European Review for Medical and Pharmacological Sciences 2020; 24: 4529-4536

In silico screening of natural compounds against COVID-19 by targeting Mpro and ACE2 using molecular docking

T. JOSHI[1], T. JOSHI[2], P. SHARMA[3], S. MATHPAL[1], H. PUNDIR[3], V. BHATT[4], S. CHANDRA[2]

[1]Department of Biotechnology, Kumaun University, Bhimtal Campus, Bhimtal, Uttarakhand, India
[2]Department of Botany, Kumaun University, S.S.J Campus, Almora, Uttarakhand, India
[3]Department of Botany, Kumaun University, D.S.B Campus, Nainital, Uttarakhand, India
[4]Sanskar College of Pharmacy and Research, Ghaziabad, Uttar Pradesh, India

Abstract. – OBJECTIVE: Currently, Coronavirus COVID-19 is spreading worldwide very rapidly and its control is very difficult because there is no effective vaccine or drugs available in markets. This virus can infect both animals and people and cause illnesses of the respiratory tract. WHO has declared Coronavirus as pandemic and the whole world is fighting against Coronavirus. Globally, more than 199,478 people have been diagnosed with COVID-19. As of March 18, 2020, more than 167 countries have been affected and more than 8000 deaths have been reported. The main country being affected is China followed by Italy, Iran, Spain, France, and the USA.

MATERIALS AND METHODS: Since there are no effective drugs available against Coronavirus, we conducted virtual screening of phytochemicals to find novel compounds against this virus. Hence, we created a phytochemical library of 318 phytochemicals from 11 plants which have been reported as antiviral, antibacterial and antifungal activity. The phytochemical library was subjected to virtual screening against molecular targets; Main protease (Mpro) and Angiotensin-Converting Enzyme 2 (ACE2).

RESULTS: Top 10 compounds were selected from each target which had better and significantly low binding energy as compared to the reference molecule.

CONCLUSIONS: Based on the binding energy score, we suggest that these compounds can be tested against Coronavirus and used to develop effective antiviral drugs.

Key Words:
Coronavirus, SARS-CoV-2, COVID-19, Molecular docking, Phytochemicals, Mpro, ACE2.

Introduction

At the current time, Coronavirus is becoming very deadly in several countries. Coronavirus primarily targets the human respiratory system. As of March 18, 2020, about 199,478 people have been infected with Coronavirus and more than 8000 deaths have been reported worldwide since its emergence in the city of Wuhan, Hubei province. Due to rapid dissemination and deaths, the whole world has declared it a pandemic disease. According to the World Health Organization (WHO) reports, there have also been more than 18,000 cases outside China. The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), previously named as 2019 novel Coronavirus (2019-nCoV), is a positive-sense, single-strand RNA virus. SARS-CoV-2 has caused an ongoing outbreak of Coronavirus disease 2019 (COVID-19), which started in December 2019[1]. The outbreak of Coronoavirus is increasing day by day all over the world. Italy is another country that has been affected most after China from the Coronavirus followed by Iran, South Korea, and Spain, etc. Despite being declared as a pandemic disease for the world by WHO, there are no appropriate vaccines and antiviral drugs available on the market to prevent and treat viral infection. On March 17, 2020, the United States reported starting vaccine trial against Coronavirus but it will take more than one year to be available. Therefore, it is an urgent demand to develop effective drugs for treatments of 2019-nCoV. The development of effective treatments will take months or years, which will hamper the control of this pandemic problem. Therefore, effective treatment or control mechanism is needed to be developed to prevent Coronavirus[2]. Therefore, to search for potential and specific inhibitors of Coronavirus, we carried out the virtual screening to identi-

Corresponding Author: Subhash Chandra, MD; e-mail: scjnu@yahoo.co.in

fy novel phytochemicals against SARS-CoV-2 from different plants. In this study, we used two enzymes; Mpro of virus-cell[3] and ACE2 receptor of a host cell[4] as molecular targets against Coronavirus. SARS-CoV-2 is a (+) SS RNA virus that encodes many structural and non-structural proteins. The Mpro is a non-structural protein that cuts two replicase polyproteins resulting in matured proteins that are required to mediate viral replication and transcription. In this way, by inhibition of the Mpro, we can stop virus replication while inhibition of ACE2 catalytic pocket by small molecules could change the conformation of ACE2 in such a way that it could block SARS-CoV-2 entry inside host cells through ACE2[5,6]. Therefore, we selected Mpro, protease as a target to inhibit virus replication and ACE2 receptor to block entry SARS-CoV-2.

