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Molecular docking identification of plant-derived inhibitors of the COVID-19 main protease

COVID-19 cases increase at a high rate and become dangerous in recent months. As a consequence, some healthcare and research organizations are attempting to find an effective cure for the COVID-19 outbreak. Many natural products have been reported to have powerful activity against COVID-19 in recent research studies. The primary aim of this article is to establish natural bioactive compounds with suitable antiviral properties. Lui et al. have reported in their study that SARS-Cov-2 main protease is present in a crystalline structure known as a novel therapeutic drug target. It is important to inhibit SARS-Cov-2 main protease to stop the replication of viral proteins. In this study natural compounds were screened using molecular modeling techniques to investigate probable bioactive compounds that block SARS-Cov-2. From these studies many natural compounds were found to have the potential to interact with viral proteins and show inhibitory activity against COVID-19 main protease (Mpro) and these natural compounds were also compared to known antiviral drugs such as Saquinavir and Remdesivir. Besides that, additional research is needed before these potential leads can be developed into natural therapeutic agents against COVID-19 to fight the epidemic.

Keywords: Natural compounds, SARS-Cov-2, Efficacy, Drug target, Molecular modeling, Viral proteins, Mpro, Binding affinity.

List of Abbreviations

Mpro: Main Protease (Covid-19)
SARS-Cov-2: Severe Acute Respiratory Syndrome Coronavirus-2
WHO: World Health Organization
PDB: Protein Data Bank
SDF: Spatial Data File
3CLPro: 3-Chromotrypsin Like Protease
CASTp: Computed Atlas of Surface Topography of Proteins

Introduction

World Health Organization (WHO) declared that the novel coronavirus infection is pandemic, and this infection going high day by day in all regions of the world [1]. This pandemic caused by novel coronavirus, SARS-Cov-2 (Severe Acute Respiratory Syndrome Coronavirus-2) was firstly reported in Wuhan, (China) in December 2019 [2]. As world's population is growing high it leads to the occurrence of many chronic diseases as well as lifestyle-related diseases. So this problem can be overcome by focusing on traditional herbal medicines to enhance as well as improve quality of life [3]. Herbal medications are commonly used by most people because they have long-term safety, good efficacy, and low toxicity, and they have shown remarkable results in the treatment of a variety of viral infections. Still, there is no specific treatment against COVID-19 infection. So to control the spread of COVID-19 infection, many research works are carried out to find effective as well as preventive therapy against COVID-19 infection [4]. So that many researchers taking an effort to design new treatments to avoid COVID-19 infection for examining secondary metabolites obtained from plants by using

molecular docking to study inhibition of enzyme-like main protease (Mpro) as well chymotrypsin-like protease (3CL pro), which is responsible for viral infection [1, 5].

Molecular docking is one of the best approaches to design, develop, and evaluate new treatment. There are various new therapeutic techniques developed to find new entities, but protease enzyme inhibitor is one of the novel therapeutic strategies, which are selected from natural bioactive compounds to find out effective medicine with minimum side effects. In the present study we analyze ten ligands for their binding affinity [5]. Most of the selected ligands are essential parts of many edibles from India and other regions. They show efficacy against the COVID-19 6LU protease. The main motive of the present study is to find out the ability of these ligands to inhibit COVID-19 main protease and to design natural products that can be effective in the treatment of COVID-19 infection. Ligands selected for docking analysis are present in spices and show tolerable binding affinity with COVID-19 6LUT protease. Further, these ligands are compared with synthetic drugs having remarkable antiviral properties, such as Remdesivir and Saquinavir [6].

Molecular docking studies are generally used for the analysis of complex structures obtained by the interaction through ligand and target molecules. Three-dimensional structure and probable binding sites are determined by molecular docking methods. The molecular docking approach is commonly used to identify several binding interactions such as enzyme-substrate interaction, lipid-protein interaction, drug-enzyme interaction, etc [7, 8]. The molecular modeling technique is widely used in various structure-based drug designs (SBDD), because of its characteristic to determine actual binding conformation in ligand and target site. Because of its ability to generate accurate conformation between ligand and target, it is rapidly used to identify binding conformation in target and drug, and therefore it is an important tool in rational drug designing [9].

In the 1980s, the molecular docking technique constituted a crucial mechanism because of the development of 1st algorithm. Molecular modeling analysis particularly analyzes the binding affinity of the target molecule with ligand and based on this; it may help to suggest a potential treatment against a specific disease. In these cases in-silico approach of molecular docking become a faster technique. In silico approach helps to reduce the time and cost of the process for the identification of complex structures and binding techniques. So in drug discovery molecular docking with in silico approach becomes a very quick and common easy to apply method [10, 11]. In general molecular docking process is shown in Figure 1.

