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Research Article

In Silico Identification of Flavonoids from Corriandrum sativum Seeds against Coronavirus Covid-19 Main Protease

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Abstract

Molecular docking analysis is routinely used in modern drug research to understand and predict the relationship between a drug molecule and a target protein from a microbe. The entry and replication of pathogens in host cells can be prevented by drugs identified in this way. The coronavirus disease associated with SARS-CoV-2, COVID-19, has become today's most infectious and lethal pandemic disease in the world. Burgeoning in the absence of any particular vaccine or therapeutic agent against SARS-CoV-2.The situation urges the need for appropriate medications to treat patients infected with the virus. Consequently, the study focus on evaluate the therapeutic potential of flavonoids present in *Corriandrum sativum* seeds that could serve as suitable remedies for COVID19.We analyzed the binding affinity of four flavonoids were screened against Mpro protein of SARS-CoV-2 by PyRx Virtual Screening tool and also results are validated with Lig-Plot Plus. Lopinavir shows binding affinity of -8.3 Kcal/mol and exhibit stable, strong interaction with active site of COVID19 main protease. Besides flavonoids, Rutin found to have the highest binding affinity compared to Lopinavir with the Mpro protease, followed by Chlorogenic acid, Quercetin and Caffeic acid. The present study concludes that Rutin present in the integrant of seeds shows the highest potentiality for acting as in inhibitor of main protease enzyme. Further, characterization of the amino acid residues comprising the viral binding site and the nature of the hydrogen bonding involved in the ligand receptor interaction shows significant findings with Rutin binding to the MPro protein at amino acid. The amino acid acid present in active sites of Mpro protease responsible for virus pathogenicity. The findings of the present study need in vivo experiments to prove the utility of Rutin compounds and further use in making *Corriandrum sativum* seeds as anti-SARS-CoV-2 product in near future.

Keywords: *Corriandrum sativum* seeds,Novel Coronavirus, SARS-CoV2, COVID-19, Protease, Molecular Docking.

INTRODUCTION

An outbreak of pneumonia of unknown origin was reported in Wuhan, Hubei Province, China[1]. Due to global spread of SARS-CoV-2 along with increased mortality caused by the coronavirus disease made the World Health Organization to declare a pandemic on 12 March 2020[1]. According to the report published by WHO, there have been 90,335,008 confirmed cases of COVID-19, including 1,954,336 deaths as of 13 January 2021[2]. Patients affected by SARS-CoV-2 infection have symptoms such as fever, dry cough, and excess sputum formation, congestion in upper respiratory tract and difficulty in breathing. It also reported some patients experiences symptoms such as headache, hemoptysis and diarrhea rarely[3]. COVID 19 considered as emerging infection originated from Wuhan, China and have been wide spread to more than 210 countries around the world including India[4].

Seven Coronaviruses (229E, NL63, OC43, HKU1, SARS, MERS and, COVID-19) was found to be infecting the human naturally. Four major viruses such as 229E-CoV, NL63-CoV, OC43-CoV, HKU1-CoV are responsible for causing mild upper respiratory infections.SARS-CoV, MERS-CoV, and COVID-19 viruses causes high mortality among humans[4]. The SARS-CoV-2 Virus has been isolated from asymptomatic individuals, and patients will be more infectious for two weeks even after cessation of symptoms[5].

SARS-CoV-2 Viruses is an enveloped, positive-sense; single stranded RNA beta-coronavirus belongs to coronaviridae family. The genome encodes for non-structural proteins like 3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase and structural proteins like spike glycoprotein. Still now, no chemotherapy or specific vaccines has yet been approved to treat human coronaviruses. To control or prevent emerging COVID-19 infections, various therapies can be envisaged including

vaccines, monoclonal anitibodies,oligonucleotide-based therapies, peptides, interferon therapies and small-molecule drugs[6]. Viral replication and transcription requires two overlapping proteins such as pp1a and pp1ab.Mpro (3c-like Protease) converts the p1a and pp1ab into functional polypeptide by extensive proteolytic processing. The functional importance of Mpro in the viral life cycle makes as a potential therapeutic target for design of antiviral drugs [7].

Naturally occurring compounds found to be an important source for the discovery and the development of novel antiviral drugs due to their availability and less side effects.Flavanoids possess significant antiviral activity against wide range of both DNA and RNA viruses. Many plant derived flavonoid found to be inhibiting various enzymes necessary for the viral life cycle [8].

Computational based screening has proven to be effective methods in order to meet the challenges in antiviral drug discovery. It is very easy in screening of natural or synthetic virtual compound libraries by computational methods. Natural compounds from plants serve as potential lead molecule for treating several human diseases [9]. Apart from antiviral activity, flavonoids also possess other important health protective effects such as anti-inflammatory, anti-cancer and antiviral properties. More than 6000 flavonoids have been structurally identified and divided into classes such as flavones, flavanols, flavins, isoflavones and anthocyanin's[10].

*Coriandrum sativum L.*also called Coriander or Chinese parsley is an annual or biennial herb belongs to umbelliferae family. It is traditionally used as folk medicines for treating various disorders of the digestive, respiratory and urinary systems, as well as diabetes, inflammatory disorders, insomnia, anxiety, convulsion and other diseases[11]. The seeds of the coriander were found to be rich in flavonoids such as Caffeic acid, Chlorogenic acid, Quercetin and Rutin. It also contains beneficial phytonutrients including, carvone, geraniol, limonene, borneol, camphor, elemol, and linalool [12]. Quercetin is a 5, 7-pentahydroxyflavone belongs to flavonoid family of glycoside rutin. It possess antiviral, anti-inflammatory, anti-proliferative, anti-oxidant, anti-bacterial, neuroprotective and hepatoprotective activity[13].

Based on the above properties of Corriandrum, the present study aimed for computational investigation of flavonoids present in *Coriandrum sativum* seeds against main protease found to be essential in the management of SARSCoV-2.

