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PREVENTIVE STRATEGIES FOR MANAGEMENT OF COVID-19 USING NATURAL MOLECULES

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Abstract

The COVID19, a fatal disease by coronavirus (SARS-CoV-2) in late 2019 in China is now pandemic caused severe acute respiratory syndrome. The pandemic of COVID-19 has reached almost all regions of the world including territories with the death toll of more than 35,000. It has been estimated that one out every six-person affected by COVID-19 developed life-threatening conditions. The difficulty is that there are no vaccines or no specific treatment modalities for the management of COVID-19, apart from symptomatic treatments. Efforts for the development of vaccines and other specific treatment modalities are co-ordinated by the World Health Organisation (WHO), with many clinical trials ongoing with modern and traditional medicines. In this regard, various Phyto-actives from the plants are getting analyzed, which has earlier shown to be effective in various viral infections. Therefore, keeping the world scenario and due to the

lack of vaccine, we have in *silico* studied the activity of tetrahydrocurcumin, a major metabolite of curcumin, a household spice, matairesinol, a major compound in wheat bran or flaxseed and vitamin K2-7 against both SARS-CoV's main peptide and COVID-19 M^{pro}.

Key words: COVID-19, SARS-CoV-2, molecular interactions, Natural inhibitors; vitamin K2-7, tetrahydrocurcumin

Introduction

The spreading of SARS-CoV-2 leading diseases is now pandemic and covered all over the world as an open challenge for human welfare. Pandemic of COVID-19, has reached to almost 203 countries and territories, accounting for more than 742,506 cases, as of March 30th, with recoveries of about 150,000 cases and death toll of more than 35,000^{1,2,3} (Fig.1).

Viruses, has large subsets of families based on the genome as per the Blatimore classification. Coronavirus (CoVs) belongs to one of such large family of viruses, Coronaviridae family. Coronaviridae family is generally characterised by an envelope, positive-sense, single-stranded RNA (ssRNA). Family further consist of species which infect mammals and birds, causing infections in respiratory and gastro-intestinal tracts. In humans COVID-19 originates like common flu but there after become more danger than severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV)⁴ and other human CoVs types -HKU1, -OC43, -NL63 and 229E, known for global threat, with high mortality rate in 2003⁵. WHO has identified a yet another high fatality of HCoV infection in Middle East, MERS-CoV, in the year 2012⁶. The recent, COVID-19 is a novel strain which was identified only in the year 2019 in humans.

The transmission of Corona viruses is zoonotic, which means it gets transmitted across humans and animal species. Upon the through interrogations it was observed that civet cats were responsible for the transmission of SARS-CoV and dromedary camels for the transmission of MERS-CoV to human. There are yet underscored coronaviruses which are present in animals and not yet identified in humans^{7,8}. The spread of virus among humans are via respiratory droplets from coughing or sneezing^{7,8} turned transmissible by direct or indirect people to people contact⁹. It is more challenging to monitored the time of infection and exposure to observed the perfect signal of symptom till few days to weeks (almost two weeks) for COVID-19. Keeping the view of Chinese region with consonance with other region, the common symptoms having fever, coughing and breathing difficulties^{10,11}, which are very common and gradual. Not all the people who are infected feel unwell or developed any symptoms. Around one out every six-person affected by COVID-19, developed life- threatening conditions. Vulnerable age group are geriatrics with causal health glitches e.g. cancer, immune-disorder, high sugar and blood pressure, heart diseases including pneumonia and respiratory disorders. Due unavailability of COVID-19 vaccine, WHO and other health care agencies recommends only social distancing with hygiene (hand sanitization, covering nose and mouth while sneezing and coughing, etc) to prevent the COVID-19^{7,8,9}.

The major problem with the pandemic of COVID-19 is that there isn't any vaccine or specific treatment modality available, only the symptomatic treatment is available. Hospitalisation with isolation is advisable most of the cases. Efforts for the development of vaccines and other specific treatment modalities are co-ordinated by World Health Organisation (WHO), with many clinical trials on going with modern and traditional

medicines. In this regards, various phyto-actives from the plants are getting tested, which has earlier shown to be effective in various viral infections. Similar is the case with the minerals. World has a long tradition of usage of herbs and minerals for the management various illnesses including viral infections. The phytochemicals within the herbs, provides a repertory for never antiviral drug development. In the recent time lot of efforts has undergone to identify the mechanism by which these phytochemicals produces its action on various check points (viral entry, multiplications and anchoring) to prevent the infection with virus-host-specific interactions mechanisms¹². Throughout the geographies and climatic conditions various herbs has been considered for the management of various viral infections. Such attempt has also been undertaken in finding the new entity for the management of infection caused by SARS-CoV and COVID-19. In view of such attempt it was observed that Curcumin (3–10 μ M) has shown the potential to inhibit or constrain SARS-CoV^{12,13}.

