 doi:10.20944/preprints202003.0333.v1

Identification of potent COVID-19 main protease (Mpro) inhibitors from natural polyphenols: An in silico strategy unveils a hope against CORONA

Sevki Adem[1], Volkan Eyupoglu[1], Iqra Sarfraz[2], Azhar Rasul[2*] Muhammad Ali[3]

[1]Department of Chemistry, Faculty of Science, Cankiri Karatekin University, 18100 Cankırı, Turkey

[2]Cell and Molecular Biology Lab, Department of Zoology, Faculty of Life Sciences, Government Collge University Faisalabad, 38000 Faisalabad, Pakistan

[3]Vice Chancellor, Quaid-i-Azam University (QAU), Islamabad, Pakistan

[*]**Corresponding Author:**

Dr. Azhar Rasul, Assistant Professor, Department of Zoology, Faculty of Life Sciences, Government Collge University Faisalabad, 38000 Faisalabad, Pakistan; Email. drazharrasul@gmail.com; azharrasul@gcuf.edu.pk; Cell phone: +92-3218409546;

Assoc.Prof. Dr. Sevki ADEM, Associate Professor, Department of Chemistry, Faculty of Science, Cankiri Karatekin University, 18100 Cankırı, Turkey; Email. sevkiadem@gmail.com Cell phone: +90 5055764413; Phone:+90 264 2956065

 doi:10.20944/preprints202003.0333.v1

Abstract

COVID-19, a rapidly spreading new strain of coronavirus, has affected more than 150 countries and received worldwide attention. The lack of efficacious drugs or vaccines against SARS-CoV-2 has further worsened the situation. Thus, there is an urgent need to boost up research for the development of effective therapeutics and affordable diagnostic against COVID-19. The crystallized form of SARS-CoV-2 main protease (Mpro) was demonstrated by a Chinese researcher Liu et al. (2020) which is a novel therapeutic drug target. This study was conducted to evaluate the efficacy of medicinal plant-based bioactive compounds against COVID-19 Mpro by molecular docking study. Molecular docking investigations were performed by using Molegro Virtual Docker 7 to analyze the inhibition probability of these compounds against COVID-19. COVID-19 Mpro was docked with 80 flavonoid compounds and the binding energies were obtained from the docking of (PDB ID: 6LU7: Resolution 2.16 Å) with the native ligand. According to obtained results, hesperidin, rutin, diosmin, apiin, diacetylcurcumin, (E)-1-(2-Hydroxy-4-methoxyphenyl)-3-[3-[(E)-3-(2-hydroxy-4-methoxyphenyl)-3-oxoprop-1-enyl]phenyl]prop-2-en-1-one, and beta,beta'-(4-Methoxy-1,3-phenylene)bis(2'-hydroxy-4',6'-dimethoxyacrylophenone have been found as more effective on COVID-19 than nelfinavir. So, this study will pave a way for doing advanced experimental research to evaluate the real medicinal potential of these compounds to cure COVID-19.

Keywords: COVID-19, SARS-CoV-2, Molecular docking, Flavonoids

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 March 2020 doi:10.20944/preprints202003.0333.v1

Introduction

An acute respiratory disorder caused by 2019-novel coronavirus [2019-nCoV, now known as SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2)] has emerged as a serious public health issue at the end of 2019 (1-3). During the 21st century, SARS-CoV-2 marked the history with third large scale coronavirus epidemic into the human population after SARS-CoV in 2002 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 (4). By the 17th March 2020, this potentially fatal virus pushed 7426 human to death beds while 179,111 infected cases are reported in more than 150 countries around the globe and SARS-CoV-2 cases are still steadily growing due to its rapid human to human transmission (WHO, 2020) (3). Although few antiviral strategies are being used to treat patients, lack of specific antiviral drugs or vaccines against SARS-CoV-2 is further aggravating the situation. Thus, there is an urgent need to identify and develop effective antivirals against SARS-CoV-2 to fight this deadly virus.

The SARS-CoV-2 has been identified as β-coronavirus, a non-segmented enveloped positive-sense RNA virus, with 29.9 kb genome (5, 3). SARS-CoV-2 causes severe respiratory tract infection in humans and utilize angiotensin-converting enzyme 2 (ACE2) receptors to infect humans (6). Chinese scientists isolated SARS-CoV-2 and sequenced the genome SARS-CoV-2 on January 7, 2020 (7). The crystallized form of COVID-19 main protease (Mpro) was demonstrated by a Chinese researcher Liu et al. (2020) that it is a potential drug target protein for the inhibition of SARS-CoV-2 replication. The Mpro is a key protein required for the proteolytic maturation of the virus (8). Thus, targeting Mpro has the potential to provide effective treatment against SARS-CoV-2 by inhibition of the viral polypeptide cleavage.