MATERIALS AND METHODS

Preparation of Protein

The X-ray crystallographic structure of main protease (Mpro, PDB ID 6LU7) of SARS-CoV-2 has been downloaded from the Protein Data Bank (PDB) (http://www.pdb.org.) database. Preparation of protein for docking simulation was achieved by using Graphical User Interface program "Auto Dock Tools (ADT) 1.5.6" (Molecular Graphics Laboratory tool or MGL tool) developed by Scripps Research Institute [14]. Receptor protein preparation for docking study was initiated by removing water molecules, hetero atoms and co-crystallized ligands from PDB crystal structure of protein 6LU7, polar hydrogen atoms along with Kollman united atom charges were added subsequently to the receptor protein and finally the receptor protein input file was saved as .pdbqt file[15, 16,17].

Preparation of ligands

The 3D structures of the natural products were obtained from PubChem Database (https://pubchem.ncbi.nlm.nih.gov). Respective CIDs of the natural and reference drug for Pubchem database are follows; Caffeic acid (CID: 689043), Chlorogenic Acid(CID: 1794427), Quercetin(CID: 5280343), Rutin (CID: 5280805) and Lopinavir (CID: 121304016).The MOL SDF format of these ligands were converted to PDBQT file by using PyRx tool. Open Babel tools were used for ligand energy minimization by using the force field uff; using conjugated gradients in 200 steps[18].

Active site identification

The active site of the protein was predicted by using Castp Server. It also measures the area, circumference of mouth openings of each binding site insolvent and molecular accessible surface. Protein was uploaded in the server in PDB format and its display the ligand binding sites bound in protein. Active sites with maximum surface area and maximum surface volume were selected and all the amino acid residues involved in binding with ligands were identified [19].

Compound screening using PyRx program

Molecular docking was performed by using PyRx 0.8 Virtual Screening Tool with AutoDock Vina as a docking engine. The Ligand was considered to be flexible and the protein was considered to be rigid during the molecular docking. COVID-19 main protease (Mpro) (PDB ID: 6LU7) were uploaded onto the program, and it was converted to .pdbqt format. Next, the ligands, Caffeic acid, Chlorogenic Acid, Quercetin, Rutin and Lopinavir were imported and all the compounds were converted into .pdbqt format. The Grid box was generated by covering the active site of the protein with coordination and box dimension. The exhaustiveness values were set to 8. Results were analyzed, value less than 1.0Å in positional root-mean-square deviation (RMSD) were considered ideal and favorable binding site was identified. Ligand showing the lowest binding affinity and ability to bind in the active site of the protein was chosen as best confirmation. The docked results are analyzed for possible interaction of protein with ligand such as hydrogen bonds, electrostatic interactions and hydrophobic interactions by using LIGPLOT[20].

Analysis and visualization

LIGPLOT + v.1.4.5 program were used to identify the interactions of an amino acid of a receptor with a ligand. It analysis the 2D Hydrogen-bond interaction of complex receptor-ligand structure. It depicts hydrogen bonds, hydrophobic bonds and their bond lengths in best docking pose in the form of graphical representation[21].

RESULTS

Virtual Screening

The binding energy of Lopinavir against Mpro was -8.3 Kcal/mol respectively (Table 2). We also estimated the binding energy of four flavonoids (Caffeic acid, Chlorogenic acid, Quercetin and Rutin) towards Mpro using PyRx Virtual Screening tool. The binding energies of flavonoids for Caffeic acid were -5.6, for Chlorogenic acid was-7.7, for Quercetin -7.5 and for Rutin -9.6 Kcal/mol. It was found that the binding energy of Caffeic acid, Chlorogenic acid and Quercetin was in the range of -5.3 to -7.5 kcal/mol which was much lower than standards, Lopinavir. On the contrary, -8.9 kcal/mol exhibited higher binding affinity towards Mpro compared to that of Lopinavir.As a whole, Rutin exhibit higher binding affinity compared to the standard.(Table1)

Table 1: Binding energy of and flavonoids of *Coriandrum sativum seeds* with Mpro along with Lopinavir inhibitor as standard.

Complex	Binding energy (kcal/mol)
Lopinavir	-8.3
Caffeic Acid	-5.7
Chlorogenic acid	-7.0
Quercetin	-7.6
Rutin	-9.6

Visualization

The 2 D interaction of the screened ligands, along with the reference compounds, in the active site of the receptor, was visualized by using Lig-Plot software (Table 2) (Figure 1-5).

The Standard drug Lopinavir of Mpro shows interaction with several amino acid residues and forms two hydrogen bonds with Gly143 and Gln189.It exhibit hydrophobic bonds with remaining sixteen amino acids in active region (Figure 2A). Caffeic acid forms hydrogen bonds with Leu 141, Gly143, Cys145 and His163 while it shows hydrophobic bonds with Phe140, Asn142, Met165, Glu166 and Gln189 **(**Figure 2B**).**Chlorogenic acid make hydrogen bond with Leu141, Gly143, Ser144, His163, Glu166, Arg188, Thr190 and Gln192 and hydrophobic bonds with Phe140, Asn142, Cys145, His164, Met165, Pro168, Gln189 and His172 (Figure 2C**)**. Quercetin forms hydrogen bonds with Leu141, His163 and Gln189, and it shows hydrophobic interaction with His41, Met49, Phe140, Met165, Glu166, Asp187 and Asp188 (Figure 2D**)**. Rutin shows interaction with Thr26, Leu141, Gly143, Ser144, His163 and Glu166 by hydrogen bonds, while it shows interaction with Thr25, Leu27, His41, Met49, Phe140, Asn142, Cys145, His164, Met165, Asp187, Arg188, and Gln189 by hydrophobic bonds (Figure 2E**)**.

Table 2 Hydrogen bond interactions of Lopinavir and flavonoids of *Coriandrum sativum seeds* with the SARS CoV-2 Mpro.

