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Research Article

COMPUTATIONAL PREDICTION OF BIOACTIVE COMPOUNDS AS POTENTIAL INHIBITORS OF COVID-19 MAIN PROTEASE, SPIKE GLYCOPROTEIN RECEPTOR-BINDING DOMAIN, AND RNA-DEPENDENT RNA POLYMERASE

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ABSTRACT

Objectives: It has been known for ages that natural products have potent antiviral activity and hence show inhibitory effects on SARS-CoV-2 infections. In this study, some promising bioactive compounds from natural sources for drug development against SARS-CoV-2 were studied.

Methods: The study was based on a computational approach using different phytochemicals for evaluating their potential against non-structural (main protease [MPro], RNA-dependent RNA polymerase [RdRp], and structural [spike [S] glycoprotein receptor-binding domain]) viral proteins. Molecular docking was conducted systematically using PyRx and AutoDock 4.2 to determine the binding affinities between bioactive compounds and Mpro, spike RBD, and RdRp. Twenty-two ligands were selected in this study from different sources including three known inhibitors of the virus remdesivir, favipiravir, and nelfinavir. The pharmacological assessment of the ligands was achieved using ADMET filters.

Results: The docking results revealed that β-carotene, piperine, and cianidanol were the best antagonists for Mpro, isovitexin, quercitin, β-carotene, piperine, and cianidanol were the best antagonists for RdRp, and in case of the spike RBD, capsaicin, cianidanol, curcumin, gingerol, isovitexin, piperine, quercitin, rhapontin, and riboflavin were found to be best.

Conclusion: All of these bioactive compounds could be considered potential drug candidates for COVID-19 inhibition due to their promising binding affinities with the viral structural and non-structural proteins.

Keywords: COVID-19 main protease, RNA-dependent RNA polymerase, Spike glycoprotein receptor-binding domain, Bioactive compounds.

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INTRODUCTION

Increasing urbanization is associated with various maladies. SARS-COV in China (2002), avian influenza in humans (2005), H1N1 influenza (2009), MERS-COV, and Ebola in West Africa (2014) are some of the viral outbreaks which have been reported in recent years [1]. A more recent strain of coronavirus, SARS-CoV-2, has expanded all over the world in a very short span and has brought the whole world to a standstill World Health Organization declared the outbreak as a Public Health Emergency of International concern on January 2022 (WHO, 2020). As per the WHO report (February 17, 2022), there have been 416,614,051 confirmed cases of COVID-19, including 5,844,097 deaths [2,3].

The major genera of coronavirus are alpha, beta, gamma, and delta. The two beta coronavirus outbreaks, that is, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) which occurred in the past have less severity and are less infectious with a fatality rate of 35%. Coronaviruses are enveloped in positive-sense, single-stranded, 3Kb RNA viruses [4,5]. The open reading frame (ORF) region of all the coronaviruses contains specific genes which encode replicative, spike, and capsid proteins. The two open reading frames of coronaviruses ORF1a and ORF1ab and the polyproteins code for structural and non-structural proteins [6].

Spike glycoprotein (S), nucleocapsid protein (N), membrane protein (M), and envelope protein are characterized as structural proteins and a range from nsp1 to nsp16 is non-structural proteins [7,8]. The nucleocapsid protein N of the capsid is surrounded by the membrane, envelope, and spike glycoproteins. The virus targets the host cells through the spike protein making it a potential target for drug discovery. Along with it, the RNA-dependent RNA polymerase is the main viral enzyme that is involved in the replication of the genome as well as in the transcription process. The structure of RNA-dependent RNA polymerase resembles a right-hand shape and resembles having a finger, palm, and thumb domains [9,10].

RdRp helps in synthesizing viral RNA, structural proteins, and assembly proteins are also synthesized which complete the viral assembly and progeny viral particles are released by the exocytosis [11].