In-silico based screening has proven to be a very useful tool to meet the challenges of antiviral drug discovery. Screening of natural or synthetic virtual compound libraries by computational screening methods as docking saves resources in terms of money as well as time (9). Natural compounds have served humans as cheaper and safer drug candidates against several diseases (10, 11). Thus, we have screened a small library of natural compounds against Mpro by in silico based screening and in this study, we report the identification of natural compounds (Hesperidin, diosmin, rutin, and apiin) as potent inhibitors of Mpro by using molecular docking approach.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 March 2020 doi:10.20944/preprints202003.0333.v1

Methods

Computational or theoretical chemistry is a sub-branch of chemistry. It explains the formation possibility of chemical bonding between atoms, molecular activation in terms of molecular dynamics, chemical reaction formation possibilities in the scope of thermodynamic and molecular orbital theory takin into consideration valence orbital interaction and potential energy molecular orbitals (12). The theoretical chemistry bases on two strong physicochemical phenomena; these are quantum mechanics (QM) and molecular dynamics (MD). The subatomic particle ***(protons, electrons, and neutrons)*** interactions form the drawback of quantum chemistry that also describes the molecular properties depending on subatomic interactions (13, 12). The molecular dynamic theory is based on the spatial conformation of molecule interaction from their active sites by intermolecular interactions like weak Van der Waals interactions or hydrogen bonding. Therefore, the frontier molecular orbital theory (FMOT) has been used to get information about the stability and reactivity of the examined compounds against target bioactive molecules like enzyme, protein, etc.

The docking study of the compound over COVID-19 Mpro was studied using Molegro Virtual Docker (MVD) program. The crystal structure of a protein essential for virus replication download from protein data bank web site (http://www.rcsb.org/pdb) (PDB ID: 6LU7: Resolution 2.16 Å) (14). Small molecules used docking studies obtained from https://pubchem.ncbi.nlm.nih.gov/ as SDF form and in the 3D Conformer. Possible docking modes between compounds and the main protease of COVID-19 were studied using the Molegro Virtual Docker 7 (15). The score function used is MolDock score with the coordinates of the position are X: -10.85 Y: 15.32, and Z: 68.39 at 120.832 Å3 volume, 417.28 Å2 surface, and 0.30 grid resolution. The selected cavity is the binding site of natural inhibitor N3. Nelfinavir, using in the treatment of the human immunodeficiency virus (HIV), utilized as a positive control.

Results

The binding energies obtained from the docking of 6LU7 were presented in Table 1. Hesperidin, rutin, diosmin, apiin, diacetyl curcumin, (E)-1-(2-Hydroxy-4-methoxyphenyl)-3 [3-[(E)-3-(2-hydroxy-4-methoxyphenyl)-3-oxoprop-1-enyl]phenyl]prop-2-en-1-one, and beta,beta'-(4-Methoxy-1,3-phenylene)bis(2'-hydroxy-4',6'-dimethoxyacrylophenone) exhibited as the best potential inhibitors against protease of COVID-19. According to in

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 March 2020 doi:10.20944/preprints202003.0333.v1

silico results, 24 of the compounds have a better affinity against COVİD 19 protease than Nelfinavir (Table 1).

Hesperidin exhibited the highest binding energy at the active site of Covid 19 (Figure 1). It formed hydrogen bond interactions Thr 26, Glu 166, Arg 188, Gln 189, Met 49, Asp 187, Tyr 54, His 163, Leu 141, and Ser 144 (Figure 1B). Results of this study shown that Cys 145, Asn 142, Phe 140, Glu 166, Gln 192, Thr 190, asp 187, Tyr 54, and His 164 were critical residues for the binding of rutin to protease protein (Figure 2, Table 2). Active site residues Gln 192, Thr 190, Arg 188, His 164, Gln 189, Glu 166, Gly 143, Ser 144, and Cys 145 participated hydrogen bond interactions with diosmin (Table 2, Figure 3). Figure 4 has been demonstrated that Ser 144, Leu 141, Cys 145, Thr 26, Thr 190, Phe 140, Asn 142, Leu 141, His 41, Arg 188, Gln 189, Met 165, and Pro 168 amino acids were responsible for apiin binding in COVİD 19 (Table 2).

Table 1. Results of the docking of some phenolic compounds on the crystal structure of COVID-19 main protease

	Compounds	**MolDock Score**	**HBond**
Native Ligand	**N3**	-162.1700	-8.1930
Drugs	**Nelfinavir**	-147.3800	-6.8731
1.	Hesperidin	-178.5910	-20.2594
2.	Rutin	-176.2740	-21.2402
3.	Diosmin	-174.1260	-27.2572
4.	Apiin	-171.0080	-10.1895
5.	Diacetylcurcumin	-169.2550	-9.5680
6.	(E)-1-(2-Hydroxy-4-methoxyphenyl)-3-[3-[(E)-3-(2-hydroxy-4-methoxyphenyl)-3-oxoprop-1-enyl]phenyl]prop-2-en-1-one	-165.8980	-13.7524
7.	beta,beta'-(4-Methoxy-1,3-phenylene)bis(2'-hydroxy-4',6'-dimethoxyacrylophenone)	-164.8720	-6.6815
8.	Myricetin	-161.7160	-16.6231
9.	(E)-1-[2,6-Dihydroxy-3-[(E)-3-(4-hydroxyphenyl)prop-2-enoyl]-4-methoxyphenyl]-3-(4-hydroxyphenyl)prop-2-en-1-one	-159.8760	-15.7715
10.	Flavone23	-159.6370	-2.2055
11.	Naringin	-158.8180	-8.5912
12.	Neohesperidin	-158.3340	-16.1224
13.	Scutellarin	-157.9020	-14.2029
14.	Neoeriocitrin	-157.5840	-18.6181
15.	7-[2-(1,3-dioxan-2-yl)ethoxy]-3-(4-	-157.4050	-7.0764

