C_{31}H_{46}O_2$	5280483	450.7
33	Ginsen radix	Kaempferol	$C_{21}H_{20}O_{11}$	5318755	448.4
34	Eriobotryae folium	Isohemiphloin	$C_{21}H_{22}O_{10}$	42607891	434.4
35	Myrrh	-	$C_{20}H_{18}O_{11}$	5317847	434.3
36	Sennae Folium	Emodin-8-glucoside	$C_{21}H_{20}O_{10}$	99649	432.4
37	Viticis fructus	Vitexin	$C_{21}H_{20}O_{10}$	5280441	432.4
38	Oat	Vitamin E	$C_{29}H_{50}O_2$	14985	430.7

39	Fritillaria pallidiflora	Imperialine	$C_{27}H_{43}NO_3$	442977	429.6
40	Ricinus	Lupeol	$C_{30}H_{50}O$	259846	426.7
41	Farfarae flos	Taraxasterol	$C_{30}H_{50}O$	115250	426.7
42	Mori cortex	Kuwanon E	$C_{25}H_{28}O_6$	6440408	424.5
43	Flemingia prostrata roxb	6,8-Diprenylorobol	$C_{25}H_{26}O_6$	21148065	422.5
44	Gossampini flos	Mangiferin	$C_{19}H_{18}O_{11}$	5281647	422.3
45	Mori cortex	Kuwanon B	$C_{25}H_{24}O_6$	44258295	420.5
46	zingiberis	beta-sitosterol	$C_{29}H_{50}O$	222284	414.7
47	Soja semen nigrum	Stigmasterin	$C_{29}H_{48}O$	5280794	412.7
48	Jimsonweed	Ipratropium Bromide	$C_{20}H_{30}BrNO_3$	657308	412.4
49	Lamiaceae	Isoforskolin	$C_{22}H_{34}O_7$	9549169	410.5
50	Ginkgo semen	Ginkgolide A	$C_{20}H_{24}O_9$	9909368	408.4
51	Shepherd's Purse	Gossypetin Hexamethyl Ether	$C_{21}H_{22}O_8$	146093	402.4
52	Caulis piperis kadsurae	-	$C_{23}H_{28}O_6$	11429497	400.5
53	Colchicum autumnale	Colchicine	$C_{22}H_{25}NO_6$	6167	399.4
54	Ephedra	Fumaricine	$C_{21}H_{23}NO_5$	442236	396.4
55	Mori cortex	1,1-Diphenyl-2-Picrylhydrazine	$C_{18}H_{13}N_5O_6$	74358	395.3
56	Mullein	Rotenone	$C_{23}H_{22}O_6$	6758	394.4
57	Ginkgo semen	16-Isopropoxystrychnine	$C_{24}H_{28}N_2O_3$	3054016	392.5
58	Pennyroyal	Cleomiscosin A	$C_{20}H_{18}O_8$	442510	386.4
59	Eribotryae folium	Farnesiferol A	$C_{24}H_{30}O_4$	7067262	382.5
60	Magnolia flos	Veraguensin	$C_{22}H_{28}O_5$	443026	372.5
61	Abri herba	-	$C_{16}H_{18}O_{10}$	10090524	370.3
62	Trachelospermum jasminoides	Voacangine	$C_{22}H_{28}N_2O_3$	73255	368.5
63	Curcuma longa	Curcumin	$C_{21}H_{20}O_6$	969516	368.4
64	Elder	(+)-Bicuculline	$C_{20}H_{17}NO_6$	10237	367.4
65	Viticis fructus	Vitetrifolin C	$C_{22}H_{32}O_4$	15543012	360.5
66	Tripterygii radix	Triptolide	$C_{20}H_{24}O_6$	107985	360.4
67	Rosemary	Rosmarinic acid	$C_{18}H_{16}O_8$	5281792	360.3