Material and Methods

Construction of Phytochemical Library

Text mining analysis of some plants by using server DLAD4U (Disease List Automatically Derived For you), PubTator and Carrot2 servers resulted in 11 plants with potential antiviral activity. Hence the phytochemicals of these plants may have anti-viral properties. Therefore, to find out anti-viral phytochemicals against Coronavirus, a library of 318 phytochemicals was constructed from 11 plants through searching the scientific literature and PubChem.

Protein Receptors Preparation

The 3D structure of Mpro from COVID-19 (PDB ID 6LU7) and ACE2 receptor from Human (PDB ID 1R4L) were downloaded from the Protein Data Bank (https://www.rcsb.org). All water molecules, ions, and ligands were removed from the protein molecule using PyMOL software. After that, the addition of hydrogen atoms to the receptor molecule was carried out by using MG Tools of AutoDock Vina software[7]. The structure of the protein was saved in PDB format for further analysis.

Ligand Preparation

The 3D structure of each phytochemical was downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov) in SDF format and then converted into PDB format using Open Babel software. The 3D structure of Reference molecules PRD_002214 **(**ChemID 4883311) and XX5 **(**ChemID 395128**)** which was co-crystallized with protein 6LU7 and 1R4L respectively were downloaded from ChemSpider.

Rigid Docking

Computational Docking is performed to obtain a population of possible orientations and conformations for the ligand at the binding site. Firstly, docking was performed with reference molecules of respective proteins to validate the docking protocol. The grid center for docking was set X= -12.71, Y= 17.14 and Z= 65.92 with dimensions of the grid box 11.68 × 24.95× 12.70Å for 6LU7. The grid center for 1R4L was set as X= 45.27, Y= 8.21, and Z= 32.65 with dimensions of the grid box 30 × 30 × 30Å. After validation of the docking protocol, virtual screening was conducted by rigid molecular docking into the active site of both proteins. Throughout the virtual screening, the ligand molecules were flexible and macromolecule was kept as rigid. Finally, the result of binding energy was extracted from the software. The best confirmation of the compounds which had lower binding energy as compared to the reference molecule was chosen for further analysis. Molecular interactions between protein-ligand complexes, including hydrogen bonds and the bond lengths, were analyzed and depicted by using Ligplot+ v.1.4.5 software.

Drug Likness Activity and AdmetSAR Prediction

The drug-likeness analysis was conducted to know any cytotoxicity to humans by DruLiTo tool; an open-source software. The pharmacological significance of a ligand is evaluated on various properties like drug bioavailability, drug-likeness or ADMET etc. These properties are calculated using certain physicochemical and structural properties. Therefore, all ligands were evaluated for its druglike nature under Lipinski's rules of five[8] by DruLiTo software.

Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) are pharmacokinetic properties of a ligand that deals primarily with its Absorption Distribution, Metabolism, Excretion, and Toxicity. The admetSAR server was used for analyzing the ADMET pharmacokinetic properties and mutagenic properties of screened compounds respectively.

Pharmacophore Study

Common pharmacophores of ligands responsible for biological activity were analyzed by

using PharmaGist web servers. All screened phytochemicals along with reference molecules were subjected for ligand-based pharmacophore studies.

Visualization

The analysis of 2D Hydrogen-bond interactions of the complex receptor-ligand structure was performed by LigPlot+ v.1.4.5 program to identify the interactions of an amino acid of a receptor with a ligand. LigPlot depicts hydrophobic bonds, hydrogen bonds, and their bond lengths in each docking pose in the form of graphical representation.