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 March 2020 doi:10.20944/preprints202003.0333.v1

	hydroxyphenyl)chromen-4-one		
16.	(−)-Catechin gallate	-156.1300	-16.8711
17.	Quercetin 3-β-D-glucoside	-156.0770	-17.2393
18.	Baicalin	-153.5950	-12.1009
19.	Pectolinarin	-152.4200	-9.0114
20.	(−)-Catechin gallate	-152.1140	-22.7023
21.	Vitexin 2-o-rhamnoside	-150.0210	-17.6290
22.	Balsacone A	-149.7000	-14.0775
23.	Flavone23	-149.4210	-2.9451
24.	Quercetin 3-D-galactoside	-148.4210	-11.7740
25.	Polydatin	-145.7310	-17.3568
26.	Bisdemethoxycurcumin	-144.4660	-8.5201

Table 2. The hydrogen bond energy of the hesperidin, rutin, diosmin, and apiin

Compounds	**Hydrogen bond Number**	**Energy**	**Length**	**Amino acid Residue**
Hesperidin	1	-0.9856	2.4183	Glu 166, Gln 192, Arg 188, Gln 189, Met 49, Asp 187, Tyr 54, Leu 141, Ser 144, His 163, Thr 26
	2	-0.6210	3.2072	
	3	-0.3780	3.5177	
	4	-2.2429	2.5691	
	5	-0.0076	3.5658	
	6	-1.8613	2.7265	
	7	-1.6205	2.8881	
	8	-1.7548	3.0822	
	9	-1.3998	2.6268	
	10	-1.6249	3.2237	
	11	-2.5000	3.0406	
	12	-0.7142	2.9028	
	13	-2.0999	3.1800	
	14	-2.4477	3.1105	
Rutin	1	-2.3382	2.6007	Cys 145, Asn 142, Phe 140, Glu 166, Gln 192, Thr 190, Asp 187,
	2	-2.5000	2.7239	

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 March 2020 doi:10.20944/preprints202003.0333.v1

	3	-0.5387	3.0627	Tyr 54, His 164
	4	-1.5691	2.6839	
	5	-2.5000	2.8474	
	6	-1.2991	2.9511	
	7	-2.5000	2.9476	
	8	-1.8469	3.0733	
	9	-0.5076	2.9664	
	10	-2.3975	3.1205	
	11	-0.1933	2.9497	
	12	-2.1954	2.7684	
	13	-1.2058	3.1335	
Diosmin	1	-2.5000	3.0954	Gln 192, Thr 190, Arg 188, His 164, Gln 189, Glu 166, Gly 143, Ser 144, Cys 145
	2	-0.7552	2.6013	
	3	-2.1507	2.5581	
	4	-1.5162	3.2849	
	5	-2.4851	3.0952	
	6	-1.9648	3.2070	
	7	-2.4992	2.5999	
	8	-2.5000	2.6883	
	9	-1.8168	3.0981	
Apiin	0	-2.5000	2.6653	Thr 190, Ser 144, Leu 141, His 163, Cys 145, Thr 26
	1	0.67561	2.2223	
	2	-0.2719	2.6857	
	3	-0.9757	2.4440	
	4	-2.5000	2.9181	

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 March 2020 doi:10.20944/preprints202003.0333.v1

	5	-2.5000	2.9183	
	6	-2.5000	2.6706	
	7	-2.5000	2.8367	
	8	-2.4982	2.5998	
	9	-2.5000	3.0996	
	10	-0.4085	3.5127	