Complex	Number of H-bonds	Amino acids of Mpro involved in H-bonding	Hydrogen bond distance (Å)
Lopinavir	2	Gly143	3.30 2.90
	2	Glu189	3.01
Caffeic Acid	2	Leu141	2.96 2.78
	3	Ser144	2.94 2.98 3.19
	1	Gly143	3.15
	1	Cys145	3.30
	1	His163	2.98
Chlorogenic acid	2	Leu141	3.07 3.22
	1	Gly143	3.17
	1	Ser144	3.26
	1	His163	3.04
	1	Glu166	2.99
	1	Arg188	2.90
	2	Thr190	2.80 3.06
	1	Gln192	2.94
Quercetin	1	Leu141	2.86
	1	His163	3.13
	1	Gln189	2.95
Rutin	3	Thr26	2.79 2.88 2.91
	3	Leu141	2.90 2.97 3.20
	1	Gly143	3.04
	1	Ser144	2.89
	1	His163	3.03
	1	Glu166	3.34

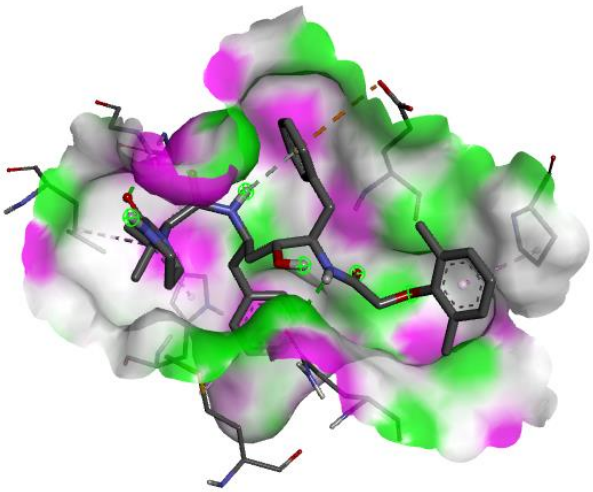


Figure 1: Molecular interaction between Lopinavir and Main Protease Protein of SARS-CoV-2

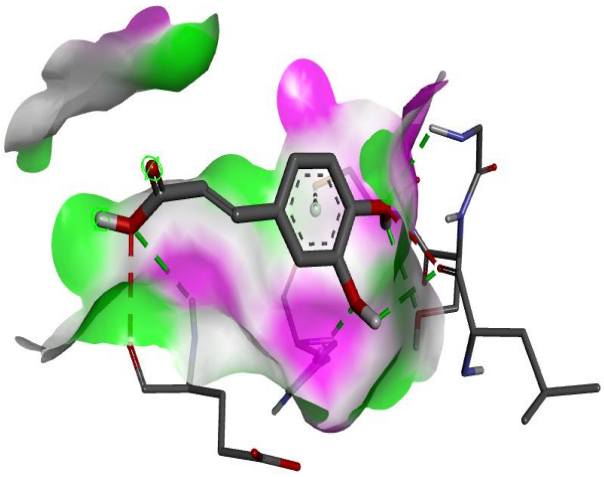


Figure 2: Molecular interaction between Caffeic Acid and Main Protease Protein of SARS-CoV-2

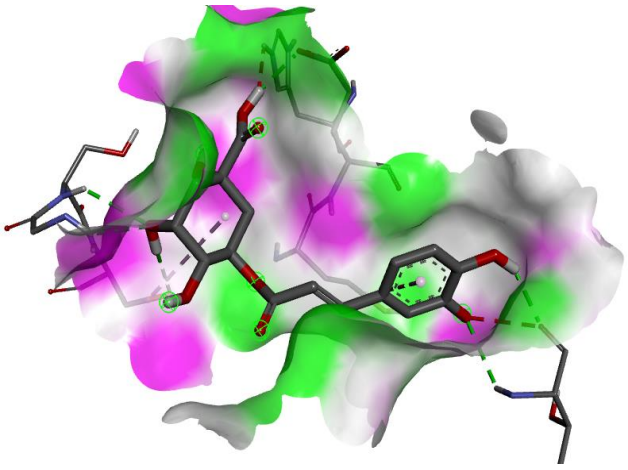


Figure 3: Molecular interaction between Chlorogenic acid and Main Protease Protein of SARS-CoV-2

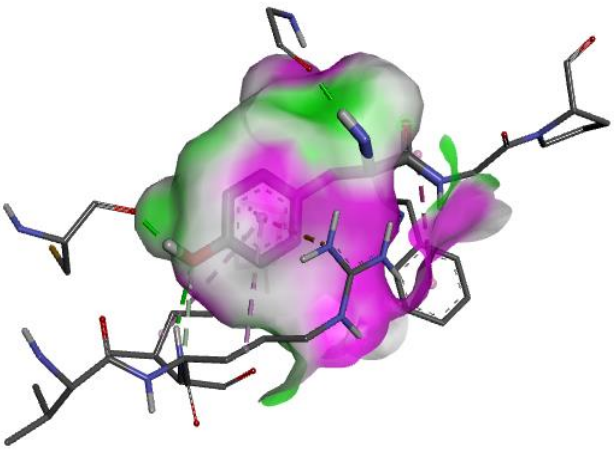


Figure 4: Molecular interaction between Quercetin and Main Protease Protein of SARS-CoV-2