Results

Virtual Screening

Before the screening, the docking protocol was validated by re-docking the reference molecules into the binding pocket of the active site of Mpro and ACE2 structure. The result showed that the docked reference molecules were partially superimposed with the co-crystallized reference molecule. Thus, the protocol was considered well enough for reproducing the docking results similar to the X-ray crystal structure and was followed for virtual screening. Virtual screening resulted in the top 10 phytochemicals from each target showing significantly lower binding energy. The binding energy of phytochemicals with Mpro was -7.8 for Reference, -8.3 for Quercetin 3-vicianoside, -8.2 for Absinthin, -8.0 for Delphinidin 3-O-glucoside, -8.0 for Petunidin 3-O-glucoside, -7.9 for Quercetin 3-glucuronide-7-glucoside, -7.8 for Chrysoeriol 8-C-glucoside, -7.7 for Piperolactam A, -7.7 for Oleanolic acid, -7.7 for Schaftoside, -7.6 for Riboflavin. The binding energy of phytochemicals with ACE2 was -9.2 for Reference, -12.5 for Anabsinthin, -11.8 for Absinthin, -11.8 for 3,4,5-tricaffeoylquinic acid, -11.7 for 3-0-caffeoylquinic, -11.3 for Quercetin 3-glucuronide-7-glucoside, -11.2 for Isosakuranetin 7-O-neohesperidoside, -11.0 for Quercetin-7-O-galactoside, -11.0 for Quercetin 3-vicianoside, -10.9 for Dicaffeoylquinic acids, -10.9 for 3,5-Dicaffeoylquinic acid. Thus, the range of binding energy with Mpro was from -8.3 to -7.6 kcal mol^{-1} which was better and significant to reference molecule (-7.8 kcal mol^{-1}) and the range of binding energy with ACE2 was from -12.5 to -10.9 kcal mol^{-1} which was better to reference molecule (-9.2 kcal mol^{-1}).

Thus, lower binding energy of screened compounds shows a higher affinity for Mpro and ACE2 enzyme. These compounds were namely: Piperolactam A from *Piper Longum,* Quercetin 3-glucuronide-7-glucoside, Quercetin 3-vicianoside, Schaftoside, Chrysoeriol 8-C-glucoside, Isosakuranetin 7-O-neohesperidoside, Delphinidin 3-O-glucoside, Petunidin 3-O-glucoside from *Phaseolus Vulgaris,* Riboflavin from *Curcuma Longa* Oleanolic acid from *Ocimum Gratissimum,* 3-0-caffeoylquinic from *Syzygium Aromaticum,* Absinthin, Anabsinthin, and Dicaffeoylquinic acids from *Artemisia Absinthium* and Quercetin-7-O-galactoside, 3,5-Dicaffeoylquinic acid, and 3,4,5-tricaffeoylquinic acid from *Inula Helenium*.

Drug-Likeness and AdmetSAR Prediction

The results of DruLiTo software shows the molecular weight of phytochemicals are under 500, LogP value is under 5, the numbers of hydrogen bond acceptors are under 10, and several hydrogen bonds are donors under 5.27 phytochemicals were found to agree with Lipinski's rule of 5. Hence the screened phytochemicals follow Lipinski's rule of 5. However, seven compounds show 2 and three compounds show 3 and three compounds show 1 violation of Lipinski's rule (Table I)[9].

Table I illustrates the relative ADMET profiles of the screened phytochemicals as compared to both references. Log S refers to the solubility of the ligand that ideally ranges between -6.5 and 0.5. All the hit phytochemicals are showing Log S values between these ranges. Among all the screened ligands, Anabsinthin Log S value (-4.53) and Schaftoside has the maximum Log S value (-2.06). The permeability of the membrane can be assessed by CaCo-2 (colorectal carcinoma) and Blood-Brain Barrier permeability (BBB). The Caco-2 and BBB permeability value for all the hit phytochemicals was comparable to the reference molecule. The computational BBB value corresponds to its entry into the central nervous system. The acceptable range of BBB values for an ideal drug candidate ranges between -3.0 and 1.2[10]. All the phytochemicals have the BBB value under this ideal range. All phytochemicals clear the carcinogenicity test all are Non-carcinogenic in nature. All compounds have above 30% Human Intestinal Absorption (HIA) except Delphinidin 3-O-glucoside and Petunidin 3-O-glucoside compounds. If a compound with the HIA% is less than 30%, it is labeled as HIA- otherwise, it is labeled as HIA+.