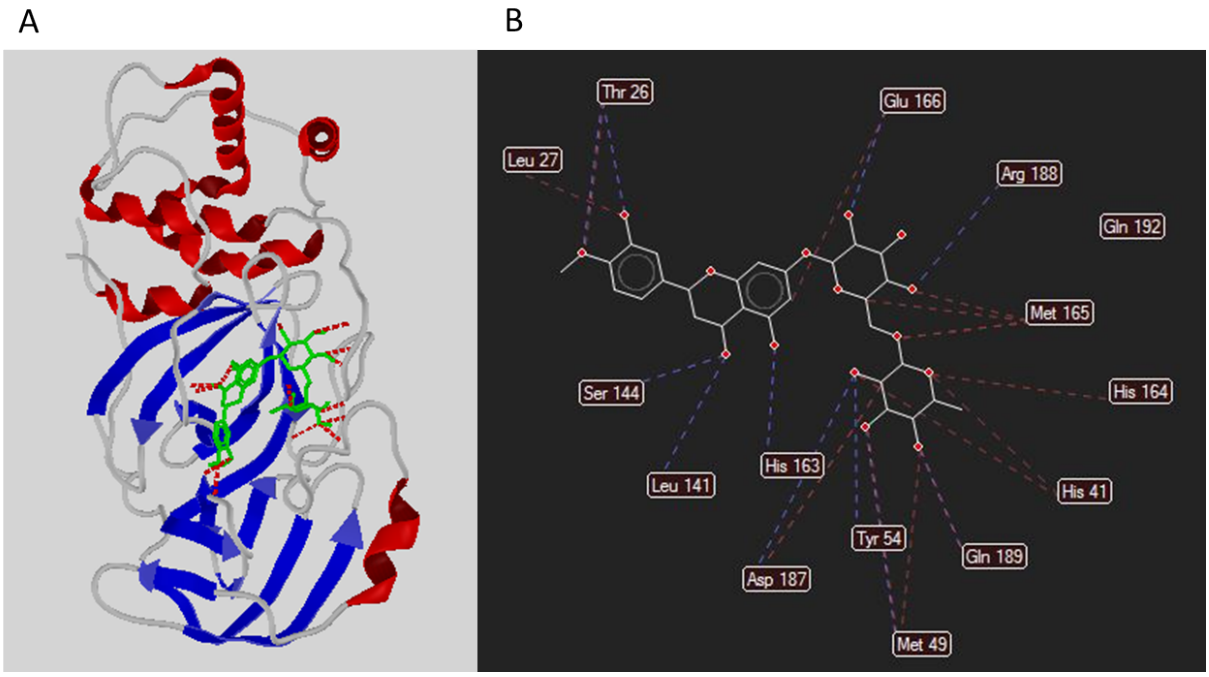

Figure 1. Representation of docked ligand-protein complex (A) 2D animation pose of hesperidin within the cavity of 6LU7, (B) Interaction of hesperidin with amino acid residues of Mpro COVID-19.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 March 2020 doi:10.20944/preprints202003.0333.v1

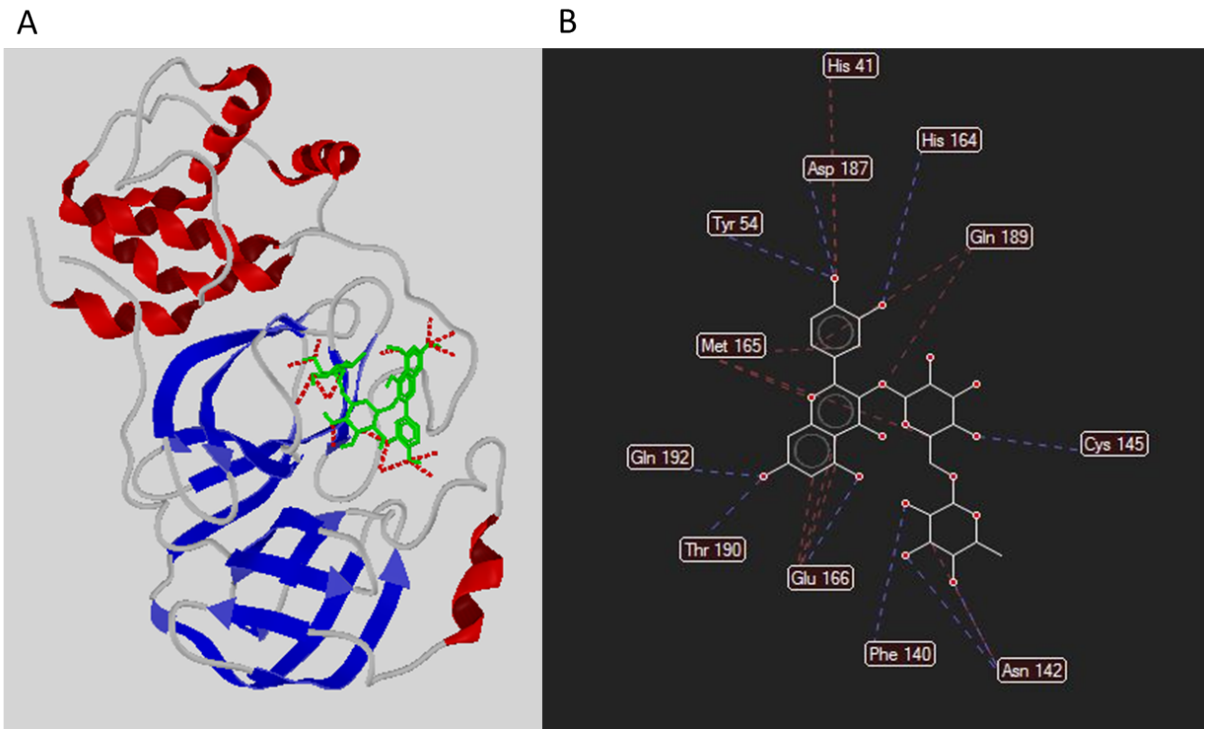

Figure 2. Representation of docked ligand-protein complex **(A)** 2D animation pose of rutin within the cavity of 6LU7, (B) Interaction of rutin with amino acid residues of M^{pro} COVID-19.