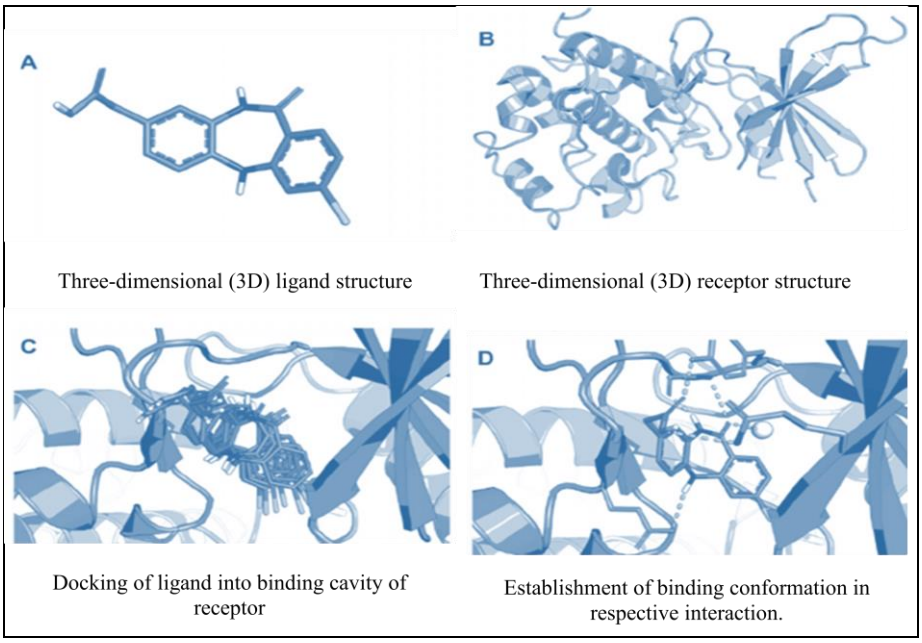


Figure 1. Molecular docking process in general

The software develops an algorithm, in which the conformation of the ligand is determined after performing docking analysis. The binding affinity resulted in a negative value of ΔG (in terms of units Kcal/mol). The binding energy shows a combination of Van der Waals as well as electrostatic energy, which concerning the interaction between ligand molecule and target molecule [14]. Also, in drug designing, the rigid system can be used, in which translational and rotational space in six dimensions can be identified for the fitting of ligand and particular binding structure. The research-based section represents a higher area of interest in molecular

modeling studies throughout recent decades. This is also true in the case of molecular modeling methods or computational methods for prediction [15].

The preliminary work in the area of molecular docking studies was initially performed using structural shape contacts and then Kuntz applied a shape matching strategy to identify potential conformations. After successful initiating work by Kuntz, various docking approaches were developed using Fourier transformations algorithms [16].

Types of docking analysis

Rigid body docking. In this type of molecular docking both molecule and receptor assumed as rigid. The occurrence of modifications in structure possesses degrees of freedom. This approach represents an example of Zdock [14].

Semi-flexible docking. This is the method of docking in which their improvement in a rigid body is docking for identification of side chains and potential torsion angles. This method of docking is different from the Fourier transformation method. This new transformation was obtained by the HADDOCK protocol [15].

Flexible docking. This type of docking uses two logarithmic approaches: systematic incremental plotting and stochastic. The first approach is commonly used to develop binding conformations based on the ligand position and binding in all possible areas. These are for example: DOCK [16], Flex [17], Glide [18], Hammerhead [19], LUDI [20], Surflex [21]. In stochastic algorithms, there is improvement in computational methods. These are, for example, DARWIN [22], GOLD [23], AutoDock [24], Carlo [25].

Experimental

Data collection. The structure of COVID-19 3CL pro or Mpro (Having PDB ID: 6LU7) were taken in PDB format from (https://www.rcsb.org/) [26]. Also, some part of this study was performed by the SwissDock web server [27, 28], which incorporates an automated in silico molecular docking procedure based on the EADock ESS docking algorithm [29]. The active binding sites of the protease enzyme were found by using the CASTp (http://sts.bioe.uic.edu/castp/index.html?3igg) [30].

Three-dimensional (3D) structures of the selected ligands were taken in SDF format from the https://pubchem.ncbi.nlm.nih.gov/ website [29]. A known anti-HIV drug Saquinavir was used as a positive control for comparative docking analysis.

Molecular Docking. The molecular docking studies analyze the mechanism of interaction between ligand and receptors. These mechanisms of interactions between ligand and receptor play a significant role in the case of drug discovery. In molecular modeling, docking analysis is a technique that is used to analyze stable complexes formed by the binding of two molecules and adaptation between them [31].

The protease file was prepared for COVID 19 6LU7 protease by using Autodock 4.2 [32]. Using A chain of protease, the macromolecule was produced by removal of a water molecule and addition of hydrogen bond. For further studies of analysis, the file was saved in PDBQT format. The calculation of binding affinity was done by using AutoDock–Vina [33]. The 3D structure of interaction between ligand and receptor was detected by using PyMOL [34].

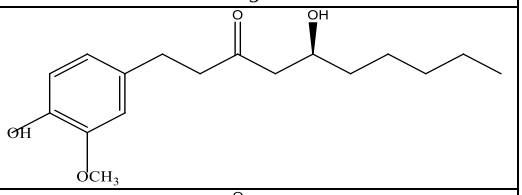
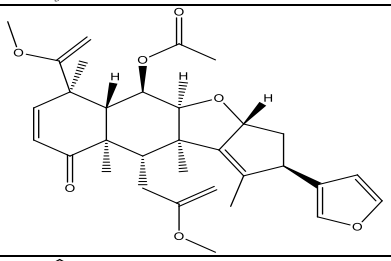
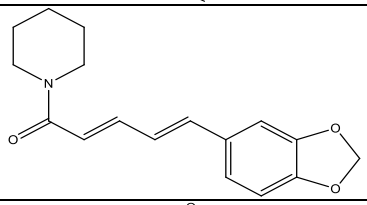
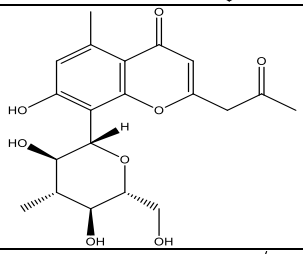
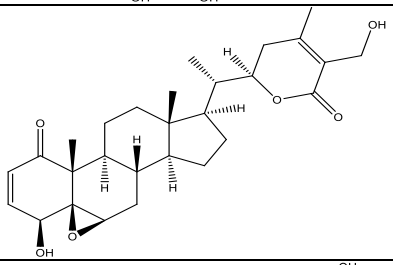
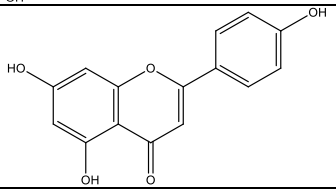
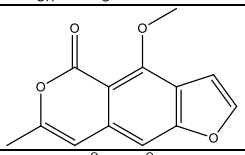
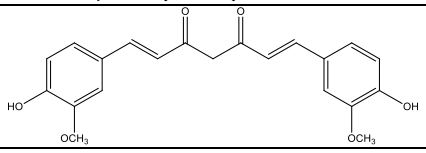
In this study we used flexible docking. Rigid-body docking, semi-flexible docking and flexible docking are three different types of docking procedures, but it was found that flexible-ligand docking shows significant results as compared to rigid body docking and semi-flexible docking