Proteases are essential for processing polyproteins that are translated from viral RNA. β-CoVs produce polyproteins pp1a and pp1ab by translation. The proteolytic cleavage of these polyproteins into structural and nonstructural proteins is carried by viral main proteases (M pro) and papain-like proteases (PLpro) [12]. Blocking the protease enzyme will lead to the inhibition of viral replication. Various antiviral agents have already been reported for the management of COVID-19 which includes remdesivir, favipiravir, and sofosbuvir (RdRp inhibitor), and lopinavir, nelfinavir, and ritonavir (protease inhibitors) [13]. Natural compounds possess antiviral properties and could become a valuable resource. The antiviral action of bioactive compounds presents in various spices and food items and against SARS-CoV-2 to inhibit main protease (Mpro) spike (S) glycoprotein receptor-binding domain (RBD) bound to ACE2 and RNA-dependent RNA polymerase of SARS-CoV-2 was studied using computational approaches [14]. This work has brought some important bioactive compounds derived from natural sources into play by displaying their *in silico* and anti-COVID-19 activity imputed by inhibiting the viral proteins by employing molecular docking tools.

METHODS

Ligands selection

To select bioactive compounds from different food items with antiviral properties, an extensive literature survey was done using PubMed and Google Scholar platforms. Based on the literature survey, a total of 22 compounds were selected (Table 1) and their virtual screening was done to find out the potential ligands. 3D structures of all the compounds were extracted from the PubChem database in SDF formats and converted into PDB formats using PYMOL2.5.1. Physicochemical properties were obtained from PubChem open chemistry database (Table 2). Three known inhibitors of COVID-19 spike protein, RdRp, and Mpro, namely, remdesivir, nelfinavir, and favipiravir, were used as controls in this study [15].

Preparation of target protein

The crystal structure of the target proteins spike (S) glycoprotein receptor-binding domain (RBD) bound to ACE2, RNA-dependent RNA polymerase, and main Protease (Mpro) with PDBIDs: 6M0J, 6M71, and 6LU7, respectively, was retrieved from Research Collaboratory for Structural Bioinformatics Protein Databank (RCSB PDB), https://www.rcsb.org [16]. All the crystal structures were prepared by removing existing ligands and water molecules using I-TASSER (Iterative Threading Assembly Refinement) [17], https://zhanggroup.org/I-TASSER/.

It provides the most accurate protein structure and functions predictions. To observe the three-dimensional (3D) structures of the target proteins, BIOVIA Discovery Studio Visualizer was used which is a feature-rich molecular modeling application employed for viewing, sharing, and analyzing proteins. Three-dimensional structures of the proteins are shown in Fig. 1a-c. Stereochemical properties were analyzed by preparing a Ramachandran plot using Zlab [18].

Suitability of ligand as a drug (ADME screening)

An *in silico* tool for analysis of absorption, distribution, metabolism, and excretion of the drug in the human body was used to screen the selected compounds which could be bioactive through oral administration. The drug-likeness of the potential ligands was evaluated using the *Lipinski filter* which is based on Lipinski's rule of five that determines the "druggability" of a chemical compound to be consumed orally as an active drug in humans [19]. The prediction tool used was SwissADME (http://www. swissadme.ch/) [20]. Canonical Smiles from PubChem were used to identify ADME properties by Swiss ADME. The parameters analyzed were lipophilicity, molecular weight, hydrogen bonding, charge, polar surface area, Ghosh violations, Lipinski's violation, etc.

Table 1: Selected bioactive compounds and their source

S. No.	Bioactive compounds	Source
1	Allicin	Garlic
2	Anethole	Aniseed
3	Capsaicin	Chili pepper
4	Cianidanol	Green tea
5	Cinnamaldehyde	Cinnamon
6	Curcumin	Turmeric
7	Estragole	Fennel seeds
8	Eugenol	Cloves
9	Gingerol	Ginger
10	Isovitexin	Fenugreek
11	Limonene	Dill seed
12	Linalool	Coriander
13	Piperine	Black pepper
14	Quercitin	Onion
15	Rhapontin	Fenugreek
16	Riboflavin	Eggs, meat, fruits, and vegetables
17	Sabinene	Eggs, meat, fruits, and vegetables
18	Thymol	Thyme and ajwain
19	β-carotene	Fruits and vegetables
20	Remdesivir	Chemical
21	Favipiravir	Chemical
22	Nelfinavir	Chemical