Table I. Pharmacophore features and ADMET properties of screened phytochemicals.

S. No	Molecule	Pharmacophore features									ADMET properties					
		Atoms	Features	Spatial Features	Ar	Hydrophobic	HBD	HBA	-ve	+ve	BBB	HIA	Caco2	Carcinogens	LogS	Rule of 5 violation
1	PRD_002214	49	17	16	2	5	1	6	2	1	BBB -	HIA +	Caco2 -	NC	-3.0683	2
2	XX5	97	27	27	2	11	5	9	0	0	BBB -	HIA +	Caco2 -	NC	-3.5639	0
3	Piperolactam A	31	10	9	4	1	2	3	0	0	BBB +	HIA +	Caco2-	NC	-3.2807	0
4	Quercetin 3-glucuronide-7-glucoside	72	32	22	3	0	10	18	1	0	BBB -	HIA +	Caco2 -	NC	-2.6195	2
5	Quercetin 3-vicianoside	70	29	19	3	0	10	16	0	0	BBB -	HIA +	Caco2 -	NC	-2.2781	2
6	Schaftoside	68	27	17	3	0	10	14	0	0	BBB -	HIA +	Caco2 -	NC	-2.0699	2
7	Chrysoeriol 8-C-glucoside	55	22	15	3	1	7	11	0	0	BBB -	HIA +	Caco2 -	NC	-2.3024	2
8	Isosakuranetin 7-O-neohesperidoside	76	25	18	2	2	7	14	0	0	BBB -	HIA +	Caco2 -	NC	-2.4297	2
9	Delphinidin 3-O-glucoside	54	24	15	3	0	9	12	0	0	BBB -	HIA -	Caco2 -	NC	-2.5111	2
10	Petunidin 3-O-glucoside	57	24	16	3	1	8	12	0	0	BBB -	HIA -	Caco2 -	NC	-2.4040	2
11	Riboflavin	48	21	17	3	4	6	7	0	1	BBB -	HIA +	Caco2 -	NC	-3.6043	0
12	Oleanolic acid	80	40	31	0	35	1	3	1	0	BBB +	HIA +	Caco2 +	NC	-4.3883	1
13	3-0-caffeoylquinic	78	29	22	3	3	7	15	1	0	BBB +	HIA +	Caco2 -	NC	-2.7589	1
14	Absinthin	76	28	26	1	19	2	6	0	0	BBB +	HIA +)	Caco2 -	NC	-3.1191	0
15	Anabsinthin	76	24	23	1	16	1	6	0	0	BBB +	HIA +	Caco2 -	NC	-4.5306	0
16	Dicaffeoylquinic acids	60	23	17	2	2	6	12	1	0	BBB +	HIA +	Caco2	NC	-2.7589	1
17	Quercetin-7-O-galactoside	74	31	20	3	0	11	17	0	0	BBB -	HIA +	Caco2 -	NC	-2.1961	3
18	3,5-Dicaffeoylquinic acid	60	23	17	2	2	6	12	1	0	BBB +	HIA +	Caco2 -	NC	-2.7589	3
19	3,4,5-tricaffeoylquinic acid	78	29	22	3	3	7	15	1	0	BBB +	HIA +	Caco2 -	NC	-2.7589	3

*Ar- Aromatic, HBD- Hydrogen Bond Donor, HBA- Hydrogen Bond Acceptors, +ve- Positive, -ve- Negative, BBB- Blood-Brain Barrier, HIA - Human Intestinal Absorption, Caco2- Caco-2 Permeability, NC- Non-Carcinogens.

Pharmacophore Study

To analyze the important features of phytochemicals and reference molecules, we used the PharmaGist server. A set of structural features in molecules was recognized and found responsible for that molecule's biological activity in a receptor site. These structural features are known as pharmacophore features. The number of features and spatial feature set for each phytochemical from pharmacophore generation are summarized in Table I. These features are useful for binding with receptors. As compared to reference screened phytochemicals also have many spatial features that are responsible for binding with receptors.