Results and Discussion

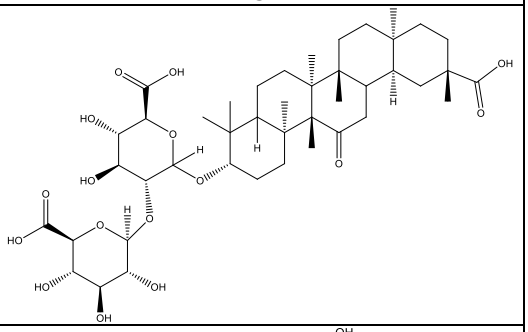
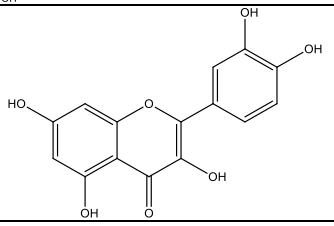
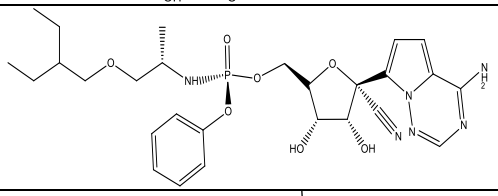
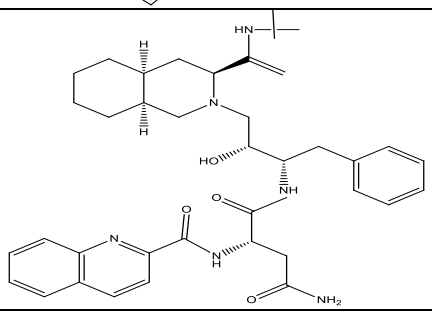
The present study is based on an analysis of ten selected bioactive compounds derived from Indian medicinal plants, and also there is a comparison of the herbal compound with known antiviral drugs based on binding affinity. The binding affinity of extracted bioactive compounds from plants with COVID-19 protease 6LU7 and their molecular structures are shown in Table [6, 35].

T a b l e

Representation of docking results including binding affinities of natural products

Compound	Ligand source	Molecular formula	Binding affinity	Structure
1	2	3	4	5
Gingerol	Ginger (*Zingiber officinale*)	$C_{17}H_{26}O_4$	–7.95	
Nimbin	Neem (*Azadirachta indica*)	$C_{30}H_{36}O_9$	–8.17	
Piperin	Black and white pepper (*Piper nigrum, Piper longum and Piper officinarum*)	$C_{17}H_{19}NO_3$	–6.98	
Aloesin	Aloe vera (*Aloe Ferox, Aloe barbadensis*)	$C_{19}H_{22}O_9$	–8.79	
Withaferin A	Ashwagandha (*Acnistus arborescens, Withania somnifera, and Withania somnifera Dunal*)	$C_{28}H_{38}O_6$	–8.05	
Apigenin	Apple (*Malus domestica*), Red pepper (*Capsicum annuum*), Thyme (*Thymus vulgaris*), Garlic (*Allium sativum*).	$C_{15}H_{10}O_5$	–7.8	
Coriandrin	Coriander (*Coriandrum sativum*)	$C_{13}H_{10}O_4$	–6.4	
Curcumin	Turmeric (*Curcuma longa*)	$C_{21}H_{20}O_6$	–7.0	

Continuation of Table

1	2	3	4	5
Glycyrrhizin	Licorice (*Glycyrrhiza glabra*)	$C_{42}H_{62}O_{16}$	–7.3	
Quercitin	Onion (*Allium cepa*), Buckwheat (*Fagopyrum esculentum*), Green tea (*Camellia sinensis*).	$C_{15}H_{10}O_7$	–7.3	
Remdesivir	Antiviral drug	$C_{27}H_{35}N_6O_8P$	−8.32	
Saquinavir	Anti-HIV drug	$C_{38}H_{50}N_6O_5$	–9.2	

Most of the selected bioactive products have anti-malarial, anti-viral and other similar activities [29]. The binding affinities of selected natural products range between –6.4 Kcal/mol (Binding affinity of Coriandrin) and –8.79 Kcal/mol (Binding affinity of Aloesin), as shown in Figure 2 [6, 35].

Coriandrin is categorized as essential oil derived from *Coriandrum sativum*. It is found in seed, stem, and leaf of *Coriandrum sativum* [36]. Coriandrin [$C_{13}H_{10}O_4$] possesses many therapeutic activities such as antiviral, antifungal, antioxidant, anthelmintic as well as anxiolytic [37].

The main bioactive constituent Aloesin ($C_{19}H_{22}O_9$) is derived from fresh leaves of aloe (*Aloe Ferox, Aloe barbadensis*) and also has antioxidant, antibacterial, anti-inflammatory, and immunomodulatory effects [35]. Glycyrrhizin, as well as licorice, is found in *Glycyrrhiza glabra*, which is a potential immunomodulator and has other therapeutic effects such as hepato-protective, neuroprotective, anti-inflammatory, antineoplastic activities; it shows binding affinity of –7.3 Kcal/mol with COVID-19 protease [38, 39]. A steroidal bioactive constituent of Ashwagandha Withaferin A ($C_{28}H_{38}O_6$) has antiviral and antibacterial activities and is obtained from *Acnistus arborescens, Withania somnifera, and Withania somnifera Dunal* and shows –8.05 Kcal/mol binding affinity with COVID-19 protease [40]. Curcumin is a primary bioactive compound found in turmeric which consists of curcuminoids as secondary metabolites which are extracted from dried rhizomes of *Curcuma longa* from *the Zingiberacea*e family. Curcumin ($C_{21}H_{20}O_6$) exhibits known anti-inflammatory, antimicrobial and antioxidant properties has –7.0 Kcal/mol binding affinity with protease [41].

Nimbin is a triterpenoid compound extracted from neem (*Azadirachta indica)* and it shows the binding affinity of –8.17 Kcal/mol with protease. Nimbin ($C_{30}H_{36}O_9$), which is a bitter compound, shows many biological activities such as potential antibacterial, antiviral, antipyretic, fungicidal, and anti-inflammatory activities [42]. Gingerols are phenolic and the most abundant pungent compounds present in ginger, show –7.95 Kcal/mol binding affinity with COVID-19 proteases. Gingerol is the main bioactive compound found in

Ginger (*Zingiber officinale)*, which belongs to the Zingiberaceae family. Gingerol ($C_{17}H_{26}O_4$) has powerful antioxidant and anti-inflammatory effects [41].