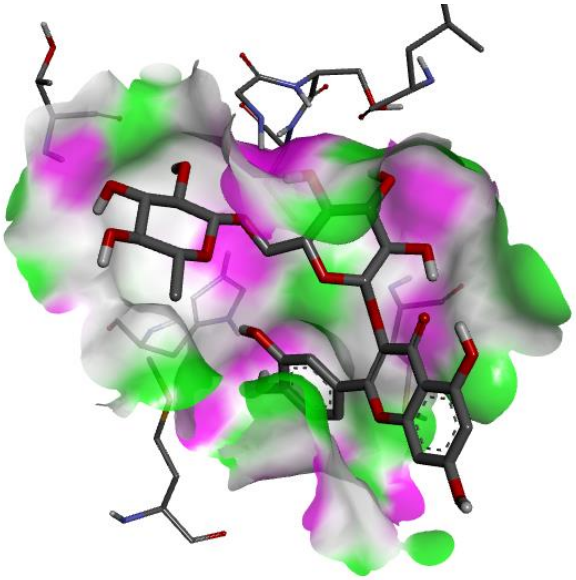
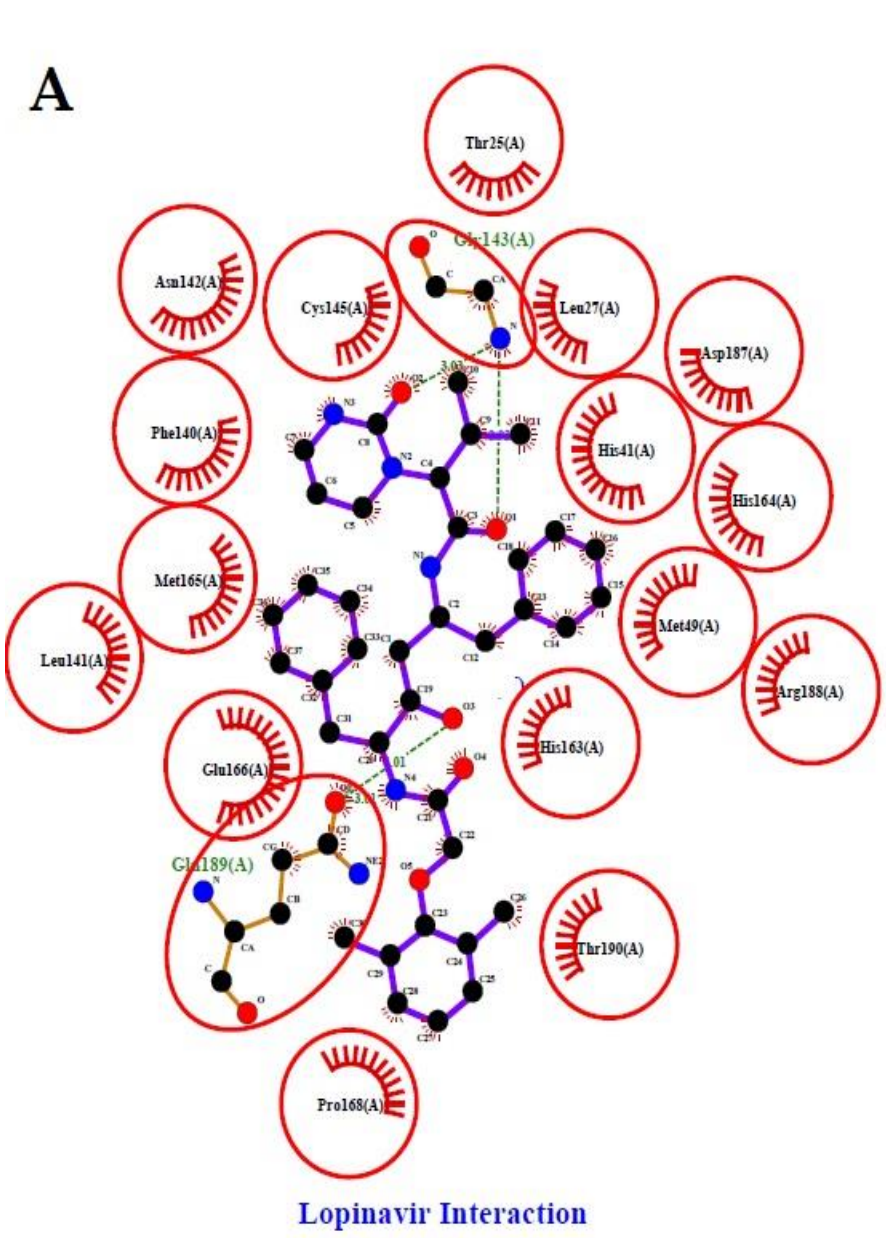
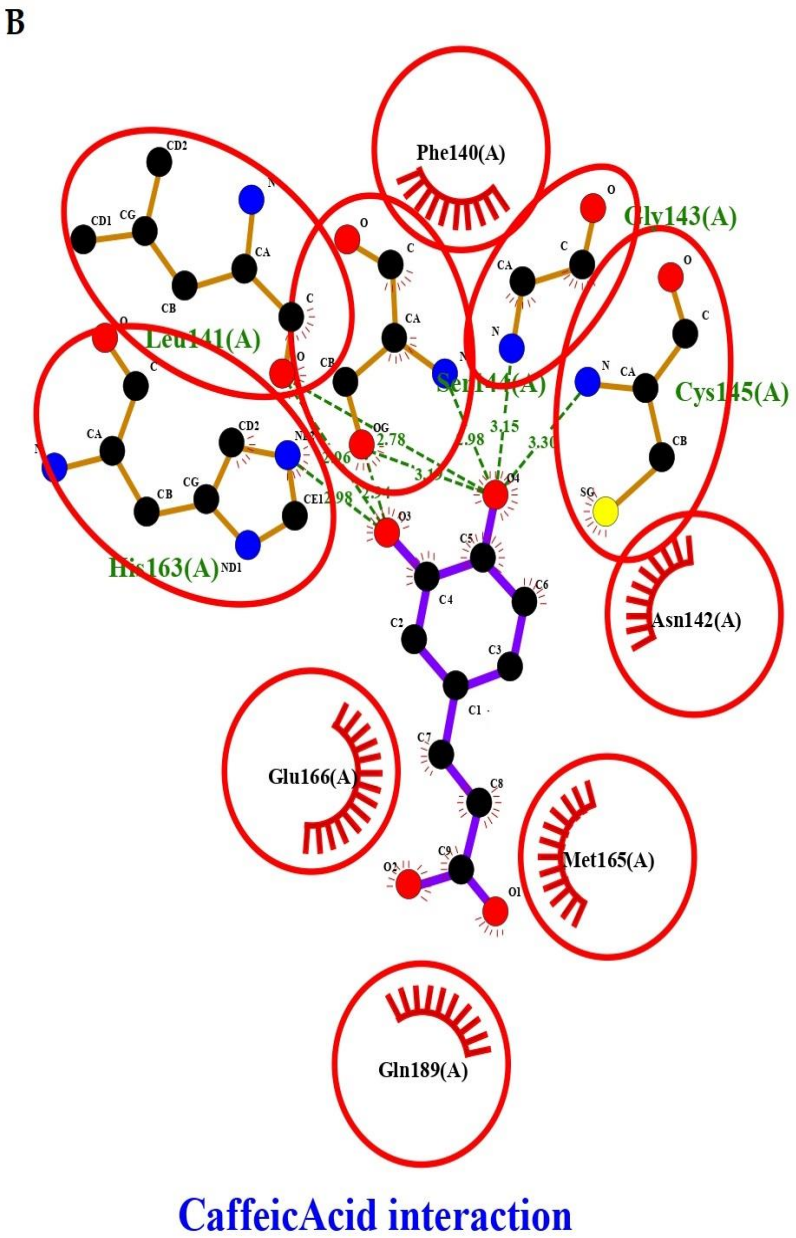
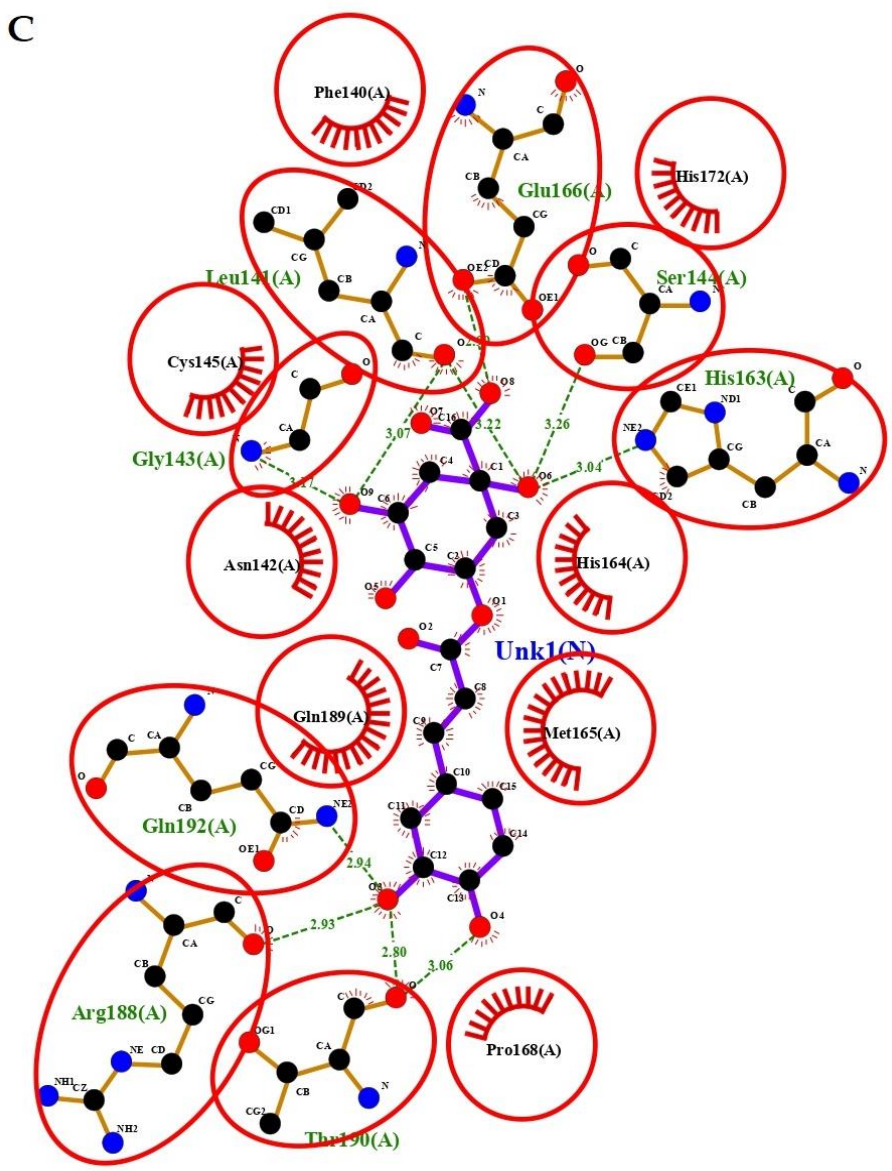