Vitamin K₂₋₇ belongs to the vitamin K group. The two general categories of vitamin K are phylloquinone (K₁) and menaquinone [MK_n, *n* being the number of side chain prenyl units (4–13)]. The physiological and patho-physiological roles of different menaquinones are specific. Vitamin K acts as an enzymatic co-factor to carboxylate Vitamin K-dependent proteins (VKD proteins)¹⁴. Early research with vitamin K was limited to carboxylation of VKD clotting proteins. At a later stage, there was recognition of VKD proteins present in extra-hepatic tissues.

Curcumin is a naturally derived, yellow polyphenolic compound from the rhizome *Curcuma longa*¹⁵. Curcumins wide range of activities is attributed to its efficacy in modulating various signalling pathways, such as ATPase, glutathione, cyclin D1, COX-2,

MMPs, protein kinase C, nuclear ErbB2, AP-1, P-gp, NF- κ B, MRP-1, MRP-2, α 1- and acid glycoprotein^{16,17}. The pharmacological activities of curcumin are attributed to major metabolites of curcumin like dimethoxycurcumin¹⁸ and tetrahydrocurcumin¹⁹. A recent molecular docking analysis of COVID-19 M^{pro}²⁰ with several phytochemicals has revealed that Demethoxycurcumin has best COVID-19 M^{pro} inhibitory activity²⁰. In spite of this still, there are no reports of the effects of tetrahydrocurcumin against COVID-19 infection. The authors of this publication have studied the activity of vitamin K2-7, tetrahydrocurcumin and matairesinol (all 3 are the products of Shreepad Shree Vallabh, SSV Phytopharmaceuticals, Mumbai) for the first time against both SARS-CoV's main peptide and COVID-19 M^{pro}.

Results and Discussions

The new strain of CoV was identified at the end of 2019, initially named COVID-19, and outraged an outbreak in Wuhan, China²³. The Emergency Committee of the WHO declared an outbreak in China on 30 January 2020, which was considered to be an international community health emergency²⁴. Currently, no specific therapies for COVID-19 are to offer and search for the treatment of COVID-19 are lacking²⁵. Thus, the measures that have been implemented remain limited to preventive and supportive therapies, designed to prevent further complications and organ damage²⁴. Some preliminary studies have investigated potential combinations which include the protease inhibitor lopinavir/ritonavir (commonly used to treat HIV patients) for the management of COVID-19-infected patients²⁵. Similarly, some other antiviral treatments tenofovir disoproxil (TDF), remdesivir, umifenovir (arbidol), lamivudine (3TC), neuraminidase inhibitors, nucleoside analogues are used for the human SARS-CoV²⁵. Unfortunately,

these drugs are un-effective and thus unapproved for therapeutic use in clinical settings against COVID-19 patients by WHO^{25,26}.

Maintaining personal hygiene is one way to reduce the chances of infection. Use of tissue while coughing and sneezing or coughing and sneezing into the inside of the elbow, along with the hand sanitization after coughing and sneezing is also recommended by the United States CDC²⁷. Due unavailability of any prominent method to control the infections, in this situation, several researchers, therefore recommended to boost the immunity. Most viral infections are dependent on the natural defences mechanism systems which is correlate with the immune systems. Various plant-based products, in addition to providing nutrients, boost the immune function of one's body. Vitamin C is such an example. Vitamin C acts as an antioxidant, which destroys free radicals and supports the body's natural immune response. Vitamin C improves immunity by enhancing both, innate and adaptive immune systems. Vitamin C also enhances white blood cell production and function. Various studies have found that vitamin C is useful in the prevention of pneumonia, a complication associated with COVID-19 mortality²⁸. Another vitamin is K2-7, also known as menaquinone-7. It is a menaquinone whose side chain contains seven isoprene units in an all-trans-configuration when derived from nature. Trans isomers have been shown to be safe, whereas cis isomers have been shown to be toxic. In fact, US Pharmacopeia (*First Supplement to USP 38–NF 33*) defined pure vitamin K2-7 to have less than 2% of cis isomers. Currently available vitamin K2-7 preparations contain more than 2% of cis isomers. Trans-isomers are safe and more effective; hence, SSV Phytopharmaceuticals has developed a vitamin K2-7 containing more than 98.5% trans isomers and less than 0.2% cis-isomers developed by us