Criteria used for Lipinski filter analysis were molecular weight ≤500, hydrogen bond donor ≤5, hydrogen bond acceptor ≤10, and an octanol-water partition coefficient (LogP) ≤5. The molecules that did not incur more violations were selected and used in molecular docking studies.

Screening of potential ligands for molecular docking

The selected ligands from the SWISS ADME analysis were further screened according to their binding energies against all three proteins using PyRx which is one of the virtual screening software used in computational drug discovery [21]. To perform molecular docking, ligands were prepared by adding hydrogen atoms followed by PDB structure generation by the Open Babel program. Further, energy minimization and optimization of the molecules were done using the universal force field at 200 descent steepest algorithm of Open Babel present in PyRX (https://pyrx.sourceforge.io/) and the molecules were converted in.pdbqt format.

All the prepared ligands were docked with the COVID-19 Mpro, RdRp, and spike RBD systematically using PyRx. The ligands with the best binding affinities were selected for docking in AutoDock [22].

Molecular docking studies

A total of nine selected natural compounds were docked with COVID-19 main protease (Mpro) and RdRp (RNA-dependent RNA polymerase) whereas 12 best compounds were docked with spike RBD. A docking study was performed to analyze the interaction of selected bioactive compounds with three selected proteins of COVID-19 using AutoDock tools 1.5.6 software. The default parameters were set in the whole study to get the accuracy. The X-ray crystal structures of the main protease (PDB ID: 6LU7), spike receptor domain complexed with ACE2 (PDB ID: 6MOJ), and RdRp (PDB ID: 6M71) were downloaded from the RCSB PDB (Protein Data Bank) database; the Graphical User Interface program "Auto-Dock Tools" was used to prepare, run, and analyze the docking simulations. In an extended PDB format; PDBQt was generated for both ligands and proteins which include atomic partial charges and atom types [22].

Grid box and grid parameters files were also generated using Autodock tools. Protein was prepared by deleting water molecules, adding polar hydrogens, Kollman charges, and salvation parameters, and saved in PDBQT format. Gasteiger charge was assigned and then non-polar hydrogens were merged in the case of ligands. AutoGrid was performed for generating the grid map by placing the whole protein into a three-dimensional grid box. AutoDock procedure requires pre-calculated grid

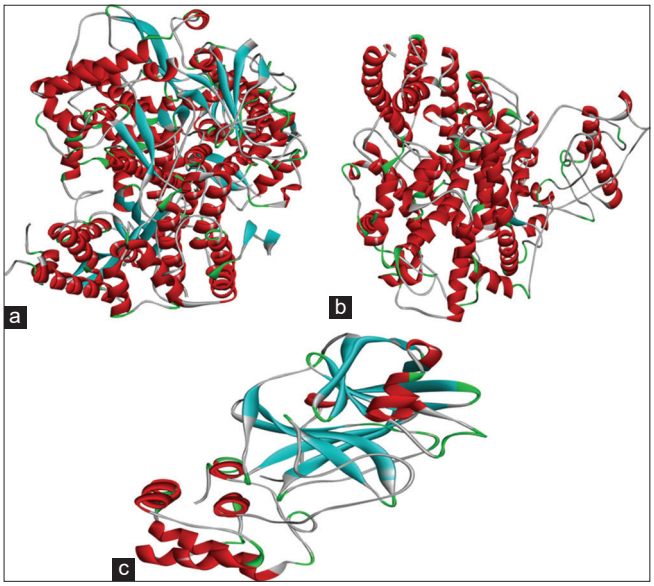

Fig. 1: Three-dimensional crystal structure of the molecular target, COVID-19 (a) spike (S) glycoprotein receptor-binding domain (RBD) (6MOJ), (b) RNA-dependent RNA polymerase (RdRp) (6M71), (c) Main protease (Mpro) (6lU7)

maps, one for each atom type, present in the ligand being docked as it stores the potential energy arising.