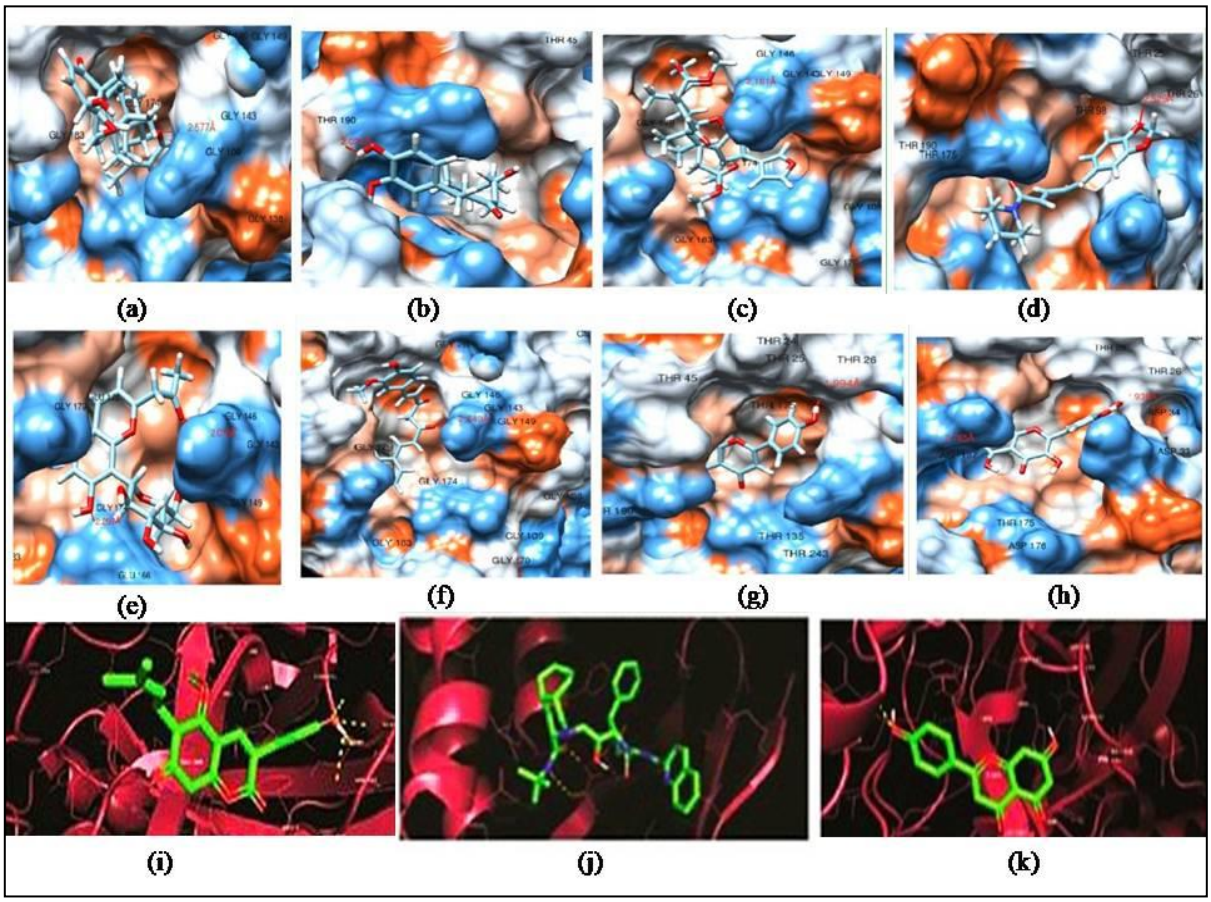


Figure 2. 3D visualization of docking analysis of 6LU7 protease binding with (*a*) Gingerol, (*b*) Nimbin, (*c*) Piperine, (*d*) Aloesin, (*e*) Withaferin, (*f*) Apigenin, (*g*) Curcumin, (*h*) Quercitin, (*i*) Coriandrin, (*j*) Glycyrrhizin, (*k*) Saquinavir

Apigenin is a flavonoid found in many plants Apple (*Malus Domestica*), Thyme (*Thymus vulgaris*), Chamomile (*Matricaria chamomilla*), Red pepper (*Capsicum annuum*), Garlic (*Allium sativum var. sativum*), etc [41]. It is a flavones class compound with a wide range of activities such as antiviral, antibacterial, antioxidant, and strong anti-inflammatory activities. Apigenin ($C_{15}H_{10}O_5$) shows –7.8 Kcal/mol binding affinity. Piperin is a pungent component found in black pepper and belongs to the vanilloid family of compounds [43]. Piperin is extracted from dried unripe fruit of black and white pepper (*Piper nigrum, Piper longum, and Piper officinarum*). Piperine ($C_{17}H_{19}NO_3$) has potent antioxidant, anti-inflammatory, and antitumor properties and shows greater (–6.98 Kcal/mol) binding affinity with COVID-19 protease [37], whereas quercitin has –7.3 Kcal/mol binding affinity with protease. Quercetin ($C_{15}H_{10}O_7$) is a flavonoid compound mainly found in onions, cherries, grapes, citrus fruits, which is obtained from various sources such as onion (*Allium cepa*), green tea (*Camellia sinensis*), apple (*Malus Domestica*), buckwheat (*Fagopyrum esculentum*) and possess antioxidant, antiviral, anticancer, cardiovascular, hepatoprotective and anti-inflammatory activities [41, 44].