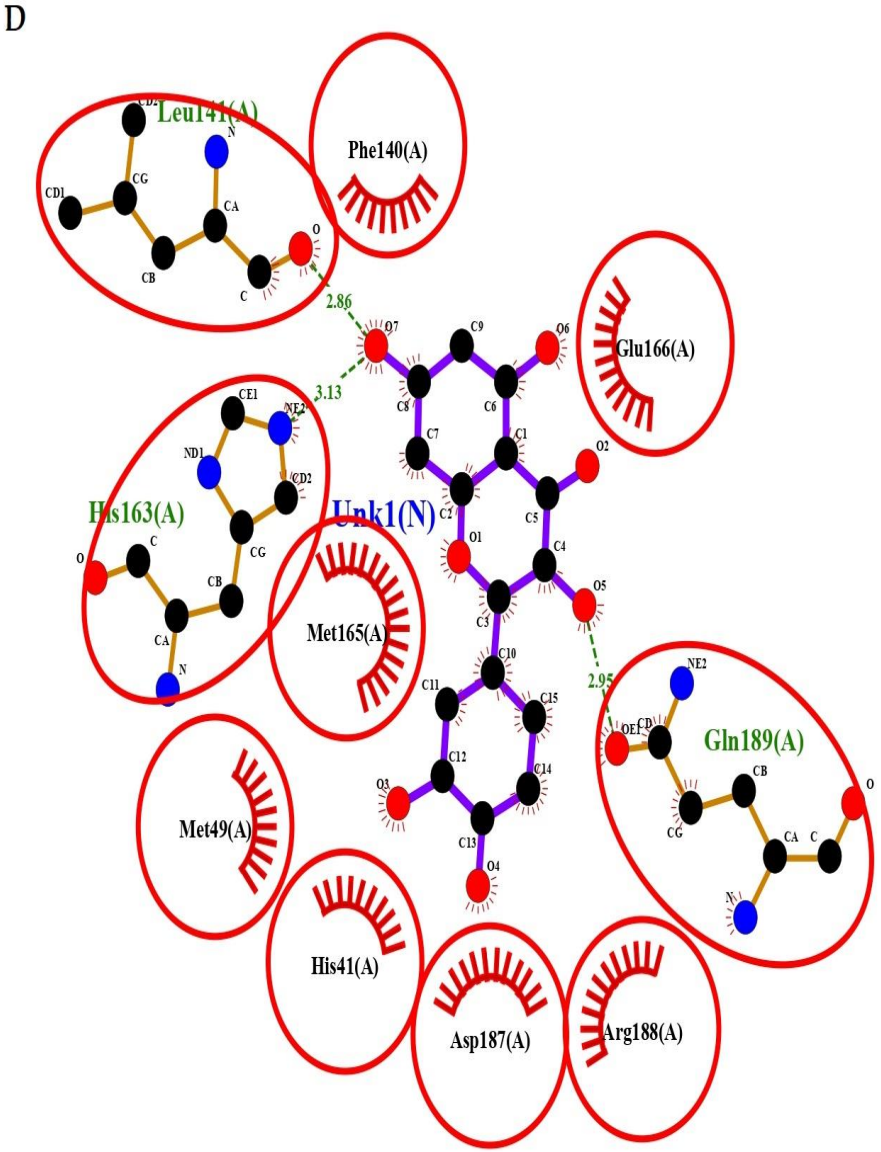
Figure 5: Molecular interaction between Rutin and Main Protease Protein of SARS-CoV-2