Docking was carried out using the Lamarckian genetic algorithm with 10 runs and the best configuration was selected from the cluster RMSD table. The lowest binding energies conformations were extracted from the DLG files and were further analyzed by aligning with protein molecules.

RESULTS

Protein preparation

The information on the proteins used in this study (PDB files) is given in Fig. 1. Moreover, the stereochemical properties were analyzed by Ramachandran plot (Fig. 2a-c). Swiss model Ramachandran plot is used for validation of stereochemical properties and analyzing the reliability of the predicted protein model. It analyses the main torsion angles Phi, Psi (ϕ, ψ) of the residues of amino acid in the polypeptide chain of the protein [23]. According to the Ramachandran plot, ~95% of residues are in the most favored region 4% in allowed regions, and 1% residues in outlier regions (Fig. 1a). Fig. 1b represents 97% residues in the most favored region, ~2% in allowed regions, and ~1% residues in outlier regions. Fig. 1c represents ~ 98% residues in the most favored region, 1% in allowed regions, and ~1% residues in outlier regions. This confirms the accuracy of the predicted models.

Generation of ligand library

The sources of bioactive compounds are listed in Table 1. Physiochemical properties of all 22 compounds retrieved from the PubChem open chemistry database are listed in Table 2.

Table 2: Physiochemical properties of the ligand molecules

Ligands	PUBCHEM ID	Molecular Weight (g/mol)	Heavy Atom Count	Topological polar surface area (Å)
Allicin	CID65036	162.3	9	61.6
Anethole	CID637563	148.2	11	9.2
Capsaicin	CID1548943	305.4	22	58.6
Cianidanol	CID9064	290.27	21	110
Cinnamaldehyde	CID637511	132.16	10	17.1
Curcumin	CID969516	368.4	27	93.1
Estragole	CID8815	148.2	11	9.2
Eugenol	CID3314	164.2	12	29.5
Gingerol	CID442793	294.4	21	66.8
Isovitexin	CID162350	432.4	31	177
Limonene	CID22311	136.23	10	0
Linalool	CID6549	154.25	11	20.2
Piperine	CID638024	285.34	21	38.8
Quercitin	CID 5280343	302.23	22	127
Rhapontin	CID637213	420.4	30	149
Riboflavin	CID493570	376.4	27	155
Sabinene	CID18818	136.23	10	0
Thymol	CID6989	150.22	11	20.2
β-carotene	CID5280489	536.9	40	0
Remdesivir	CID 121304016	602.6	42	204
Favipiravir	CID492405	157.1	11	84.6
Nelfinavir	CID 64143	567.8	40	127

Table 3: Evaluation of selected bioactive compounds through Lipinski's rule of five

S. No.	Ligand	Molecular properties					
		MW (<500 Dalton)	HBD (≤5)	HBA≤10)	LogP (<5)	A (40–130)	Violation
1	Allicin	162.27	0	1	1.95	45.88	0
2	Favipiravir	157.1	2	4	0.39	32.91	0
3	Estragole	148.2	0	1	2.47	47.04	0
4	Cinnamaldehyde	132.16	0	1	1.65	41.54	0
5	Piperine	285.34	0	3	3.38	85.47	0
6	Anethole	148.2	0	1	2.55	47.83	0
7	Linalool	154.25	1	1	2.7	50.44	0
8	Limonene	136.23	0	0	2.72	47.12	0
9	Riboflavin	376.36	5	8	0.97	96.99	0
10	Cianidanol	290.27	5	6	1.47	74.33	0
11	Curcumin	368.38	2	6	3.27	102.8	0
12	Capsaicin	305.41	2	3	3.15	90.52	0
13	Gingerol	294.39	2	4	3.48	84.55	0
14	Eugenol	164.2	1	2	2.37	49.06	0
15	Thymol	150.22	1	1	2.32	48.01	0
16	Quercetin	302.24	5	7	1.63	78.03	0
17	Remdesivir	602.58	4	12	3.24	150.43	3
18	Sabinene	136.23	0	0	2.65	45.22	1
19	Beta-carotene	536.87	0	0	7.79	184.43	3
20	Rhapontin	420.41	6	9	2.39	106.5	1
21	Isovitexin	432.38	7	10	1.94	106.61	1
22	Nelfinavir	567.78	4	5	3.87	166.17	1