68	Viper's-buglosses	-	$C_{20}H_{22}O_6$	12309637	358.4
69	Caulis piperis kadsura	-	$C_{21}H_{26}O_5$	11439770	358.4
70	Papaveris pericarpium	-	$C_{22}H_{29}NO_3$	21287385	355.5
71	Phellodendari chinrnsis	D-Tetrahydropalmatine	$C_{21}H_{25}NO_4$	969488	355.4
72	Fumaria officinalis	Protopine	$C_{20}H_{19}NO_5$	4970	353.4
73	Andrographis paniculata	Andrographolide	$C_{20}H_{30}O_5$	5318517	350.4
74	Asteris radix Et rhizoma	-	$C_{20}H_{15}NO_5$	1081125	349.3
75	Knotweed	-	$C_{22}H_{20}O_4$	11163864	348.4
76	Arctium	Aucubin	$C_{15}H_{22}O_9$	91458	346.3
77	Artemisia annua	-	$C_{17}H_{14}O_8$	5321861	346.3
78	Cassiae Semen	Omeprazole	$C_{17}H_{19}N_3O_3S$	4594	345.4
79	Papaveris pericarpium	(S)-Laudanine	$C_{20}H_{25}NO_4$	821396	343.4
80	Tinospora cordifolia	Magnoflorine	$C_{20}H_{24}NO_4^+$	73337	342.4
81	Farfarae flos	-	$C_{15}H_{22}N_2O_5S$	9862875	342.4
82	Licorise	Glepidotin A	$C_{20}H_{18}O_5$	5281619	338.4
83	Hemp	Dronabinol	$C_{21}H_{30}O_2$	16078	314.5
84	Peucedani radix	Sesibiricin	$C_{20}H_{24}O_4$	12315487	328.4
85	Mallow	-	$C_{20}H_{24}N_2O_2$	5748152	324.4
86	Peganum harmala	Vasicinone	$C_{11}H_{10}N_2O_2$	442935	202.2
87	Stemonae radix	-	$C_9H_{10}FNO_3$	9543530	198.2
88	Cordyceps	Caffeine	$C_8H_{10}N_4O_2$	2519	194.2
89	Orange blossom	3-Nitrosalicylic Acid	$C_7H_5NO_5$	6807	183.1
90	Lindens	Theobromine	$C_7H_8N_4O_2$	5429	180.2

*ChemSpider codes

After the preparation of the protein, the ligand, and the files of docking including the configuration file that contains the grid box information, and the cmd file that specifies the command line for docking, the docking operation is done as follows:

The following commands are run in cmd:
vina --config conf.txt --log A.txt
after receiving the output files with the pdbqt extension, the following command was entered:

vina-split –input ligand_out.pdbqt

Finally, the software provided 9 modes with various energies per Kcal/mol, with the most ideal mode usually being the first mode, which has the highest value of negative energy.

Docking Data Analysis:
The BIOVIA Discovery Studio software was used to analyze the outputs of the performed dockings. The receptor and ligand obtained from the docking process

are entered into the Discovery Studio, and then, in the Interaction tab, all the bindings and final complex information are investigated (26).

Measurement of Root Mean Square Deviation:

The RMSD is usually used to confirm the docking protocol. The validation of the docking protocol means that one crystallography of the complex protein should be considered alongside its ligand and the validation should be done for the same complex. Then, the RMSD values should be evaluated. If the docking protocol is able to create a similar docking of the ligand based on the biological configuration of the same ligand in the crystal structure of the complex protein, it means that the docking is approved. In this case, the lower RMSD value is desirable regarding the status of the real docking (Ideally, under 1.5 angstroms, or even better, under 1 angstrom).

The RMSD values were calculated using the PyMol in the present study (27,28). To calculate the RMSD in PyMol, first, the pre-docking ligand, and then, the post-docking ligand were entered into the software with the same format, and then, the following commands were entered:

Align Ligand name before docking , Ligand name after docking

Or

Fit Ligand name before docking , Ligand name after docking

Findings:

Among 720 dockings done, 18 plant compounds docked with coronavirus receptors had energy values above -10 and more suitable RMSD values (Tables 4 and 5).