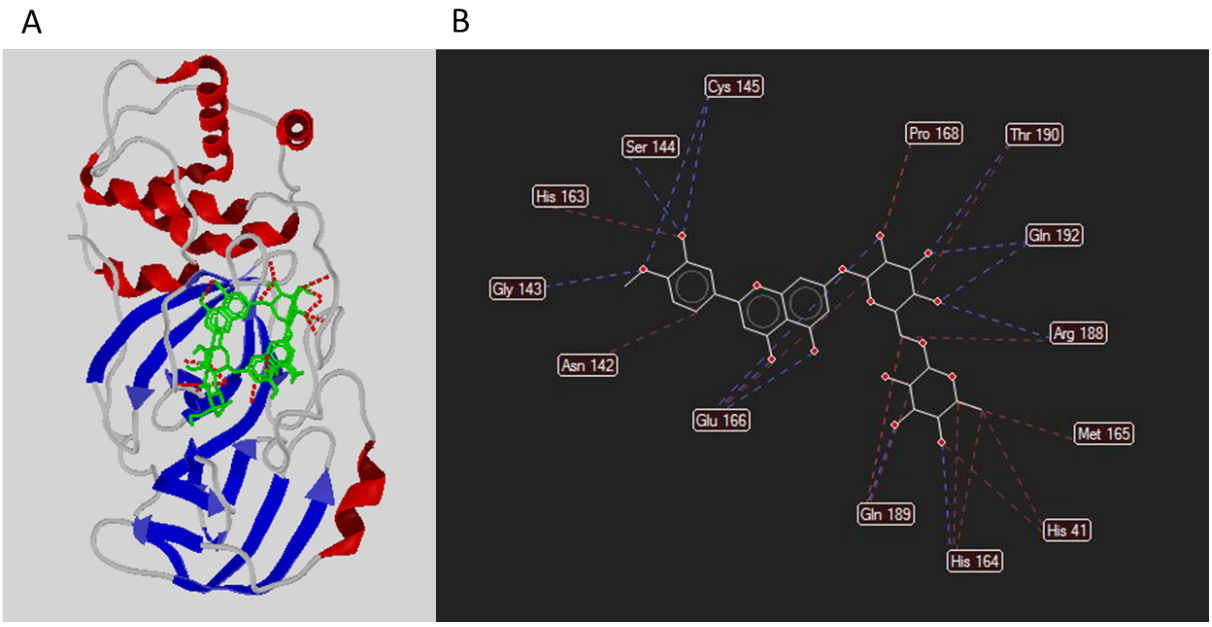

Figure 3. Representation of docked ligand-protein complex **(A)** 2D animation pose of diosmin within the cavity of 6LU7, (B) Interaction of diosmin with amino acid residues of M^{pro} COVID-19.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 March 2020 doi:10.20944/preprints202003.0333.v1

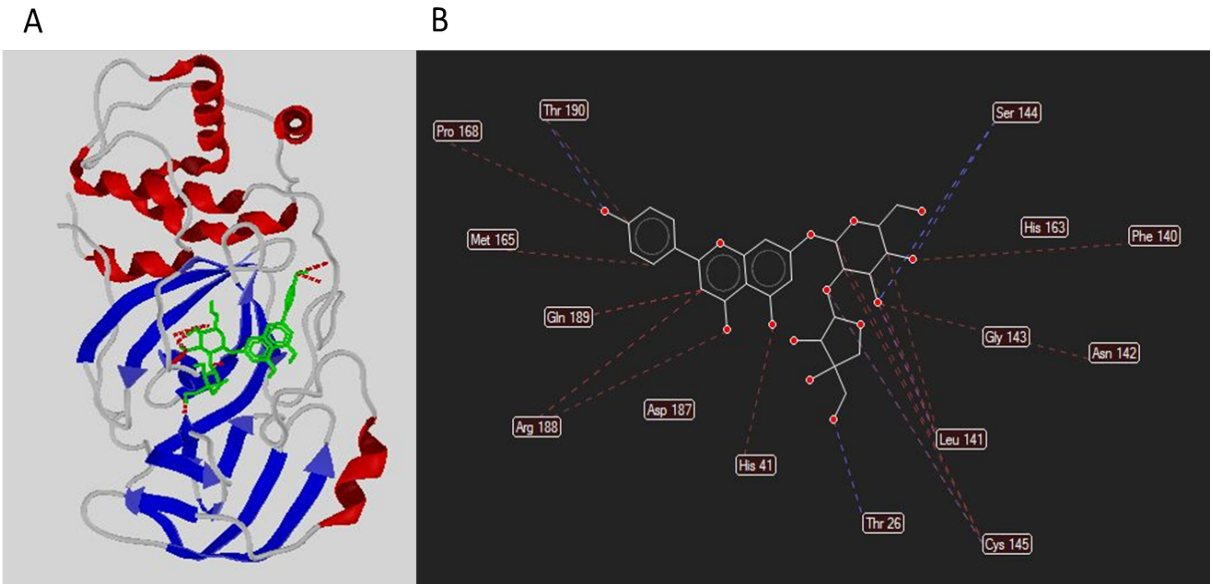

Figure 4. Representation of docked ligand-protein complex **(A)** 2D animation pose of apiin within the cavity of 6LU7, (B) Interaction of apiin with amino acid residues of M^{pro} COVID-19.