MW: Molecular weight; HBD: Number of hydrogen bond donors; HBA: Number of hydrogen bond acceptors; log P: The logarithm of octanol/water partition coefficient; A: Molar refractivity

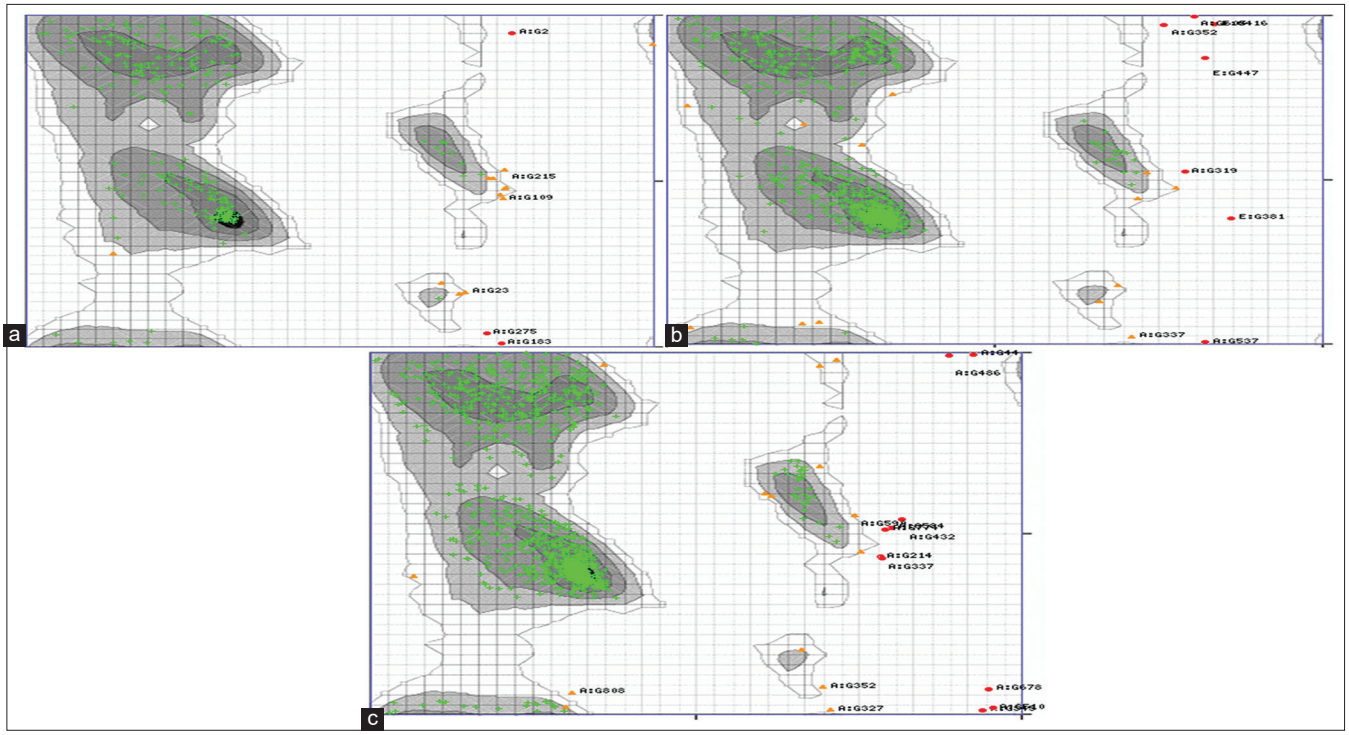

Fig. 2: (a) Ramachandran plot for COVID-19 main protease (Mpro) (PDB ID: 6LU7). The plot represents ~95% residues in the most favored region, 4% in allowed regions while 1% residues in outlier regions. (b) Ramachandran plot for glycoprotein receptor bound to ACE2 (PDB ID: 6M0J). The plot represents 97% residues in the most favored region, ~2% in allowed regions while 1% in the outliers region. (c) Ramachandran plot for RNA-dependent RNA polymerase (RdRp) (PDB Code: 6M71) of SARS-CoV-2. The plot represents ~ 98% residues in the most favored region, 1% in allowed regions while ~1% residues in outlier regions

Druglikeness analysis

For the first layer of screening, all the bioactive compounds were subjected to a Lipinski filter (Table 3). All the molecules with reasonable stereochemical properties were selected for further screening.

Screening of ligands using PyRx

All the selected bioactive compounds after Lipinski filter analysis were screened based on their binding energies with all three proteins (Tables 4-6). Finally, nine best ligands are selected which show the best binding affinities with main protease (Mpro) and RdRp whereas 12 ligands showed the best affinities with spike RBD. The selected ligands are chosen and are subjected to molecular docking using the AutoDock tool 1.5.6.

Docking results

Molecular docking studies of three proteins COVID-19 main protease (Mpro,) spike (S) glycoprotein receptor-binding domain (RBD), and RNA-dependent RNA polymerase (RdRp) with the selected ligands (9, 9, and 12) were performed using Lamarckian genetic algorithm. The most favorable configurations among the 10 runs were selected from the cluster RMSD table for further analysis. Docking results are presented in Tables 7-9.