Table 4: Interactions and energy results of complexes above = -10ΔG

Plant Name	Compound Name	Receptor	ΔG	H - Bond	Van der Waals	Pi _ Alkyl	Instructions
Lady's glove	Digoxin	7BV2	-12.8	A T:13_U P:13_A P:15_A P:14_U P:17	G P:16	A T:11	-
Arachis hypogaea	Soyasaponin I	7BV2	-12.6	A T:13_ A T:14_ U T:16_ A P:14_U P:13_C T:15_ ASN A:497_G P:16_A P:15	-	-	-
Lady's glove	Digoxin	3VB3	-11.7	LEU B:287_LYS B:137_LYS A:5_ LEU B:271_ASP B:289_ARG B:4	LEU B:272	MET B:276	-
Mint	Eriocitrin	7BV2	-11.7	A P:14_U P:12_A T:18_C T:15_A T:13_A T:14_A T:11	-	U P:12	U T:12 Pi-Pi T-shaped _ LYS A:500 Pi-Cation
Water lily	Nupharin A	6XHL	-11.6	VAL B:135_ALA A:7_LEU A:282_ARG A:4_LEU A:287_ASP A:289_LYS A:5_GLU B:288_SER A:284	-	ARG A:4 , LYS B:5, LYS A:5	Pi-Alkyl _ GLU B:288 , ARG A:131 ,ARG A:4,LYS A:5Pi-Anion_ARG B:4,GLU A:290 Pi-Cation
Mint	Hesperidin	7BV2	-11.4	U P:20_A P:19_G P:16_A T:13_C T:15_A P:14	U P:18_ A P:19 _ A T:14	U P:13_A P:14	LYS A:500 Pi-Cation
Cissampelos	Warifteine	7BV2	-11.3	U P:13_A T:18_ A P:14	U P :12	U T:12_A T:13	A P:14 Pi-Pi T-shaped
Arachis hypogaea	Soyasaponin I	3VB3	-11.0	LYS B:137_LEU A:282_GLU B:290_ASP B:289	SER A:284	-	-

				LYS B:5_LEU B:282_GLU B:288			
Water lily	Nupharin A	7BV2	-11.0	U T17_U P:17_U T:12_U P:13_U P:12_G P:16_A P:14_ASN A:497_A P:15_C T:15ASN A:496	-	-	A T:13,A P:14 Pi-Pi T-shaped_ LYS A:577,U P:13 Pi-Anion
Water pepper	Rutoside	7BV2	-10.9	A T:14_U T:16_U P:18_A P:14_A P:15_A T:13	-	-	-
Arachis hypogaea	Soyasaponin I	7MBI	-10.8	ALA C:285_SER C:284_LYS B:5_GLU B:288_ARG C:4			ARG C:4_GLY C:283_LEU B:282
Citrus reticulata	Naringin	7BV2	-10.7	A T:11_ ASN A:497_ASN A:496_A T:14_C T:15	U T:12	-	U P:18 Pi-Pi T-shaped
Chrysantb emi flos	Isorhoifolin	6XHL	-10.7	LYS A:5_VAL A:125_LEU B:287	-	LYS A:5_LYS B:5_ALA A:7_ARG A:4	LYS B:5 Pi-Cation
Pheasant's eye	Adonitoxin	7BV2	-10.7	A T:13_G P:10_A P:14_U P:12_A T:19_A P:11	-	-	-
Mint	Hesperidin	3VB3	-10.6	LEU B:282_TRP B:207_THR B:285_SER A:284LEU A:282	GLU A:288	LYS A:5	-
Ziziphi Spinosae Semen	Spinosin	7BV2	-10.5	C T:15_A T :14_U P:17_G P:16_A P:19_ASN A:497	-	U T:12_ A T:11	U P:18 Pi_Pi T-Shaped
Chrysantb emi flos	Isorhoifolin	7BV2	-10.5	ASN A:496_A T:13_U T:16_C T:15_A P:14_A P:15	A T:13_A T:14	-	-
Periwinkl e	vinblastine	7D7K	-10.4	-	GLY B:163	LEU A:162_T YR A:264	TYR B:264 Pi_Sigma
Lady's glove	Digoxin	7D7K	-10.4	LEU B:162_TYR B:273_THR A:301	ASP B:164	-	-
Chrysantb emi flos	Isorhoifolin	3VB3	-10.4	ARG A:4_GLU A:288_VAL A:125_LYS A:5_TRP B:27_SER B:284_GLU B:288	-	LYS B:5 _ LYS A:5	LYS B:5 Pi-Cation
جنسینگ	Ginsen radix	7BV2	-10.3	A P:15_G P:16_U P:17_A T:11_C T:15_ASN A:496	U T:12_ A P:14	-	A T:14_ A T:13_U T:12 Pi_Pi T-Shaped
Myrrh	-	7BV2	-10.3	A T:13_ G P:16_ASN A:497_A P:15_A P:14_U P:13_ A P:14_U P:12	-	-	-