Visualization

The 2D interactions of the screened ligands, as well as reference compounds, in the active sites of the receptor, were visualized by using LigPlot+ v.1.4.5 software (Figure 1). The reference molecule PRD_002214 of Mpro shows interaction with the several residues and forms three hydrogen bonds with Tyr54, Glu166 and Gln189 and fifteen hydrophobic bonds and yields the binding energy is -7.8 kcal mol^{-1}. Quercetin 3-vicianoside forms hydrogen bonds with His163, Glu166, Ser144, Leu1141, Gly143, and Thr26 while it shows hydrophobic bonds with Arg188, Asp187, Met165, His164, Gln189, His41, Thr25, Asn142, Phe140, and Cys145. Absinthin makes hydrogen bonds with His163 and Hydrophobic bonds with Ser144, Gly143, Cys145, Met49, Met165, Gln189, Pro168, Phe140, Glu166, and Leu141. Delphinidin 3-O-glucoside forms hydrogen bonds with His41, Met165, Thr26, and Phe140, and it shows hydrophobic bonds with Leu141, His163, Glu166, arg188, Gln189, Asp187, Thr25, His164, Leu27, GLy143, Asn142, and Ser144. Petunidin 3-O-glucoside makes interaction with hydrogen bonds

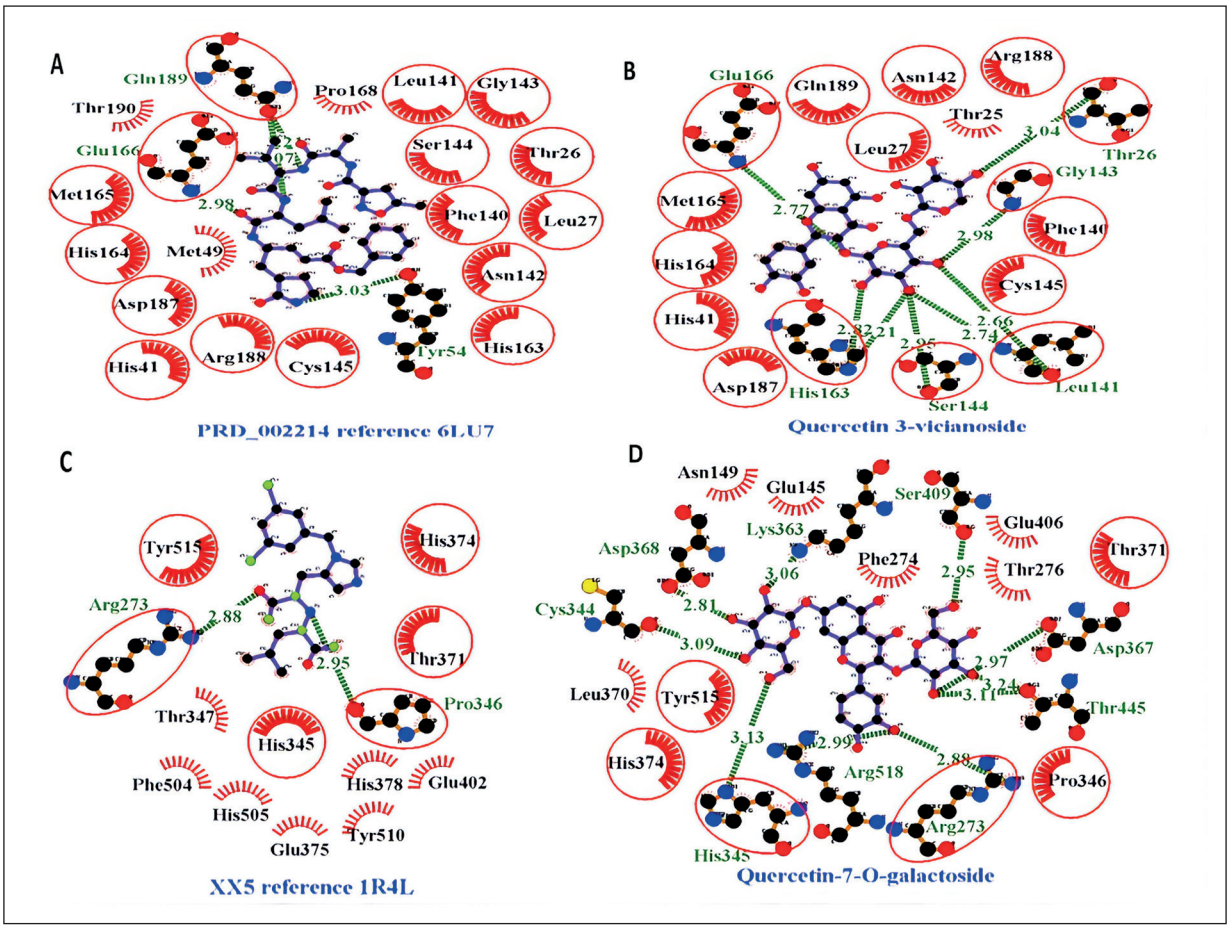

Figure 1. Depiction of hydrogen bonds and hydrophobic interactions by Lig plot between protein-ligand complexes. **A**, Interactions between Mpro and Reference molecule. **B**, Interactions between Mpro and ligand molecule. **C**, Interactions between ACE2 and Reference molecule. **D**, Interactions between ACE2 and ligand molecule.