Remdesivir is a known antiviral drug whereas saquinavir is an anti-HIV drug; both are subjected for analysis of binding affinity with COVID-19 protease by using a molecular docking approach. This study shows that Remdesivir ($C_{27}H_{35}N_6O_8P$) has –8.32 Kcal/mol and Saquinavir ($C_{38}H_{50}N_6O_5$) has –9.2 Kcal/mol binding affinity [45]. In summary, it shows that some of the selected natural products exhibit greater binding affinity with COVID-19 protease compared to known antiviral drugs, remdesivir and saquinavir [45, 46]. In this study we have conducted molecular docking studies used to identify the potential of herbal products which are isolated from plants. Substances taken for the study show inhibitory action of COVID-19 main protease [27]. We have studied 10 herbal drugs and their comparison with two reported antiviral drugs. Molecular docking analysis of these products helps to identify their binding potency with COVID-19 protease 6LU7 and their inhibition extent [6]. These docking studies show that some of the selected natural products show powerful inhibition

based on their binding affinities. Aloe vera shows a greater binding affinity among all selected herbal drugs. Also, other natural products such as glycyrrhizin, curcumin, coriandrin, and apigenin show potential inhibition of COVID-19 protease [47]. The plot of Binding affinity in comparison with natural compounds is shown in Figure 3.

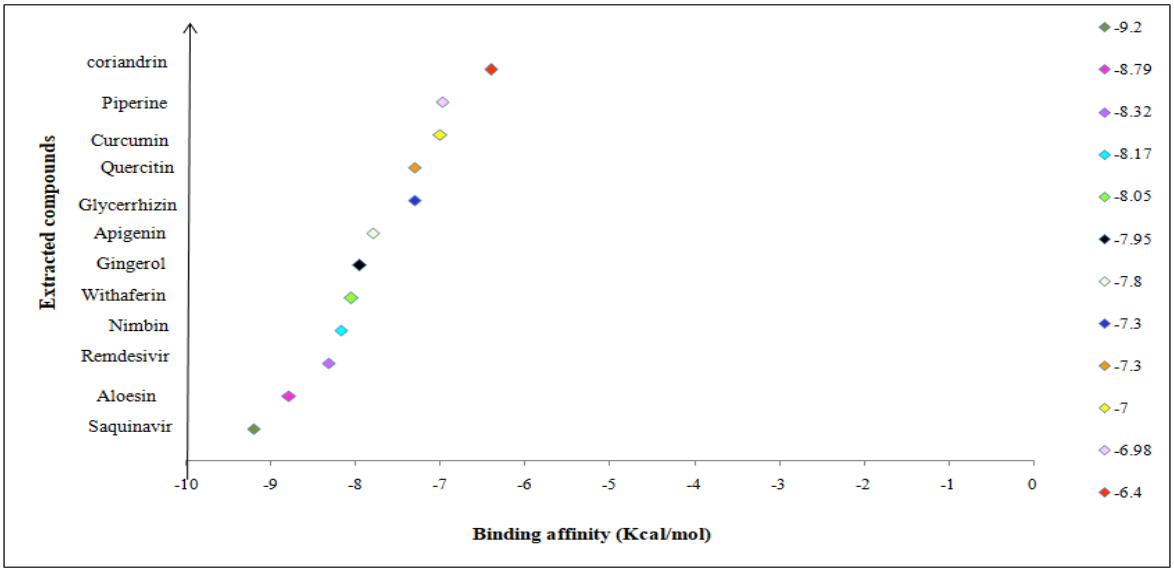


Figure 3. A plot of binding affinity extracted bioactive compounds from Indian herbal plants and a few drugs for comparison of inhibition potential against COVID-19 protease

Conclusions

All of these natural bioactive compounds are biologically safe and have a high binding potential. Saquinavir is already reported as an anti-HIV drug for inhibition of replication of SARS-Cov-2 protease, also Remdesivir is known for inhibition of replication of protease but it has reported hepatotoxicity in some patients. Docking studies show that some of the selected natural extracts show greater COVID-19 protease inhibition potential compared to these known antiviral drugs. Some of the identified natural products show promising results in these studies and may require additional investigation. Because they are safer than synthetic drugs, these natural medicines can be used as important alternatives to synthetic treatments in the prevention of COVID-19 infection. These findings could become a significant starting point for drug development and provide great promise to develop potent therapeutics against COVID-19 infection.

References

1 Adem, S., Eyupoglu, V., Sarfraz, I., Rasul, A., & Ali, M. (2020). Identification of Potent COVID-19 Main Protease (Mpro) Inhibitors from Natural Polyphenols: An in Silico Strategy Unveils a Hope against CORONA. *Preprints*. https://doi.org/10.20944/preprints202003.0333.v1

2 Narkhede, R.R., Pise, A.V., & Cheke, R.S. et al. (2020) Recognition of Natural Products as Potential Inhibitors of COVID-19 Main Protease (Mpro): In-Silico Evidences. *Nat. Prod. Bioprospect.*, 10, 297–306. https://doi.org/10.1007/s13659-020-00253-1

3 Rodríguez-Morales, A.J., MacGregor, K., Kanagarajah, S., Patel, D., & Schlagenhauf, P. (2020) Going global — Travel and the 2019 novel coronavirus. *Travel Med Infect. Dis*., 33, 101578. https://dx.doi.org/10.1016 %2Fj.tmaid.2020.101578

4 Medicinal plants and primary health care: part 2. (1991) Essent Drugs Monit, WHO (11):15–17.

5 Gideon A. Gyebi, Olalekan B. Ogunro, Adegbenro P. Adegunloye, Oludare M. Ogunyemi & Saheed O. Afolabi (2021). Potential inhibitors of coronavirus 3-chymotrypsin-like protease ($3CL^{pro}$): an *in silico* screening of alkaloids and terpenoids from African medicinal plants, *Journal of Biomolecular Structure and Dynamics*, 39:9, 3396–3408. https://doi.org/10.1080/07391102.2020.1764868

6 Sampangi-Ramaiah, M.H., Vishwakarma, R., & Shaanker, R.U. (2020) Molecular docking analysis of selected natural products from plants for inhibition of SARS-CoV-2 main protease. *Current Science*.; 118(7):1087-92.

7 Alejandra Hernández-Santoyo AYT-B, Altuzar V, Vivanco-Cid H, & Mendoza-Barrera C. (2013). Protein-protein and protein-ligand docking, protein engineering. In: Ogawa T, editor. *Technology and Application. IntechOpen*.