Sennae Folium	Emodin-8-glucoside	7BV2	-10.2	A P:15_G P:16_A T:13_U P:17_ C T:15_U T:12	-	-	U T:12 Pi_Pi T-Shaped
Water lily	Nupharin A	3VB3	-10.1	ASP B:197_ASN B:238_ASN A:214_GLY B:138_PHE A:3_ARG A:4_ASP B:289_LEU B:287_LYS B:137			LYS B:137 Pi-Cation_ARG B:131 Pi-Anion
Forsythiae fructus	Forsythiaside A	7BV2	-10.1	U T:17_U T:16_A T:13_A T:14_A P:15_A P:14_ASN A:497	G P:16	-	-
Mint	Eriocitrin	3VB3	-10.1	SER B:284_PHE A:3_GLN B:127_ARG A:4_LYS B:5	-	LYS A:5_PHE B:291	GLU A:288 Pi-Anion
Ginkgo semen	Ginkgolide A	7BV2	-10.1	A P:15_ASN A:497_A T:13_A T:14_U P:18	-	G P:16	-
Water Lilly	Nupharin A	7D7K	-10.0	GLN A:269_LEU A:162_TYR B:268_TYR A:273		LEU A:162	TYR A:264 Pi-Pi Stacked_ LYS A:157,LYS B:157, ARG A:166 Pi-Cation
Periwinkle	vinblastine	7MBI	-10.0	GLY B:283_THR C:199	LEU C:272	-	-
Lady's glove	Digoxin	7MBI	-10.0	MET C:276_THR C:199_ALA B:285_LYS C:137	-	LEU C:284_LEU B:271_LEU B:287_MET B:276	-
Impatiens semen	Isoquercitrin	7BV2	-10.0	G P:16_A P:14_U T:12	-	-	U P:17 Pi_Pi T-Shaped

Table 5: Validation of data obtained from the interaction between the supreme plant compounds and coronavirus proteins

Compound Name	Receptor	RMSD (A°)
Warifteine	7BV2	0.000
Ginkgolide A	7BV2	0.000
Emodin-8-glucoside	7BV2	0.081
2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2R,3R,4S,5S)-3,4,5-trihydroxyoxan-2-yl]oxychromen-4-one	7BV2	0.242
Soyasaponin I	3VB3	0.421
Adonitoxin	7BV2	0.673
Digoxin	3VB3	0.752
Soyasaponin I	7BV2	0.791
Panasenoside	7BV2	1.116
Eriocitrin	7BV2	1.144
Soyasaponin I	7MBI	1.258
Naringin	7BV2	1.300
Spinosin	7BV2	1.338
Hesperidin	3VB3	1.451
Nupharin A	3VB3	1.465
Nupharin A	6XHL	1.700
Eriocitrin	3VB3	1.736

Isorhoifolin	3VB3	1.916
Nupharin A	7BV2	2.039
Digoxin	7MBI	2.097
Isoquercitrin	7BV2	2.118
Isorhoifolin	6XHL	2.278
Nupharin A	7D7K	2.433
Isorhoifolin	7BV2	2.808
Forsythiaside A	7BV2	3.052
Digoxin	7D7K	3.281
Digoxin	7BV2	3.293
vinblastine	7MBI	3.461
vinblastine	7D7K	3.579
Rutoside	7BV2	3.812
Hesperidin	7BV2	5.161

Regarding the fact that the least number of hydrogen bonds should be made for the placebo to affect the receptor (29), the RMSD value is used for approval of the docking protocol. The results without hydrogen bonds and RMSD values above 1 Angstrom are ignored despite having the highest ΔG.