and found that vitamin K2-7 exhibits antiviral activity against HIV and HBV (unpublished Patent number – IN202021007016). Taking a molecular mimicry and interactions we have now in *silico* evaluated the activity of vitamin K2-7 against SARS-CoV's main peptide and COVID-19 M^{pro} (un-published patent number– IN202021013430). It has been observed that vitamin K2-7 has activity against SARS-CoV's main peptide (binding energy of -6.92 and inhibition constant of 8.48 μ M) and COVID-19 M^{pro} (binding energy of -6.54 and inhibition constant of 16.24 μ M), suggesting its potential role in prevention of COVID-19 (Fig.3a and 4a)

Based on the previous study, the antiviral activity of curcumin used against hepatitis, influenza and emerging arboviruses have been used by several investigators targeting the signalling pathways of cell cycle dependant protein cyclin D1, cyclin E, apoptosis process, PI3K/AKT pathway, invasion, adhesion molecules, angiogenesis, metastasis and inflammation targeting pathways molecules such as NF- κ B, TNF, IL-6, IL-1, COX-2 and 5-LOX in term of immunity^{16,28}. Interestingly, all these effects are commonly attributed to all three curcuminoids: demethoxycurcumin, bisdemethoxycurcumin and curcumin. Curcumin is the most important of all the curcuminoid in turmeric and it the most studied compound.

Interestingly, Curcumin reduces to dihydrocurcumin which is further reduced to tetrahydrocurcumin (THC) as an end product³⁰. Tetrahydrocurcumin has shown to be similar to the curcumin in its physiological and pharmacological activities but has also a greater anti-oxidant capacity³¹.

In one of another study based, we have also studied the curcumin role against SARS-CoV. Based on the previous studies with curcumin have shown that it inhibits SARS-CoV

¹⁰. In Another study, when COVID-19 M^{pro} was docked with dimethoxycurcumin, showed that demethoxycurcumin appeared to be promising contender to act as a COVID-19 M^{pro} inhibitor. Keeping view of all the points, we have used the tetrahydrocurcumin against COVID-19 is one of the major compounds of the liposomal curcumin BriyelTM, developed by our groups(SSV Phytopharmaceuticals;patent number–IN202021013430: unpublished) showed for the first time, the promising antiviral effect which inhibited SARS-CoV's main peptide (binding energy of -8.08 and inhibition constant of 1.2 μ M) and COVID-19 M^{pro} (binding energy of -7.67 and inhibition constant of 2.32 μ M; Fig 3b and 4b).

Similarly, another plant-based molecule, which is structurally similar to tetrahydrocurcumin, is matairesinol. Matairesinol occurs within numerous foods, such as oil seeds, whole grains, vegetables and fruits grain sources include rapeseed, flaxseeds, & sesame, whole-grain cereals such as wheat, barley, rye, oats, & millet and legumes such as soybean^{32,33}. Matairesinol has been shown to attenuate specific types of cancer and cardiovascular diseases³⁴. Based on the properties of matairesinol, we have also evaluated the activity of matairesinol in docking studies for SARS-CoV's main peptide and COVID-19 M^{pro}. It was observed that matairesinol shows great effect on SARS-CoV's main peptide (binding energy of -8.67 and inhibition constant of 444.88 nM) and COVID-19 M^{pro} (binding energy of 9.03 and inhibition constant of 241.7 nM), suggesting its potential role in prevention of COVID-19. This activity is more prominent than the standard reference compounds used against SARS-CoV's main peptide (binding energy of -4.96 and inhibition constant of 229.46 μ M) and complex inhibitor N3 of COVID-19 (binding energy of -7.59 and inhibition constant of 2.72 μ M; Fig 3c and 4c). This is 1st

study we have studied and compared the three natural molecules against the SARS-CoV's and COVID-19 M^{pro}.

In this alarming situation of the COVID19 and their escalating infection rate worldwide, for the first time, we have reported the vitamin K2-7, tetrahydrocurcumin and matairesinol oriented molecules may play promising role against both SARS-CoV's main peptide and COVID-19 M^{pro} as antiviral agents. All three compounds are primarily used in food supplements and as nutritional ingredients and be an immunity supplements for the human body. Hence, vitamin K2-7, tetrahydrocurcumin and matairesinol ideally would be used as preventive measures for the management of novel COVID-19.