via His41, Thr26, Phe140, and Glu166 while it shows hydrophobic bonds Cys145, Ser144, His163, Gln189, Met165, Arg188, Leu27, Gly143, Thr25, Asn142, and Leu141. Quercetin 3-glucuronide-7-glucoside shows interaction with His41, Phe140, Gly143, and Glu166 by making hydrogen bonds and show hydrophobic interaction with Thr190, Pro168, Leu141, Asn142, Leu27, His164, Met49, Met165, Cys145, Gln189, The25, and Arg188. Chrysoeriol 8-C-glucoside forms hydrogen bonds with Thr190, Glu166, and Phe140 and hydrophobic bonds with Met165, His41, Cys145, Arg188, Asn142, and Gln189. Piperolactam A interacts with Leu141, Gly143, ser144, Cys145, His163, and Gln189 by hydrogen bonds while it shows interaction with Thr25, Thr26, His41, Met49, Phe140, Asn142 and Met165 by hydrophobic bonds. Oleanolic acid form hydrogen bonds with Leu141, Ser144, and Cys145 and hydrophobic bonds with Gly143, Asn142, His164, Gln189, Met165, and Glu166. Schaftoside makes hydrogen bonds with Thr190, Glu166, Gly143, and Asn142, and it shows hydrophobic bonds with Thr25, Cys145, His41, Met49, Gln192, Met165, Gln189, Pro168, Thr26, Leu27, and Arg188. Riboflavin shows the interaction of hydrogen bonds with Leu141, ser144, Cys145, and His163, and it shows hydrophobic bonds with Gly143, His41, His164, Met165, Gln189, Glu166, and Asn142.