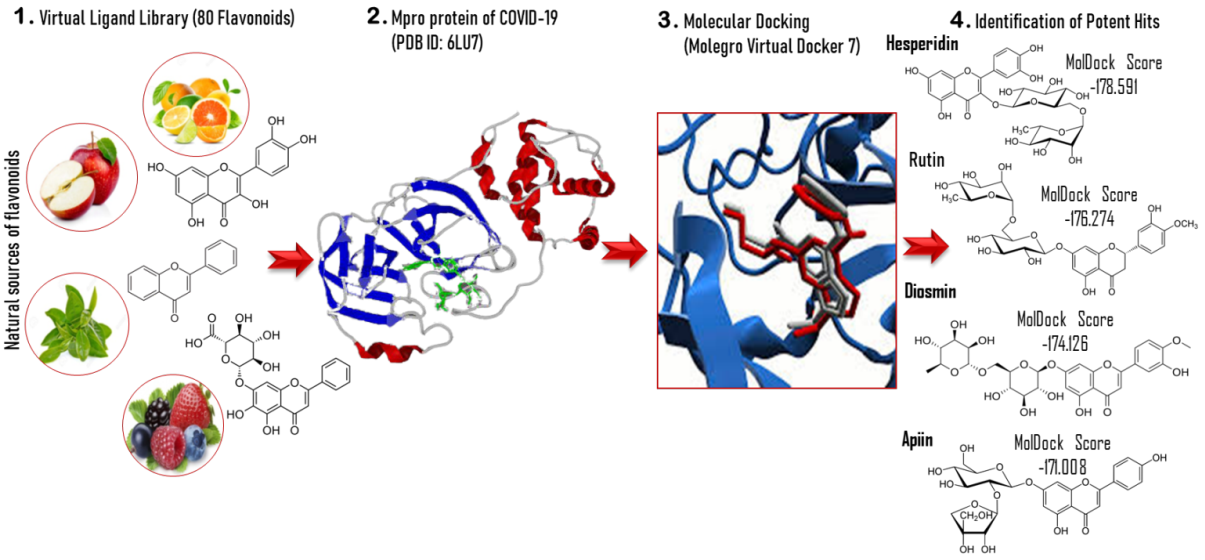

Figure 5. Summary of the in-silico based screening of natural product library and identification of natural inhibitors of Mpro of COVID-19

Discussion

Coronaviruses have a long history of infecting humans and animals and causing respiratory, digestive, liver and central nervous system diseases in them (16). A novel newly emerged SARS-CoV-2 is presenting major threats to human health nowadays (3). Currently, no

 doi:10.20944/preprints202003.0333.v1

specific clinical therapeutics are available for the treatment of SARS-CoV-2-mediated infections (17). Thus, the need of the hour is to identify and characterize novel drug candidate to overcome the health loses caused by SARS-CoV-2. In this context, natural products have gained importance as potent anti-viral agents during recent years (18, 19). Considering the immediate need of therapeutics against COVID-19 and services of natural products in drug discovery, we have screened flavonoids against novel drug target, Mpro, of SARS-CoV-2 for the identification of Mpro inhibitors to provide natural scaffolds for drug development.

Antiviral effects of flavonoids have been the subject matter of several reports (20-22). It has been previously reported that flavonoids exert their antiviral effects via blockage of cellular receptors, inhibiting viral antigenic determinants, loss of enzymatic functions, and/or inhibition of particle biosynthesis which is consistent with our findings (23-25). Furthermore, the antiviral activity of specific flavonoid subclass groups, such as catechins, flavanones, flavonols has been reported previously against various viral strains (26, 27). Song et al. (2005) reported reduced viral infectivity by catechins (26). Antiviral natural product-based medicines have also been used for two previous coronavirus outbreaks of SARS-CoV and MERS-CoV which suggests that nature has tremendous potential to provide treatment for the ongoing epidemic of COVID-19 (28-30).

Previous reports also suggest anti-influenza virus potential of hesperidin and apiin (31, 32), the anti-DENV activity of rutin (33) while the anti-rotavirus potential of diosmin (34) which further affirm the potential of these compounds against COVID-19. Hesperidin and diosmin are flavanone glycoside which is richly found in the citrus including lemons, grapefruits and sweet oranges (35, 36). Rutin is a vital nutritional component and abundant flavonol found in tea, and apples (37). Parsely has been reported to be enriched with apiin (38). Interestingly, all the compounds possessing binding energies more than Nelfinavir are nutraceuticals and important nutritional components of fruits and vegetables, thus, we anticipate that consumption of citrus fruits, cherries and apples has the potential to boost immunity to fight against COVID-19 infections.

Conclusions

The rapidly spreading outbreak of COVID-19 has challenged the healthcare sector of the world in the last few months. To contribute to this fight against COVID-19, virtual screening-based molecular docking was performed to identify novel compounds having the potential to bind M^{pro} of COVID-19. Our results propose that flavonoids such as hesperidin and rutin have

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 March 2020 doi:10.20944/preprints202003.0333.v1

a better binding affinity to M^{pro} of COVID-19 than Nelfinavir. According to moldock binding score, the potent flavonoids can be ranked as following by affinity hesperidin > rutin > diosmin > apiin > diacetylcurcumin (Figure 5). All the compounds bearing good binding potency are components of dietary foods that suggest the biologically safe profile of these compounds further supporting the potential of these compounds as starting points for therapeutics against COVID-19. However, further studies should be conducted for the validation of these compounds using *in vitro* and *in vivo* models to pave a way for these compounds in drug discovery.