The lower the binding energies, the more stable the binding. Docking results revealed that among the binding energies of chosen ligands with MPro, B-carotene, piperine, and cianidanol showed the binding energies (−9.6, −6.25, and −6.06) were much lower than the known inhibitors or drugs (remdesivir: −3.17 and nelfinavir: −5.19). Hence, these bioactive compounds are an important drug target against the main protease (Mpro) of COVID-19.

Docking results of chosen ligands with RNA-dependent RNA polymerase (RdRp) revealed that the binding energies of cianidanol, isovitexin, piperine, quercitin, and b-Carotene (−4.78, −3.47, −5.61, −4.47, and −8.2, respectively) are much less than remdesivir and nelfinavir (−2.75 and −3.1, respectively) which qualifies them as a potent drug candidate against RNA-dependent RNA polymerase of COVID-19.

Docking results of chosen ligands with spike RBD revealed that the binding energies of piperine and B-carotene (−7.18 and −9.8) are much

Table 4: Binding affinity of all the ligands with COVID-19 main protease (Mpro) using PyRx virtual screening tool

S. No.	Protein	Ligands	Binding affinity (Kcal/mol)
1	Main protease (Mpro)	Allicin	−3.7
2		Anethole	−4.6
3		Capsaicin	−5
4		Cianidanol	−6.7
5		Cinnamaldehyde	−5.1
6		Curcumin	−6
7		Estragole	−4.5
8		Eugenol	−5.3
9		Gingerol	−5.2
10		Isovitexin	−7.4
11		Limonene	−4.8
12		Linalool	−3.8
13		Piperine	−6.2
14		Quercitin	−6.9
15		Rhapontin	−6.7
16		Riboflavin	−7.1
17		Sabinene	−4.6
18		Thymol	−5.2
19		β-carotene	−7.8
20	Known inhibitors	Remdesivir	−6.8
21		Favipiravir	−5.7
22		Nelfinavir	−8.4

Table 5: Binding affinity of all the ligands with COVID-19 RNA-dependent RNA polymerase (RdRp) using PyRx virtual screening tool