The Reference molecule XX5 of ACE2 shows interaction with the several residues and forms two hydrogen bonds with Arg273 and Pro346 and eleven hydrophobic bonds and yields the binding energy is -92 kcal mol^{-1}. Other phytochemicals Anabsinthin form hydrogen bond with Thr371 and hydrophobic bonds with Arg273, His345, Leu5.3, Trp271, Asp269, Asn149, Glu145, asp367, Thr876, Glu406, Phe274, Arg518, and Thr445. Absinthin makes interaction with Thr371, Thrr445, and Asp269 by hydrogen bond and it also makes interaction with Trp271, Pro346, Phe274, Arg518, Asp367, Thr276, Asn277, Ala153, and Asn149 by hydrophobic bonds. 3,4,5-tricaffeoylquinic acid makes hydrogen bonds with His378, Asp382, His345, Asn149, Asp368, Cys361, Arg273, Thr371, Arg518, Glu402, and Arg514 and also makes hydrophobic bonds Tyr510, Pro346, Trp271, Met360, Asp269, Cys344, Glu145, Phe274, Glu406, His374, Tyr515, and Glu375. 3-0-caffeoylquinic form interacts with Leu144, Cys361, Lys363, Glu145, Glu375, His345, and Pro346 by hydrogen bonds and while it shows interaction with Cys344, Ser128, Tyr127, Leu143, Thr129, Asn149, Trp271, Met360, Asp367, Phe274, Thr276, Thr371, Arg273, and His374 by hydrophobic bonds. Quercetin 3-glucuronide-7-glucoside forms hydrogen bonds with Asp368, Thr371, His345, Arg273, Tyr515, Asp382, His378, and Glu402 and it also shows hydrophobic bonds with Pro346, Glu375, Tyr510, Arg518, Glu400, His374, Phe274, Ser409, Thr445, Leu370, Thr276, Asp367, Phe504, Thr347, and His505. Isosakuranetin 7-O-neohesperidoside makes hydrogen bonds with Arg518, Thr371, Asp367, Glu406, His345, Pro346, and His374 while it also makes hydrophobic bonds with Tyr515, Leu370, Phe274, Cys344, Ser128, Glu145, Leu144, Tyr127, Asn149, and His505. Quercetin-7-O-galactoside form hydrogen bonds with Thr445, Arg518, Arg273, Asp368, Cys344, His345, Lys363, and Ser409 and it also forms hydrophobic bonds Thr276, Phe274, Tyr515, Thr371, His374, Pro346, Glu145, Asn149, Leu370, and Glu406. Quercetin 3-vicianoside forms hydrogen bonds with His374, Glu402, Tyr515, Lys363, Glu406, Arg518, His378, and Asp382 while it shows hydrophobic bonds with Arg514, Tyr510, Asp367, Leu370, Thr371, Phe874, Asn149, His345, and His505. Dicaffeoylquinic acids make hydrogen bonds with leu144, Tyr127, Thr129, Glu145, Cys361, and His345, and it also shows hydrophobic bonds withTrp271, Phe274, Asp367, Thr276, Pro346, Met360, Lys363, Cys344, Ser128, Leu143. 3,5-Dicaffeoylquinic acid makes interaction with Tyr127, Leu144, His345, Cys361, and Glu145 by hydrogen bonds and it also makes interaction with Thr276, Phe274, Thr129, Ser128, Leu143, Cys344, Met360, Lys363, Pro346, and Asp367 by hydrophobic bonds.

Discussion

Currently, Coronavirus has become a big challenge for every country. The outbreak of this virus is spreading worldwide and causing several deaths. As we know that no drugs are available for the prevention of the disease, we can use some natural products which can be helpful to stop the dissemination of Coronavirus and at the same time, they can enhance immunity. Natural products can be used both ways to prevent viral disease and stop the virus from spreading. Our study is based on specific targeting of Mpro and ACE2 to find novel compounds that can be used as a new drug against Coronavirus. Targeting Mpro can be efficient as it could stop the replication of viral

RNA while inhibiting ACE2 can lead to such structural changes which will not allow entering this virus inside the host cells[11]. Therefore, to find out novel compounds against Coronavirus, we prepared a phytochemicals library from 11 medicinal plants. These phytochemicals were subjected to molecular docking against two enzymes Mpro and ACE2. Based on molecular docking study, we found seven plants namely *Piper Longum, Phaseolus Vulgaris, Curcuma Longa, Ocimum Gratissimum, Syzygium Aromaticum, Artemisia Absinthium, Inula Helenium* which have such compounds showing better and significant binding energy against these receptors. *Phaseolus Vulgaris* has maximum phytochemicals which show binding with Mpro and ACE2. Many studies[12-14] have reported that *the Phaseolus Vulgaris* plant has antiviral activity against the Drosophila C virus, human immunodeficiency virus-1. Three phytochemicals Absinthin, Quercetin 3-glucuronide-7-glucoside, and Quercetin 3-vicianoside gave better binding energy with both the targets.

We have also compared pharmacophoric features of screened photochemical and reference compounds. The typical pharmacophore of a molecule consists of features like hydrophobic, aromatic, a hydrogen bond acceptor, a hydrogen bond donor, negative and positive functional groups[15]. The pharmacophore study revealed that the screened phytochemicals also have essential features as similar to the reference. The comparison of pharmacophore features shows that these compounds can be utilized as drug candidates against Coronavirus. Moreover, ADMET results show that these compounds have a non-carcinogen property for humans. As a suggestion since there are no effective drugs against Coronavirus, the infected people should keep the immune system healthy because a healthy immune system reduces the chance of viral infection and help the body to clear the virus rapidly. Many such medicinal plants are available which have antiviral, antibacterial and antifungal activity as well as these plants can enhance the immune system. The phytochemicals of these medicinal plants can be used against Coronavirus.