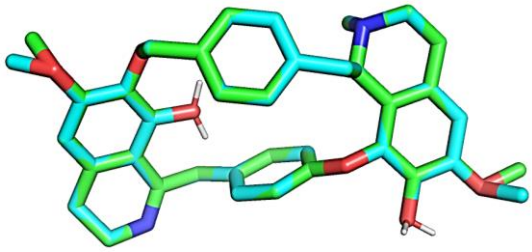

Figure 2: RMSD equal to A° 0.0 for Warifteine compound of Cisamplos by PyMol software

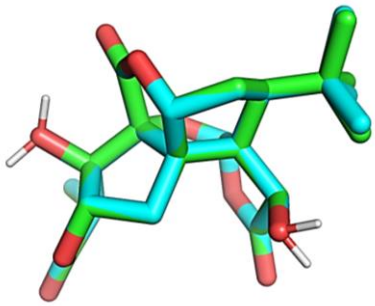

Figure 3. RMSD equal to A° 0.0 for Ginkgolide A compound of Ginkgo semen by PyMol software

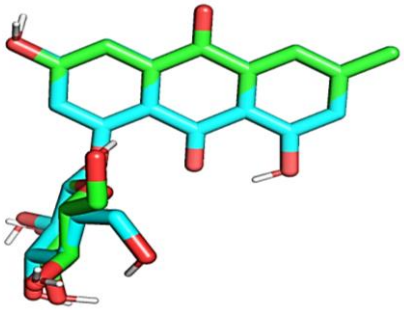

Figure 4: RMSD equal to A° 0.081 for the Emodin-8-glucoside compound of Sennae Folium by PyMol software

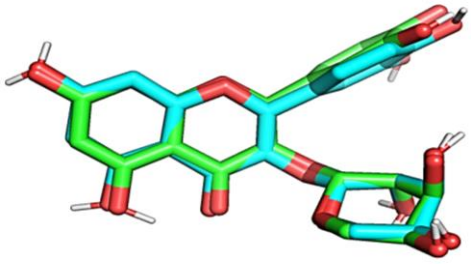

Figure 5: RMSD of A° 0.242 for 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2R,3R,4S,5S)-3,4,5-trihydroxyoxan-2-yl]oxychromen-4-one compound of Myrrh by PyMol software

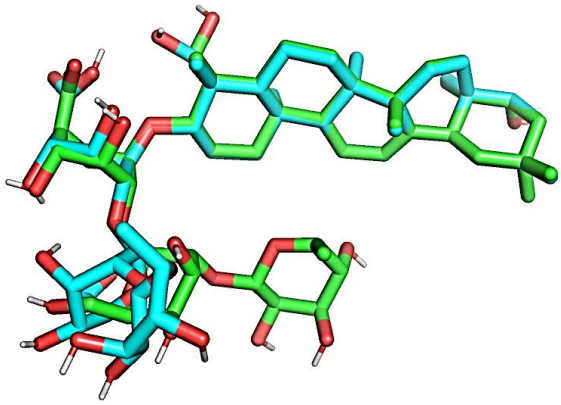

Figure 6: RMSD of A° 0.421 for peanut Soyasaponin I compound (3bv3) of Arachis hypogaea by PyMol software

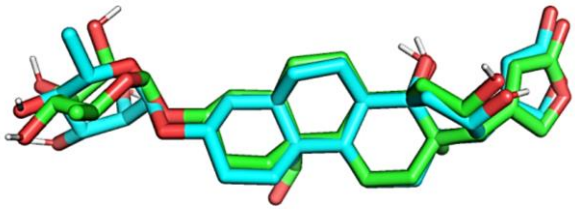

Figure 7: RMSD equal to A° 0.673 for Adonitoxin compound of Pheasant's eye by PyMol software