A
Thr25(A)
Gly143(A)
Asn142(A)
Cys145(A)
Leu27(A)
Asp187(A)
Phe140(A)
His41(A)
His164(A)
Met165(A)
Leu141(A)
Met49(A)
Arg188(A)
His163(A)
Glu166(A)
Gln189(A)
Thr190(A)
Pro168(A)
Lopinavir Interaction


B
Phe140(A)
Gly143(A)
Leu141(A)
Ser144(A)
Cys145(A)
His163(A)
Asn142(A)
Glu166(A)
Met165(A)
Gln189(A)
CaffeicAcid interaction



Cholegenic Acid interaction



Quercetin Interaction

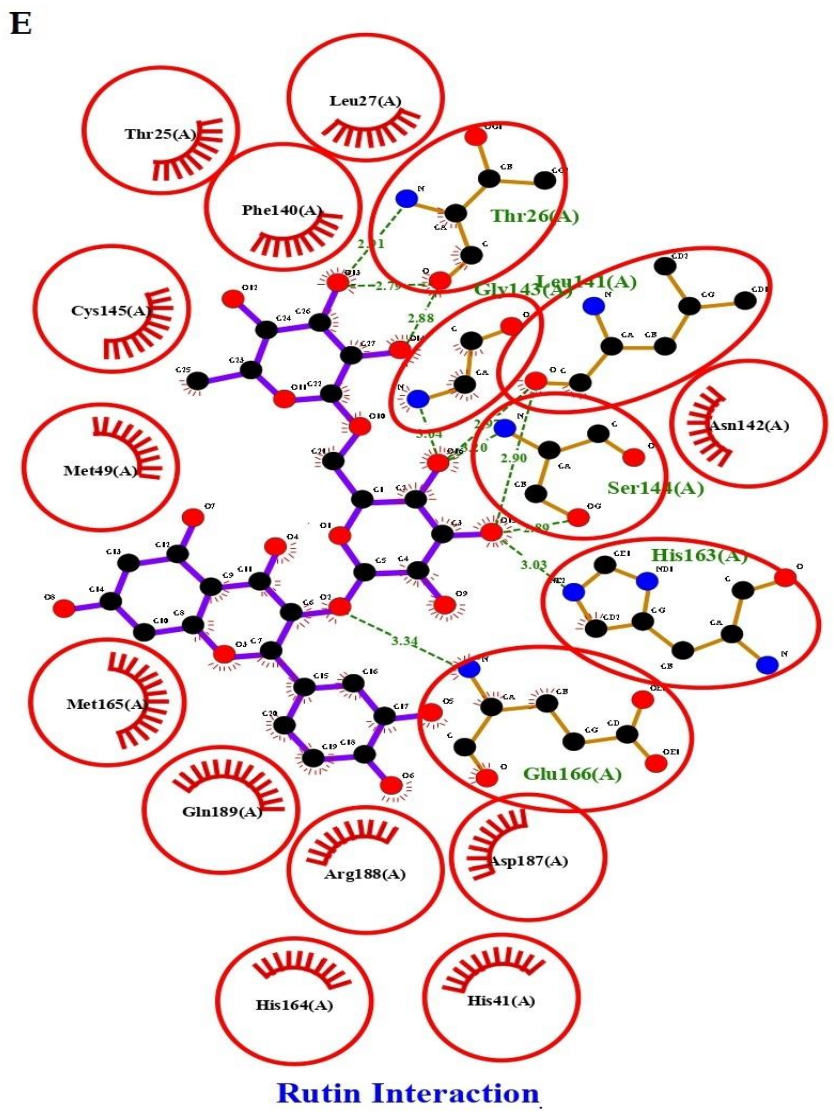


Figure 6: Molecular interactions and Two dimensional representations of H-bonds and hydrophobic interactions of selected compound with M Pro receptor using LigPlot and Biovia Discovery studio. (A) Lopinavir (B) Caffeic Acid (C) Chlorogenic acid (D) Quercetin (E) Rutin. Ligands are colored and represented in purple color, H-bonds are displayed in green dotted lines, red stellations represents hydrophobic interactions, and bonds of proteins are shown in red color.