Conclusions

The present study was carried to discover novel inhibitor molecules against two enzymes Mpro and ACE2. Consequently, a library of 318 phytochemicals was analyzed by molecular docking techniques. The results of the top 10 ligands were compared with reference molecules of protein which demonstrates that these phytochemicals can bind more efficiently and act as inhibitors. Thus, we conclude that these phytochemicals can be utilized as potential antiviral candidates. These novel molecules could be utilized for further innovation and development of antiviral compounds against Coronavirus.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

The authors acknowledge the Department of Botany, Kumaun University, S.S.J Campus, Almora for providing basic facilities to conduct this research work. The authors also acknowledge Kumaun University, Nainital for providing high-speed internet facilities. We also extend our acknowledge to Rashtriya Uchchattar Shiksha Abhiyan (RUSA), Ministry of Human Resource Development, Government of India to provide Computational infrastructure for the establishment of Bioinformatics Centre in Kumaun University, S.S.J Campus, Almora, India.

The authors thank European Review for Medical and Pharmacological Sciences for allowing the quick publication of this article without a fee.

References

1) Huang C, Wang Y, Li X, Vijayalakshmi, P, Selvaraj, C, Rajalakshmi, M, Suveena, S. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.
2) Zhang DH, Wu KL, Zhang X, Deng SQ, Peng B. In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus. J Integr Med 2020; 18: 152-158.
3) Wit ED, van Doremalen NV, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol 2016; 14: 523-534.
4) Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS. J Virol 2020; 94: e00127-20.
5) Du L, He Y, Zhou Y, Liu S, Zheng BJ, Jiang S. The spike protein of SARS-CoV--a target for vaccine and therapeutic development. Nat Rev Microbiol 2009; 7: 226-236.
6) Towler P, Staker B, Prasad SG, Menon S, Tang J, Parsons T, Ryan D, Fisher M, Williams D, Dales NA, Patane MA, Pantoliano MW. ACE2 X-ray structures reveal a large hinge-bending motion important for

inhibitor binding and catalysis. J Biol Chem 2004; 279: 17996-18007.

7) Trott O, Olson AJ. Software news and update AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem 2010; 31: 455-461.

8) Leeson P. Drug discovery: chemical beauty contest. Nature 2012; 481: 455-456.

9) Joshi T, Joshi T, Sharma P, Chandra S, Pande V. Molecular docking and molecular dynamics simulation approach to screen natural compounds for inhibition of Xanthomonas oryzae pv. Oryzae by targeting peptide deformylase. J Biomol Struct Dyn 2020; 1-18.

10) Nisha C, Kumar A, Vimal A, Bai B, Pal D, Kumar A. Docking and ADMET prediction of few GSK-3 inhibitors divulges 6-bromoindirubin-3-oxime as a potential inhibitor. J Mol Graph Model2016; 65: 100-107.

11) Zhang JJ, Shen X, Yan YM, Wang Y, Xian Y. Discovery of anti-SARS-CoV-2 agents from commercially available flavor via docking screening. OSF Preprints 2020.

12) Ekowati H, Arai J, Damana Putri AS, Nainu F, Shiratsuchi A, Nakanishi Y. Protective effects of Phaseolus vulgaris lectin against viral infection in Drosophila. Drug Discov Ther 2017; 11: 329-335.

13) Kumar RV. Plant antiviral immunity against geminiviruses and viral counter-defense for survival. Front Microbiol 2019; 10: 1460.

14) Ye XY, Ng TB, Tsang PW, Wang J. Isolation of a homodimeric lectin with antifungal and antiviral activities from red kidney bean (Phaseolus vulgaris) seeds. J Protein Chem 2001; 20: 367-375.

15) Daisy P, Singh S, Vijayalakshmi P, Selvaraj C, Rajalakshmi M, Suveena S. A database for the predicted pharmacophoric features of medicinal compounds. Bioinformation 2011; 6: 167-168.