References

[1] Coronaviridae Study Group of the International Committee on Taxonomy of V. (2020) The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol.*

[2] Lee P. I., Hsueh P. R. (2020) Emerging threats from zoonotic coronaviruses-from SARS and MERS to 2019-nCoV. *J Microbiol Immunol Infect.*

[3] Zhu N., Zhang D., Wang W., Li X., Yang B., Song J., Zhao X., Huang B., Shi W., Lu R., Niu P., Zhan F., Ma X., Wang D., Xu W., Wu G., Gao G. F., Tan W., China Novel Coronavirus I., Research T. (2020) A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med.* **382**, 727-733.

[4] Guo Y. R., Cao Q. D., Hong Z. S., Tan Y. Y., Chen S. D., Jin H. J., Tan K. S., Wang D. Y., Yan Y. (2020) The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. *Mil Med Res.* **7**, 11.

[5] Wu F., Zhao S., Yu B., Chen Y. M., Wang W., Song Z. G., Hu Y., Tao Z. W., Tian J. H., Pei Y. Y., Yuan M. L., Zhang Y. L., Dai F. H., Liu Y., Wang Q. M., Zheng J. J., Xu L., Holmes E. C., Zhang Y. Z. (2020) A new coronavirus associated with human respiratory disease in China. *Nature.* **579**, 265-269.

[6] Li Q., Guan X., Wu P., Wang X., Zhou L., Tong Y., Ren R., Leung K. S. M., Lau E. H. Y., Wong J. Y., Xing X., Xiang N., Wu Y., Li C., Chen Q., Li D., Liu T., Zhao J., Li M., Tu W., Chen C., Jin L., Yang R., Wang Q., Zhou S., Wang R., Liu H., Luo Y., Liu Y., Shao G., Li H., Tao Z., Yang Y., Deng Z., Liu B., Ma Z., Zhang Y., Shi G., Lam T. T. Y., Wu J. T. K., Gao G. F., Cowling B. J., Yang B., Leung G. M., Feng Z. (2020) Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med.*

[7] Lu R., Zhao X., Li J., Niu P., Yang B., Wu H., Wang W., Song H., Huang B., Zhu N., Bi Y., Ma X., Zhan F., Wang L., Hu T., Zhou H., Hu Z., Zhou W., Zhao L., Chen J., Meng Y., Wang J., Lin Y., Yuan J., Xie Z., Ma J., Liu W. J., Wang D., Xu W., Holmes E. C., Gao G. F., Wu G., Chen W., Shi W., Tan W. (2020) Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet.* **395**, 565-574.

[8] Structure of Mpro from COVID-19 virus and discovery of its inhibitors. http://www.rcsb.org/structure/6LU7.

[9] Murgueitio M. S., Bermudez M., Mortier J., Wolber G. (2012) In silico virtual screening approaches for anti-viral drug discovery. *Drug Discov Today Technol.* **9**, e219-225.

[10] Shen B. (2015) A New Golden Age of Natural Products Drug Discovery. *Cell.* **163**, 1297-1300.

[11] Thomford N. E., Senthebane D. A., Rowe A., Munro D., Seele P., Maroyi A., Dzobo K. (2018) Natural Products for Drug Discovery in the 21st Century: Innovations for Novel Drug Discovery. *Int J Mol Sci.* **19**.

[12] Nabati M., Bodaghi-Namileh V. (2020) In silico study of the active components (17 alpha-ethinyl estradiol and segesterone acetate) of annovera as a novel vaginal contraceptive system by docking of their binding to estrogen and progesterone receptors. *Eurasian Chemical Communication.* **2**, 234-246.

[13] Formagio A. S. N., Volobuff C. R. F., Kassuya C. A. L., Cardoso C. A. L., do Carmo Vieira M., Pereira Z. V., Bagatin M. C., de Freitas Gauze G. (2019) Psychotria leiocarpa Extract and Vincosamide Reduce Chemically-Induced Inflammation in Mice and Inhibit the Acetylcholinesterase Activity. *Inflammation.* **42**, 1561-1574.

[14] Liu X., Zhang B., Jin Z., Yang H., Rao Z., (2020).

[15] Molegro A. (2019) MVD 7.0 Molegro Virtual Docker. *DK-8000 Aarhus C, Denmark.*

[16] To K. K., Hung I. F., Chan J. F., Yuen K. Y. (2013) From SARS coronavirus to novel animal and human coronaviruses. *J Thorac Dis.* **5 Suppl 2**, S103-108.

[17] Zhou Y., Hou Y., Shen J., Huang Y., Martin W., Cheng F. (2020) Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discovery.* **6**.

[18] Lin L. T., Hsu W. C., Lin C. C. (2014) Antiviral natural products and herbal medicines. *J Tradit Complement Med.* **4**, 24-35.

[19] Martinez J. P., Sasse F., Bronstrup M., Diez J., Meyerhans A. (2015) Antiviral drug discovery: broad-spectrum drugs from nature. *Nat Prod Rep.* **32**, 29-48.