S. No.	Protein	Ligands	Binding affinity (Kcal/mol)
1	RNA-dependent RNA polymerase (RdRp)	Allicin	−3.6
2		Anethole	−5.1
3		Capsaicin	−5.3
4		Cianidanol	−7
5		Cinnamaldehyde	−4.9
6		Curcumin	−5.7
7		Estragole	−4.9
8		Eugenol	−5.1
9		Gingerol	−4.7
10		Isovitexin	−8.5
11		Limonene	−5
12		Linalool	−4.6
13		Piperine	−6.9
14		Quercitin	−7.4
15		Rhapontin	−8.1
16		Riboflavin	−6.7
17		Sabinene	−5.2
18		Thymol	−5.2
19		β-carotene	−7.6
20	Known inhibitors	Remdesivir	−8
21		Favipiravir	−5
22		Nelfinavir	−8.2

Table 6: Binding affinity of all the ligands with COVID-19 spike (S) glycoprotein receptor-binding domain (RBD) using PyRx virtual screening tool

S. No.	Protein	Ligands	Binding affinity (Kcal/mol)
1	Spike RBD	Allicin	−4.2
2		Anethole	−5.8
3		Capsaicin	−7.1
4		Cianidanol	−7.8
5		Cinnamaldehyde	−5.7
6		Curcumin	−8.8
7		Estragole	−5.6
8		Eugenol	−5.9
9		Gingerol	−6.9
10		Isovitexin	−9.5
11		Limonene	−5.7
12		Linalool	−5
13		Piperine	−8.2
14		Quercitin	−8.6
15		Rhapontin	−9
16		Riboflavin	−7.6
17		Sabinene	−5.9
18		Thymol	−6
19		β-carotene	−8.4
20	Known inhibitors	Remdesivir	-8.2
21		Favipiravir	−5.6
22		Nelfinavir	−9.3

Table 7: Binding energy of the nine potential ligands with main protease (Mpro) using AutoDock

S. No.	Protein	Ligands	Binding energy (Kcal/mol)-AutoDock
1	Main protease (Mpro)	Cianidanol	−6.06
2		Isovitexin	−4.5
3		Piperine	−6.25
4		Quercitin	−5.07
5		Rhapontin	−4.35
6		Riboflavin	−5.03
7		β-carotene	−9.6
8		Remdesivir	−3.17
9		Nelfinavir	−5.19

Table 8: Binding energy of the nine potential ligands with COVID-19 RNA-dependent RNA polymerase (RdRp) using AutoDock

S. No.	Protein	Ligands	Binding energy (Kcal/mol)-AutoDock
1	RNA-dependent RNA polymerase (RdRp)	Cianidanol	−4.78
2		Isovitexin	−3.47
3		Piperine	−5.61
4		Quercitin	−4.47
5		Rhapontin	−3.06
6		Riboflavin	−2.25
7		β-carotene	−8.2
8		Remdesivir	−2.75
9		Nelfinavir	−3.1

Table 9: Binding energy of the 12 potential ligands with COVID-19 spike (S) glycoprotein receptor-binding domain (RBD) using AutoDock

S. No.	Protein	Ligands	Binding energy (Kcal/mol)-AutoDock
1	Spike RBD	Capsaicin	−5.92
2		Cianidanol	−5.8
3		Curcumin	−5.41
4		Gingerol	−4.08
5		Isovitexin	−5.06
6		Piperine	−7.18
7		Quercitin	−5.71
8		Rhapontin	−5.37
9		Riboflavin	−3.53
10		β-carotene	−9.8
11		Remdesivir	−3.36
12		Nelfinavir	−6.91

below than the nelfinavir (−6.91) whereas binding energies of all 10 ligands (capsaicin, cianidanol, curcumin, gingerol, isovitexin, piperine, quercitin, rhapontin, and riboflavin); −5.92, −5.8, −5.41, −4.08, −5.06, −7.18, −5.71, −5.37, and −3.53 are either close to or lesser than the COVID-19 drug remdesivir which makes them a promising drug target against spike RBD of the COVID-19.