8 Ferreira, L.G., Dos Santos, R.N., Oliva, G., & Andricopulo, A.D. (2015). Molecular Docking and Structure-Based Drug Design Strategies. *Molecules, 20*, 13384–13421. https://doi.org/10.3390/molecules200713384

9 DesJarlais, R.L., Sheridan, R.P., Seibel, G.L., Dixon, J.S., Kuntz, I.D., & Venkataraghavan R. (1988). Using shape complementarity as an initial screen in designing ligands for a receptor binding site of known three-dimensional structure. *J. Med. Chem., 31*, 722–729. https://pubs.acs.org/doi/pdf/10.1021/jm00399a006

10 Kitchen, D.B., Decornez, H., Furr, J.R., & Bajorath, J. (2004). Docking and scoring in virtual screening for drug discovery: methods and applications. *Nature reviews Drug discovery, 3(11)*, 93549. https://doi.org/10.1038/nrd1549

11 Lavecchia A, & Di Giovanni C. (2013). Virtual screening strategies in drug discovery: A critical review. *Current Medicinal Chemistry, 20(23)*, 2839–2860.

12 Levinthal, C., Wodak, S.J., Kahn, P., & Dadivanian, A.K. (1975). Hemoglobin interaction in sickle cell fibers. I: Theoretical approaches to the molecular contacts. *Proceedings of the National Academy of Sciences of the United States of America, 72(4)*, 1330–1334 https://doi.org/10.1073/pnas.72.4.1330

13 Menchaca TM, Juárez-Portilla C, & Zepeda RC. (2020). Past, Present, and Future of Molecular Docking. *InDrug Discovery and Development-New Advances, IntechOpen.*

14 Dominguez, C., Boelens, R., & Bonvin, A.M. (2003). HADDOCK: A proteinprotein docking approach based on biochemical or biophysical information. *Journal of the American Chemical Society, 125(7)*, 1731–1737. https://doi.org/10.1021/ja026939x

15 Bohm, H.J. (1992). The computer program LUDI: A new method for the de novo design of enzyme inhibitors. *Journal of Computer-Aided Molecular Design, 6(1)*, 61–78. https://doi.org/10.1007/BF00124387

16 Kramer, B., Rarey, M., & Lengauer, T. (1999). Evaluation of the FLEXX incremental construction algorithm for protein–ligand docking. *Proteins: Structure, function. Bioinformatics, 37(2)*, 228-241. https://doi.org/10.1002/(SICI)10970134(19991101)

17 Welch, W., Ruppert, J., & Jain, A.N. (1996). Hammerhead: Fast, fully automated docking of flexible ligands to protein binding sites. *Chemistry & Biology, 3(6)*, 449–462.

18 Spitzer, R., & Jain, A.N. (2012). Surflexdock: Docking benchmarks and real-world application. *Journal of Computer-Aided Molecular Design, 26(6)*, 687–699. https://doi.org/10.1007/s10822-011-9533-y

19 Morris, G.M., Huey, R., Lindstrom, W., Sanner, M.F., Belew, R.K., & Goodsell, D.S., et al. (2009). AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *Journal of Computational Chemistry, 30(16)*, 2785–2791. https://doi.org/10.1002/jcc.21256

20 Taylor, J.S., & Burnett, R.M. (2000). DARWIN: A program for docking flexible molecules. *Proteins, 41(2)*, 173–191. https://doi.org/10.1002/1097-0134(20001101

21 Liu, M., & Wang, S. (1999). MCDOCK: A Monte Carlo simulation approach to the molecular docking problem. *Journal of Computer-Aided Molecular Design, 13(5)*, 435–451. https://doi.org/10.1023/A:1008005918983

22 Jones, G., Willett, P., Glen, R.C., Leach, A.R., & Taylor, R. (1997). Development and validation of a genetic algorithm for flexible docking. *Journal of Molecular Biology*, 267(3), 727–748. https://doi.org/10.1006/jmbi.1996.0897

23 Oshiro, C.M., Kuntz, I.D., & Dixon, J.S. (1995). Flexible ligand docking using a genetic algorithm. *Journal of Computer-Aided Molecular Design, 9(2)*, 113–130. https://doi.org/10.1007/BF00124402

24 Salomon-Ferrer, R., Case, D.A., Walker, R.C. (2013). An overview of the Amber biomolecular simulation package. *Wiley Interdisciplinary Reviews: Computational Molecular Science, 3(2)*, 198–210. https://doi.org/10.1002/wcms.1121

25 Liu, X., Zhang, B., Jin, Z., Yang, H. & Rao, Z. (2020). The crystal structure of 2019-NCoV main protease in complex with an inhibitor N3. *RCSB Protein Data Bank.*

26 Grosdidier, A., Zoete V., & Michielin, O. (2011). Fast docking using the CHARMM force field with EADock DSS. *Journal of computational chemistry, 30, 32(10)*, 2149–2159. https://doi.org/10.1002/jcc.21797

27 Tian, W., Chen, C., Lei, X., Zhao, J., & Liang, J. (2018). CASTp 3.0: computed atlas of surface topography of proteins. *Nucleic acids research, 46(W1)*, W363–367.

28 Srivastava, A.K., Kumar, A., & Misra, N. (2020). On the Inhibition of COVID-19 Protease by Indian Herbal Plants: An In Silico Investigation. *arXiv preprint arXiv*: 2004.03411.

29 Lengauer, T., & Rarey, M. (1996). Methods for predicting molecular complexes involving proteins. *Curr. Opin. Struct. Biol., 5*, 402-6. https://doi.org/10.1002/0471721204

30 Grosdidier, A., Zoete, V., & Michielin, O. (2011). SwissDock, a protein-small molecule docking web service based on EADock DSS. *Nucleic acids research, 39(suppl_2)*, W270-277. https://doi.org/10.1093/nar/gkr366

31 Morris, G.M., Goodsell, D.S., Huey, R., & Olson, A.J. (1996). Distributed automated docking of flexible ligands to proteins: parallel applications of AutoDock 2.4. *Journal of computer-aided molecular design, 10(4)*, 293–304. https://doi.org/10.1007/BF00124499

32 Trott, O., & Olson, A.J. (2010). AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of computational chemistry, 31(2)*, 455-61. https://doi.org/10.1002/jcc.21334

33 DeLano, W.L. (2002) Pymol: An open-source molecular graphics tool. CCP4 *Newsletter on protein crystallography, 40(1)*, 82–92.