DISCUSSION

COVID-19 Infection has been wide spread in nearly 210 countries with nearly 9 million confirmed cases and 1 million deaths. Fatality rate found to be lower in Asian region compared to European, American, or the world. In view of this, we considered the food habits of people and found a few popular medicinal ingredients in India and some neighboring countries that are currently used in food preparation[22]. For their antiviral activity against SARS CoV-2 virus, several drug candidates have been evaluated. But recent experiments have used chemical libraries to detect better SARS-CoV-2 virus drug candidates with limited success.

The Mpro in CoV is important to the virus's proteolytic maturation and has been investigated as a possible target protein to prevent infection from spreading by inhibiting the viral polyprotein cleavage. Different diseases can lead to the disruption of protease activity; host proteases can thus usually be used as potential therapeutic targets. Proteases play an important role in viral replication in many viruses, so proteases are also used as protein targets during the production of antiviral therapeutics.Nelfinavir and Lopinavir are high-cytotoxic protease inhibitors against HIV-infected cells. Lopinavir and Ritonavir are protease inhibitors that have similar modes of action to HIV and are recommended for the treatment of SARS and MERS.

Corriandrum sativum seeds are one of the common ingredients that are used routinely in lifestyle. Based on the literature, we selected to evaluate the antiviral potential of flavonoids present in the seeds against COVID-19 infection. Among four ligands, PyRx tool identified the best fitting ligand Rutin followed by Quercetin**,** chlorogenic acid and Caffeic acid towards Mpro protein. These compounds are having a better binding with Mpro protein in the form of hydrogen bonding and hydrophobic bonds. The compound Rutin is binding with MPro protein with six amino acid through H-bonding.

Quercetin, 3, 3′, 4′, 5, 7-pentahydroxy flavone, is widely distributed bioflavonoids in the plants and it is a common constituent found in fruits and vegetable. It have been identified by *invitro* studies that Quercetin able to block SARS-Coronavirus entry into Vero E6 cells [23,24].

Rutin (3.3', 4', 5, 7-pentahydroxyflavone-3-rhamnoglucoside) is a flavonol abundantly present in plants such as passion flower, buckwheat, tea, and apple. It is a crucial nutritional part of food items. It has been proven that rutin exhibit anti-retroviral activity against HIV viruses by blocking the viral entry and viral cell-fusion[25]. It has been proven that rutin exhibit antiretroviral activity against HIV viruses by blocking the viral entry and viral cell-fusion. The highest affinity of the drug is depending on the type and amount of bonding occurs with the active site of the protein. Rutin shows highest affinity towards Mpro protein by forming many chemical bonds including hydrogen and hydrophobic bond.

The present study investigate the potential binding efficiency of common food constituents by molecular docking and to further elucidate the participation of amino acids of Mpro protein during ligand binding. This study found that among the tested flavonoids, rutin was the most potent ligand against the Mpro protein, based on having the lowest ligand binding energy.

Global Scientific community primarily focusing on discovery and development of antiviral drugs rather than finding any compounds that can able to unregulate the immune system. This *Corriandrum sativum* seeds possess many nutritional value mainly involved in modulating both adaptive and innate immunity. Compounds used for the treatment of disease should also have certain additional immune regulatory roles

CONCLUSION

The molecular docking analyses helped to evaluate the probable binding modes of four flavonoids with the Mpro protein. Among the tested compounds, Rutin, found to be potential constituent of *Corriandrum sativum* seeds, possess highest binding affinity to this protein. Therefore, routine intake of seeds in the diet might help the people to protect against COVID-19. Moreover, *in vivo* studies should be carried out in order to validate the results and for developing more potent drugs for the control of COVID19.