DISCUSSION

COVID-19 is declared a public health emergency (WHO, 2020), and searching for effective drugs is the need of the hour. There are four major structural proteins and 16 non-structural proteins coded by the genome of the novel coronavirus [24]. In the present study, three proteins of COVID-19, main protease (Mpro,) spike (S) glycoprotein receptor-binding domain (RBD), and RNA-dependent RNA polymerase (RdRp) were selected. The main protease (Mpro) and spike protein play a major role in coronavirus propagation whereas RNA-dependent RNA polymerase plays a key role in the replication, transcriptions, and RNA processing machinery of the virus. Thus, they have the potential to be targeted by drugs and different antiviral agents, thereby inhibiting coronavirus infections.

Many antiviral agents have already been reported and antiviral effects of the extracts from medicinal plants have also been demonstrated. The phytochemicals block the viral receptors, interrupt the enzymatic functioning, and inhibit the biosynthetic machinery of the virus [25]. This study aims to screen 19 bioactive compounds present in various eatables based on their pharmacokinetic properties, druglikeness, and the ability to bind to the three different proteins of COVID-19. Three well-known inhibitors of the novel coronavirus (remdesivir, favipiravir, and nelfinavir) were used as standard reference drugs for comparison. ADME-based properties of drug molecules were checked using the Lipinski rule of five.

All the selected ligands overall fulfilled the criteria of being good drug candidates. Molecular docking is the modern drug discovery tool through which the active site targeting of a particular macromolecule can be analyzed. It is a detailed method to uncover the interactions of different macromolecules as drugs against the receptor. In the present investigation, computational docking of the bioactive compounds from different food items was performed to explore the antagonists of Mpro, RdRp, and spike RBD proteins of COV-2. Among 22 ligands, nine best ligands are selected which show the best binding affinities with main protease (Mpro) and RdRp whereas 12 ligands showed the best affinities with spike RBD using PyRX, a virtual screening tool used in computational drug discovery.

The selected ligands were subjected to molecular docking using AutoDock. The compounds with the potential to inhibit the main protease and RNA-dependent RNA polymerase (RdRp) based on the binding energy include cianidanol, isovitexin, piperine, quercitin, rhapontin, riboflavin, and β-carotene. Among these bioactive compounds, B-carotene, piperine, and cianidanol were at the top with the best binding energy and most satisfactory parameters with Mpro while with RdRp β-carotene, piperine, cianidanol, isovitexin, and quercitin gave the best results. Among the 12 compounds docked with spike RBD, 10 bioactive compounds capsaicin, cianidanol, curcumin, gingerol, isovitexin, piperine, quercitin, rhapontin, and riboflavin showed the binding energy as good as the chemical counterpart whereas piperine and β-carotene gave the best results as the binding energies are much lower than the control (nelfinavir) used.

CONCLUSION

This work seeks to find out the potential inhibitors of COVID-19 main protease (Mpro,) spike (S) glycoprotein receptor-binding domain (RBD), and RNA-dependent RNA polymerase (RdRp). Out of 19 bioactive compounds used for screening, β-carotene, piperine, and cianidanol were the best antagonists for Mpro. In addition to them, isovitexin and quercitin were the best antagonists for RdRp and in the case of the spike RBD. Capsaicin, cianidanol, curcumin, gingerol, isovitexin, piperine, quercitin, rhapontin, and riboflavin were found to be best. And among them, piperine and β-carotene were with the lowest binding energies. In light of the results obtained from the present study, it is concluded that all of these bioactive compounds could be good antagonists of the viral proteins and can help to stop their spread. Therefore, we propose them as potential inhibitors of viral proteins. These bioactive compounds could lead as a potential drug candidate against COVID-19. To validate these computational findings, further *in vitro*, *in vivo*, and clinical studies are still needed.

AUTHORS' CONTRIBUTIONS

All the authors have contributed equally to the paper.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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