34 Sampangi-Ramaiah, M.H., Vishwakarma, R., & Shaanker, R.U. (2020). Molecular docking analysis of selected natural products from plants for inhibition of SARS-CoV-2 main protease. *Current Science, 118(7)*, 1087–1092.

35 Ceska, O., Chaudhary, S.K., Warrington, P., Ashwood-Smith, M.J., Bushnell, G.W. & Poultont, G.A. (1988) Coriandrin, a novel highly photoactive compound isolated from Coriandrum sativum. *Phytochemistry, 27*, 2083–2087. https://doi.org/10.1016/0031-9422(88)80101-8

36 Gonzalez-Paz, L.A., Lossada, C.A., & Moncayo, L.S. et al. (2020). Theoretical Molecular Docking Study of the Structural Disruption of the Viral 3CL-Protease of COVID19 Induced by Binding of Capsaicin, Piperine and Curcumin Part 1: A Comparative Study with Chloroquine and Hydrochloroquine Two Antimalaric Drugs, 06 April, PREPRINT (Version 1) available at *Research Square* https://doi.org/10.21203/rs.3.rs-21206/v1

37 Zhang, Q., & Ye, M. (2009) Chemical analysis of the Chinese herbal medicine Gan-Cao (licorice). *Journal of Chromatography A, 1216(11)*, 1954–1969. https://doi.org/10.1016/j.chroma.2008.07.072

38 Qiao, X., Song, W, Ji.S., Wang, Q., Guo, D.A., & Ye, M. (2015) Separation and characterization of phenolic compounds and triterpenoid saponins in licorice (*Glycyrrhiza uralensis*) using mobile phase-dependent reversed-phase× reversed-phase comprehensive two-dimensional liquid chromatography coupled with mass spectrometry. *Journal of Chromatography A, 1402*, 36–45. https://doi.org/10.1016/j.chroma.2015.05.006

39 Tripathi, M.K., Singh, P., Sharma, S., Singh, T.P., Ethayathulla, A.S., & Kaur, P. (2020). Identification of bioactive molecule from Withania somnifera (Ashwagandha) as SARS-CoV-2 main protease inhibitor. Jou*rnal of Biomolecular Structure and Dynamics*, 1–4. https://doi.org/10.1080/07391102.2020.1790425

40 Khaerunnisa, S., Kurniawan, H., Awaluddin, R., Suhartati, S. & Soetjipto, S. (2020). Potential inhibitor of COVID-19 main protease (Mpro) from several medicinal plant compounds by molecular docking study. *Preprints 2020*, 2020030226. https://doi.org/10.20944/preprints202003.0226.v1

41 Kumar A.HS. (2020). Molecular Docking of Natural Compounds from tulsi (Ocimum sanctum) and neem (Azadirachta indica) against SARS-CoV-2 Protein Targets. *BEMS Reports, 6(1)*, 11–13. https://doi.org/10.5530/bems.6.1.4

42 Choudhary, P., Chakdar, H., Singh, D., Selvaraj, C., Singh, S.K., Kumar, S., & Saxena, A.K. (2020). Computational studies reveal piperine, the predominant oleoresin of black pepper (Piper nigrum) as a potential inhibitor of SARS-CoV-2 (COVID-19). *Current Science* (00113891);119(8). https://doi.org/10.18520/cs/v119/i8/1333-1342

43 Derosa, G., Maffioli, P., D'Angelo, A., & Di Pierro, F. (2020). A role for quercetin in coronavirus disease 2019 (COVID-19). *Phytotherapy Research*. https://doi.org/10.1002/ptr.6887

44 Elfiky, A.A. (2020). Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): A molecular docking study. *Life sciences;* 117592. https://doi.org/10.1016/j.lfs.2020.117592

45 Keretsu, S., Bhujbal, S.P., & Cho, S.J. (2020) Rational approach toward COVID-19 main protease inhibitors via molecular docking, molecular dynamics simulation and free energy calculation. *Scientific reports, 10(1)*, 1–4. https://doi.org/10.1038/s41598-020-74468-0

46 Mpiana, P.T., Tshibangu, D.S., Kilembe, J.T., Gbolo, B.Z., Mwanangombo, D.T., Inkoto, C.L., Lengbiye, E.M., Mbadiko, C.M., Matondo, A., Bongo, G.N., & Tshilanda, D.D. (2020). Identification of potential inhibitors of SARS-CoV-2 main protease from Aloe vera compounds: a molecular docking study. *Chemical Physics Letters*, 754, 137751. https://doi.org/10.1016/j.cplett.2020.137751

47 Joshi, T., Joshi, T., Sharma, P., Mathpal, S., Pundir, H., Bhatt, V., & Chandra, S. (2020). In silico screening of natural compounds against COVID-19 by targeting Mpro and ACE2 using molecular docking. *Eur Rev Med Pharmacol Sci., 24(8)*, 4529–4536.

48 Amin, S.A., Ghosh, K., Gayen, S., & Jha, T. (2020) Chemical-informatics approach to COVID-19 drug discovery: Monte Carlo based QSAR, virtual screening and molecular docking study of some in-house molecules as papain-like protease (PLpro) inhibitors. *Journal of Biomolecular Structure and Dynamics*, 1-0. https://doi.org/10.1080/07391102.2020.1780946

49 Mohammadi, N., & Shaghaghi, N. (2020). Inhibitory effect of eight Secondary Metabolites from conventional Medicinal Plants on COVID_19 Virus Protease by Molecular Docking Analysis. Preprint; 11987475: v1. https://doi. org/10.26434/chemrxiv

50 Alrasheid, A.A., Babiker, M.Y., & Awad, T.A. (2021). Evaluation of certain medicinal plants compounds as new potential inhibitors of novel corona virus (COVID-19) using molecular docking analysis. *In Silico Pharmacology, 9(1)*, 1–7. https://doi.org/10.1007/s40203-020-00073-8