Declaration of interest: The authors declare that they have no conflict interest

REFERENCES

1. Ciotti M, Ciccozzi M, Terrinoni A, Jiang W-C, Wang C-B, Bernardini S. The COVID-19 pandemic. Crit Rev Clin Lab Sci [Internet]. 2020 Aug 17 [cited 2021 Jan 20];57(6):365–88. Available from: https://www.tandfonline.com/doi/full/10.1080/10408363.2020.1783198
2. WHO Coronavirus Disease (COVID-19) Dashboard | WHO Coronavirus Disease (COVID-19) Dashboard [Internet]. [cited 2021 Jan 21]. Available from: https://covid19.who.int/
3. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, et al. Virology, epidemiology, pathogenesis, and control of covid-19 [Internet]. Vol. 12, Viruses. MDPI AG; 2020 [cited 2021 Jan 20]. Available from: https://pubmed.ncbi.nlm.nih.gov/32230900/
4. Kaushik S, Kaushik S, Sharma Y, Kumar R, Yadav JP. The Indian perspective of COVID-19 outbreak [Internet]. Vol. 31, VirusDisease. Springer; 2020 [cited 2021 Jan 20]. p. 146–53. Available from: https://pubmed.ncbi.nlm.nih.gov/32368570/
5. Dashraath P, Wong JLJ, Lim MXK, Lim LM, Li S, Biswas A, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol [Internet]. 2020 Jun 1 [cited 2021 Jan 20];222(6):521–31. Available from: https://pubmed.ncbi.nlm.nih.gov/32217113/
6. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV) [Internet]. Vol. 19, Nature reviews. Drug discovery. NLM (Medline); 2020 [cited 2021 Jan 21]. p. 149–50. Available from: https://pubmed.ncbi.nlm.nih.gov/32127666/
7. Jin Z, Du X, Xu Y, Deng Y, Liu M, Zhao Y, et al. Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors. Nature [Internet]. 2020 Jun 11 [cited 2021 Jan 21];582(7811):289–93. Available from: https://pubmed.ncbi.nlm.nih.gov/32272481/
8. Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: An overview [Internet]. Vol. 2013, The Scientific World Journal. ScientificWorld Ltd.; 2013 [cited 2021 Jan 21]. Available from: https://pubmed.ncbi.nlm.nih.gov/24470791/
9. Adem S, Eyupoglu V, Sarfraz I, Rasul A, Ali M. Identification of Potent COVID-19 Main Protease (Mpro) Inhibitors from Natural Polyphenols: An in Silico Strategy Unveils a Hope against CORONA [Internet]. Preprints; 2020 [cited 2021 Jan 21]. Available from: https://doi.org/10.20944/preprints202003.0333.v1
10. Ninfali P, Antonelli A, Magnani M, Scarpa ES. Antiviral properties of flavonoids and delivery strategies. Nutrients [Internet]. 2020 Sep 1 [cited 2021 Jan 21];12(9):1–19. Available from: https://pubmed.ncbi.nlm.nih.gov/32825564/
11. Wei JN, Liu ZH, Zhao YP, Zhao LL, Xue TK, Lan QK. Phytochemical and bioactive profile of Coriandrum sativum L. [Internet]. Vol. 286, Food Chemistry. Elsevier Ltd; 2019 [cited 2021 Jan 21]. p. 260–7. Available from: https://pubmed.ncbi.nlm.nih.gov/30827604/
12. Vo A. International Journal of Basic and Applied Sciences Reverse phase HPLC for the detection of flavonoids in the ethanolic extract of Coriandrum sativum L. seeds. Int J Basic Appl Sci [Internet]. 2012 [cited 2021 Jan 21];1(1):21–6. Available from: www.crdeep.org
13. Omrani M, Keshavarz M, Nejad Ebrahimi S, Mehrabi M, McGaw LJ, Ali Abdalla M, et al. Potential Natural Products Against Respiratory Viruses: A Perspective to Develop Anti-COVID-19 Medicines. Front Pharmacol [Internet]. 2021 Feb 17 [cited 2021 Mar 5];11:2115. Available from: https://www.frontiersin.org/articles/10.3389/fphar.2020.586993/full
14. Chhetri A, Chettri S, Rai P, Mishra DK, Sinha B, Brahman D. Synthesis, characterization and computational study on potential inhibitory action of novel azo imidazole derivatives against COVID-19 main protease (Mpro: 6LU7). J Mol Struct [Internet]. 2021 Feb 5 [cited 2021 Jan 22];1225. Available from: https://pubmed.ncbi.nlm.nih.gov/32963413/
15. Meng X-Y, Zhang H-X, Mezei M, Cui M. Molecular Docking: A Powerful Approach for Structure-Based Drug Discovery. Curr Comput Aided-Drug Des [Internet]. 2012 Nov 11 [cited 2021 Jan 22];7(2):146–57. Available from: https://pubmed.ncbi.nlm.nih.gov/21534921/
16. Ferreira LG, Dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies [Internet]. Vol. 20, Molecules. MDPI AG; 2015 [cited 2021 Jan 22]. p. 13384–421. Available from: https://pubmed.ncbi.nlm.nih.gov/26205061/
17. Khan T, Lawrence AJ, Azad I, Raza S, Khan AR. Molecular Docking Simulation with Special Reference to Flexible Docking Approach. JSM Chem [Internet]. 2018 [cited 2021 Jan 22];6(1):1053. Available from: http://zinc.docking.org/
18. O'Boyle NM, Banck M, James CA, Morley C, Vandermeersch T, Hutchison GR. Open Babel: An Open chemical toolbox. J Cheminform [Internet]. 2011 Oct [cited 2021 Jan 22];3(10). Available from: https://pubmed.ncbi.nlm.nih.gov/21982300/
19. Latha MS, Saddala MS. Molecular docking based screening of a simulated HIF-1 protein model for potential inhibitors. Bioinformation [Internet]. 2017 Nov 30 [cited 2021 Jan 22];13(11):388–93. Available from: https://pubmed.ncbi.nlm.nih.gov/29225432/
20. Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. Methods Mol Biol [Internet]. 2015 [cited 2021 Jan 22];1263:243–50. Available from: https://pubmed.ncbi.nlm.nih.gov/25618350/
21. Wallace AC, Laskowski RA, Thornton JM. Ligplot: A program to generate schematic diagrams of protein-ligand interactions. Protein Eng Des Sel [Internet]. 1995 Feb [cited 2021 Jan 22];8(2):127–34. Available from: https://pubmed.ncbi.nlm.nih.gov/7630882/
22. Latha MS, Saddala MS. Molecular docking based screening of a simulated HIF-1 protein model for potential inhibitors. Bioinformation [Internet]. 2017 Nov 30 [cited 2021 Jan 23];13(11):388–93. Available from: https://pubmed.ncbi.nlm.nih.gov/29225432/
23. El-Saber Batiha G, Beshbishy AM, Ikram M, Mulla ZS, Abd El-Hack ME, Taha AE, et al. The pharmacological activity, biochemical properties, and pharmacokinetics of the major natural polyphenolic flavonoid: Quercetin [Internet]. Vol. 9, Foods. MDPI Multidisciplinary Digital Publishing Institute; 2020 [cited 2021 Jan 23]. Available from: /pmc/articles/PMC7143931/?report=abstract
24. Colunga Biancatelli RML, Berrill M, Catravas JD, Marik PE. Quercetin and Vitamin C: An Experimental, Synergistic Therapy for the Prevention and Treatment of SARS-CoV-2 Related Disease (COVID-19) [Internet]. Vol. 11, Frontiers in Immunology. Frontiers Media S.A.; 2020 [cited 2021 Jan 23]. p. 1451. Available from: /pmc/articles/PMC7318306/?report=abstract
25. Ganeshpurkar A, Saluja AK. The Pharmacological Potential of Rutin [Internet]. Vol. 25, Saudi Pharmaceutical Journal. Elsevier B.V.; 2017 [cited 2021 Jan 23]. p. 149–64. Available from: https://pubmed.ncbi.nlm.nih.gov/28344465/