[20] Gescher K., Hensel A., Hafezi W., Derksen A., Kuhn J. (2011) Oligomeric proanthocyanidins from Rumex acetosa L. inhibit the attachment of herpes simplex virus type-1. *Antiviral Res.* **89**, 9-18.

[21] Roh C., Jo S. K. (2011) (-)-Epigallocatechin gallate inhibits hepatitis C virus (HCV) viral protein NS5B. *Talanta.* **85**, 2639-2642.

[22] Chen C., Qiu H., Gong J., Liu Q., Xiao H., Chen X. W., Sun B. L., Yang R. G. (2012) (-)-Epigallocatechin-3-gallate inhibits the replication cycle of hepatitis C virus. *Arch Virol.* **157**, 1301-1312.

[23] Bae E. A., Han M. J., Lee M., Kim D. H. (2000) In vitro inhibitory effect of some flavonoids on rotavirus infectivity. *Biol Pharm Bull.* **23**, 1122-1124.

[24] Calzada F., Cedillo-Rivera R., Bye R., Mata R. (2001) Geranins C and D, additional new antiprotozoal A-type proanthocyanidins from Geranium niveum. *Planta Med.* **67**, 677-680.

[25] Chang L. K., Wei T. T., Chiu Y. F., Tung C. P., Chuang J. Y., Hung S. K., Li C., Liu S. T. (2003) Inhibition of Epstein-Barr virus lytic cycle by (-)-epigallocatechin gallate. *Biochem Biophys Res Commun.* **301**, 1062-1068.

[26] Song J. M., Lee K. H., Seong B. L. (2005) Antiviral effect of catechins in green tea on influenza virus. *Antiviral Res.* **68**, 66-74.

[27] Savi L. A., Caon T., de Oliveira A. P., Sobottka A. M., Werner W., Reginatto F. H., Schenkel E. P., Barardi C. R., Simoes C. M. (2010) Evaluation of antirotavirus activity of flavonoids. *Fitoterapia.* **81**, 1142-1146.

[28] Li S. Y., Chen C., Zhang H. Q., Guo H. Y., Wang H., Wang L., Zhang X., Hua S. N., Yu J., Xiao P. G., Li R. S., Tan X. (2005) Identification of natural compounds with antiviral activities against SARS-associated coronavirus. *Antiviral Res.* **67**, 18-23.

[29] Lin C. W., Tsai F. J., Tsai C. H., Lai C. C., Wan L., Ho T. Y., Hsieh C. C., Chao P. D. (2005) Anti-SARS coronavirus 3C-like protease effects of Isatis indigotica root and plant-derived phenolic compounds. *Antiviral Res.* **68**, 36-42.

[30] Lau K. M., Lee K. M., Koon C. M., Cheung C. S., Lau C. P., Ho H. M., Lee M. Y., Au S. W., Cheng C. H., Lau C. B., Tsui S. K., Wan D. C., Waye M. M., Wong K. B., Wong C. K., Lam C. W., Leung P. C., Fung K. P. (2008) Immunomodulatory and anti-SARS activities of Houttuynia cordata. *J Ethnopharmacol.* **118**, 79-85.

[31] Liu A. L., Liu B., Qin H. L., Lee S. M., Wang Y. T., Du G. H. (2008) Anti-influenza virus activities of flavonoids from the medicinal plant Elsholtzia rugulosa. *Planta Med.* **74**, 847-851.

[32] Dong W., Wei X., Zhang F., Hao J., Huang F., Zhang C., Liang W. (2014) A dual character of flavonoids in influenza A virus replication and spread through modulating cell-autonomous immunity by MAPK signaling pathways. *Sci Rep.* **4**, 7237.

[33] Zandi k., Teoh B. T., Sam S. S., F. W. P., Mustafa M. R., Bakar S. A. (2011) In vitro antiviral activity of Fisetin, Rutin and Naringenin against Dengue virus type-2. *Journal of medicinal plant research* **5**, 5534–5539.

[34] Lipson S. M. (2013) Flavonoid-associated direct loss of rotavirus antigen/antigen activity in cell-free suspension. *Journal of Medicinally Active Plants.* **2**.

 doi:10.20944/preprints202003.0333.v1

[35] Hsu C. C., Lin M. H., Cheng J. T., Wu M. C. (2017) Diosmin, a Citrus Nutrient, Activates Imidazoline Receptors to Alleviate Blood Glucose and Lipids in Type 1-Like Diabetic Rats. *Nutrients.* **9**.

[36] Hajialyani M., Hosein Farzaei M., Echeverria J., Nabavi S. M., Uriarte E., Sobarzo-Sanchez E. (2019) Hesperidin as a Neuroprotective Agent: A Review of Animal and Clinical Evidence. *Molecules.* **24**.

[37] Ganeshpurkar A., Saluja A. K. (2017) The Pharmacological Potential of Rutin. *Saudi Pharm J.* **25**, 149-164.

[38] Meyer H., Bolarinwa A., Wolfram G., Linseisen J. (2006) Bioavailability of apigenin from apiin-rich parsley in humans. *Ann Nutr Metab.* **50**, 167-172.