51 Rameshkumar, M.R., Indu, P., Arunagirinathan, N., Venkatadri, B., El-Serehy, H.A, & Ahmad, A. (2021). Computational selection of flavonoid compounds as inhibitors against SARS-CoV-2 main protease, RNA-dependent RNA polymerase and spike proteins: A molecular docking study. *Saudi journal of biological sciences, 28(1)*, 448–458, https://doi.org/10.1016/j.sjbs.2020.10.028

52 Llanes, A., Cruz, H., Nguyen, V.D., Larionov, O.V, & Fernández, P.L. (2021) A Computational Approach to Explore the Interaction of Semisynthetic Nitrogenous Heterocyclic Compounds with the SARS-CoV-2 Main Protease. *Biomolecules, 11(1)*, 18. https://doi.org/10.3390/biom11010018

53 Bharadwaj, S., Dubey, A., Yadava, U., Mishra, S.K., Kang, S.G., & Dwivedi, V.D. (2021). Exploration of natural compounds with anti-SARS-CoV-2 activity via inhibition of SARS-CoV-2 Mpro. *Briefings in Bioinformatics. J*. https://doi.org/10.1093/bib/bbaa382).

54 Su JT, Li XL, Huang YG, Lin HW, Luo H, & Luo LX. (2021). Network analysis and molecular docking of the mechanism of Shengmai decoction in treating patients with severe novel coronavirus pneumonia. *Tradit. Med. Res., 6(4)*, 33. https://doi.org/10.12032/TMR20201117207

55 Badavath, V.N., Kumar, A., Samanta, P.K., Maji, S., Das, A., Blum, G., Jha, A., & Sen, A. (2020) Determination of potential inhibitors based on isatin derivatives against SARS-CoV-2 main protease (mpro): a molecular docking, molecular dynamics and structure-activity relationship studies. *Journal of Biomolecular Structure and Dynamics*, 1–9, https://doi.org/10.1080/07391102.2020.1845800

56 Shah, A., Patel, V., & Parmar, B. (2020) Discovery of Some Antiviral Natural products to fight against Novel Corona Virus (SARS-CoV-2) using Insilico approach. *Combinatorial Chemistry & High Throughput Screening.* https://doi.org/10.2174/1386207323666200902135928

57 Yuan, S.I., Jiu, W.A., Liang, Z.H., Xue-wen, L.I., & Ying, L.I. (2020) Molecular docking prediction of three active components of Paris polyphylla against SARS-CoV-2. *Natural product research and development*, 32(7), 1. https://doi.org/10.16333/j.1001-6880.2020.7.002

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Молекулалық қондыру әдістерімен COVID-19 негізгі протеиназасының өсімдіктік ингибиторларын анықтау

Кейінгі айларда COVID-19 жағдайлары тез артып, қауіпті бола бастауда. Нәтижесінде бірнеше медициналық және ғылыми ұйымдар COVID-19 індетінің тиімді емін табуға тырысуда. Соңғы зерттеулерге сәйкес, көптеген табиғи өнімдердің COVID-19-ға қарсы белсенділігі жоғары. Мақаланың негізгі мақсаты — вирусқақарсы қасиеттері бар, табиғи түрде кездесетін биоактивті қосылыстарды анықтау. Луи және басқалар өз зерттеулерінде SARS-Cov-2 протеазасының негізгі емдік препаратқа нысана ретінде белгілі кристалды құрылымда болатынын хабарлады. Вирустық ақуыздардың репликациясын тоқтату үшін SARS-Cov-2 негізгі протеазасын тежеу маңызды. Бұл зерттеуде табиғи қосылыстар SARS-Cov-2 бөгейтін ықтимал биоактивті қосылыстарды зерттеу үшін молекулалық модельдеу әдістерінің көмегімен сыналды. Осы зерттеулердің нәтижесінде көптеген табиғи қосылыстардың вирустық ақуыздармен әрекеттесу және COVID-19 (Mpro) негізгі протеазасына қарсы ингибиторлық белсенділігі бар екендігі анықталды. Табиғи қосылыстар саквинавир мен ремдесивир сияқты белгілі вирусқақарсы препараттармен салыстырылды. Бұл потенциалды індетпен күресу үшін COVID-19-ға қарсы табиғи емдік агенттерге айналдырмас бұрын қосымша зерттеулер қажет екенін атап өтті.

Кілт сөздер: табиғи қосылыстар, SARS-Cov-2, тиімділігі, дәрілік нысана, молекулалық модельдеу, вирустық ақуыздар, Mpro, байланыстырушы аффинирлік.

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Идентификация растительных ингибиторов основной протеиназы COVID-19 методами молекулярного докинга

В последние месяцы количество случаев заражения COVID-19 быстро увеличивается и становится опасным. Как следствие, несколько медицинских и исследовательских организаций пытаются найти эффективное лекарство от вспышки COVID-19. Согласно недавним исследованиям, многие натуральные продукты обладают мощной активностью против COVID-19. Основная цель этой статьи — установить природные биологически активные соединения с подходящими противовирусными свойствами. Lui с соавторами сообщили в своем исследовании, что основная протеаза SARS-Cov-2 присутствует в кристаллической структуре, известной как мишень для нового терапевтического препарата. Важно ингибировать основную протеазу SARS-Cov-2, чтобы остановить репликацию вирусных белков. В этом исследовании природные соединения были проверены с использованием методов молекулярного моделирования для изучения возможных биоактивных соединений, которые блокируют SARS-Cov-2. В результате этих исследований было обнаружено, что многие природные соединения обладают способностью взаимодействовать с вирусными белками и проявляют ингибирующую активность в отношении основной протеазы COVID-19 (Mpro). Кроме того, эти природные соединения сравнивали с известными противовирусными препаратами, такими как Саквинавир и Ремдесивир. Отмечено, что необходимы дополнительные исследования, прежде чем эти потенциальные зацепки можно будет превратить в естественные терапевтические агенты против COVID-19 для борьбы с эпидемией.

Ключевые слова: природные соединения, SARS-Cov-2, эффективность, лекарственная мишень, молекулярное моделирование, вирусные белки, Mpro, аффинность связывания.

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