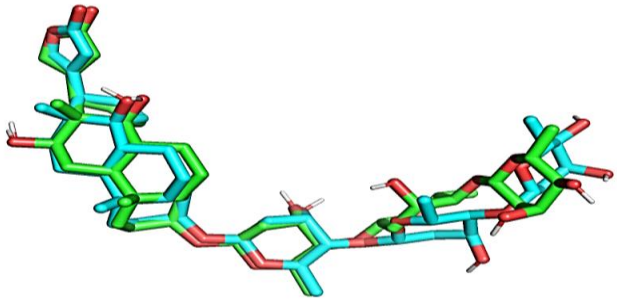

Figure 8: RMSD equal to 0.752 A° for Digoxin compound of Lady's glove by PymMol software

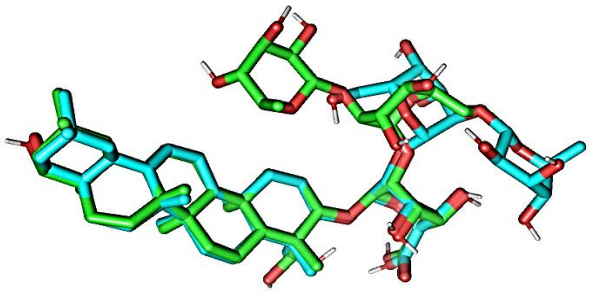

Figure 9: RMSD of A° 0.421 for peanut Soyasaponin I compound (7bv2) of Arachis hypogaea by PyMol software

DISCUSSION:

The RMSD is used for data verification. The lower the RMSD value, the more stable the complex created. Regarding the status of the docking, the values under 1 Angstrom are more acceptable. According to Table 6, 18 compounds are expressed among which 8 showed the best RMSD values, which is indicative of the accuracy of the data in the present study.

Table 6: validity of the data obtained from the interaction between plant compounds and coronavirus proteins

Compound Name	Receptor	RMSD (A°)
Warifteine	7BV2	0.000
Ginkgolide A	7BV2	0.000
Emodin-8-glucoside	7BV2	0.081
2 (3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2R,3R,4S,5S)-3,4,5-trihydroxyoxan-2-yl]oxychromen-4-one	7BV2	0.242
Soyasaponin I	3VB3	0.421
Adonitoxin	7BV2	0.673
Digoxin	3VB3	0.752
Soyasaponin I	7BV2	0.791

Despite having the best docking energy, Digoxin did not have an acceptable RMSD when docked with the 7BV2 receptor. Warifteine and Ginkgolide A made the protein unstable when docked with the 7BV2, which can be seen in RMSD analysis. The RMSD value obtained from Warifteine and Ginkgolide A is equal to zero, which is indicative of the verification of the docking protocol. Also, it should be noted that these two compounds are not toxic (30,31).

CONCLUSION:

The analysis of RMSD parameters, interactions, number of hydrogen bonds as well as RO5 criteria and their non-toxic properties show better performance. These compounds have better potential as anti-viral herbal chemicals to solve respiratory, inflammatory, infectious, and coagulation problems that may prevent the virus proliferation or help to treat this disease. It can be said that these 4 inhibitors are suitable candidates as medicines to inhibit the main enzyme of SARS-CoV-2 in in vitro and in vivo studies. Nevertheless, it should be admitted that the present study is purely theoretical. To ensure the validity of the data, experimental work is required. It cannot be claimed that the compounds introduced in the present study alone can inhibit the COVID-19 proteins.

It is recommended to perform dynamic molecular simulations for Warifteine, Ginkgolide A, Emodin-8-glucoside, and Adonitoxin compounds to validate the results. Also, after ensuring the dynamic molecular results, it is recommended to do experiments for docking of Warifteine, Ginkgolide A, Emodin-8-glucoside, and Adonitoxin compounds with coronavirus proteins.

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