Material and Methods

Target proteins

COVID-19 M^{pro} (PDB ID: 6LU7)²¹ and SARS coronavirus main peptidase (PDB ID: 2GTB) structures were taken from the PDB (<https://www.rcsb.org/>), in PDB format. The 6LU7 protein contains two chains, A and B, which form a homodimer. The 2GTB protein contains one chain, A. The native ligand for 6LU7 is n-[(5-methylisoxazol-3-yl)carbonyl]alanyl-l-valyl-n~1~-((1r,2z)-4-(benzyloxy)-4-oxo-1-{[(3r)-2-oxopyrrolidin-3-yl]methyl}but-2-enyl)-l-leucinamide, whereas the 2GTB native ligand is (5s,8s,14r)-ethyl 11-(3-amino-3-oxopropyl)-8-benzyl-14-hydroxy-5-isobutyl-3,6,9,12-tetraoxo-1-phenyl-2-oxa-4,7,10,11-tetraazapentadecan-15-oate (Scheme 1).

Scheme 1: The native ligands for 6LU7 and 2GTB

Ligands selections

Vitamin K2-7 (CID_5287554), tetrahydrocurcumin(CID_124072) and matairesinol(CID_119205) three-dimensional structures(Scheme 2) were obtained from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>), in SDF format. PubChem is a database which stores chemical substances and biological activities.

Scheme 2: Structures of vitamin K2-7, tetrahydrocurcumin and matairesinol

Molecular Docking

The active site of a protein was determined using LIGPLOT v.4.5.3 and Biovia Discovery Studio 4.5 and is described in Table1.1 about covid19 main protease and Table1.2 about SARS coronavirus main peptidase. The images showing the active sites are given in the supplementary images Fig.2a and b. Ligand optimization was done using the Marvin tools of ChemAxon. The ligands of vitamin K2-7, tetrahydrocurcumin and matairesinol were docked with three-dimensional structures of the protein target using AutoDock4.2. The binding modes of vitamin K2-7, tetrahydrocurcumin and matairesinol with all protein targets are shown in Table2.

Competing interests: The authors declare no competing interests.

References

1. World Health Organization. Novel Coronavirus (2019-nCoV) SITUATION REPORT –1.21January 2020 (accessed on 29th March 2020).

- https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200121-sitrep-1-2019-ncov.pdf?sfvrsn=20a99c10_4
2. World Health Organization. Novel Coronavirus (2019-nCoV) SITUATION REPORT –51. 11 March 2020 (accessed on 29th March 2020). https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10
 3. World Health Organization. Novel Coronavirus (2019-nCoV) SITUATION REPORT –71. 31 March 2020 (accessed on 31st March 2020). https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200331-sitrep-71-covid-19.pdf?sfvrsn=4360e92b_6
 4. Van der Hoek, L. Human Coronaviruses: What do they cause? *Antivir. Ther.***12**, 651–8 (2007).
 5. Geller, C. et al. Human coronaviruses: Insights into environmental resistance and its influence on the development of new antiseptic strategies. *Viruses***4**, 3044–68 (2012).
 6. World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV). 11 January 2020 (accessed on 29th March 2020). [https://www.who.int/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-\(mers-cov\)](https://www.who.int/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov))
 7. Rabi, F.A. et al. SARS-CoV-2 and Coronavirus Disease 2019: What We Know So Far. *Pathogens***9**, 231 (2020).
 8. Centers for Disease Control and Prevention. How coronavirus spreads (accessed on 29th March 2020). https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/how-covid-spreads.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fprepare%2Ftransmission.html
 9. Lai, C-C. et al. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Facts and myths. *J. Microbiol. Immunol. Infect.* (2020). <https://doi.org/10.1016/j.jmii.2020.02.012>

10. Rothan, H. A., & Byrareddy, S. N. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J. Autoimmun.* 102433 (2020). <https://doi.org/10.1016/j.jaut.2020.102433>
11. Lin, L-T., Hsu, W-C., & Lin, C-C. Antiviral natural products and herbal medicines. *J. Tradit. Complement. Med.* **4**, 24–35 (2014).
12. Wen, C. C. et al. Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. *J. Med. Chem.* **50**, 4087–4095 (2007).
13. Furie, B., Bouchard, B. A., & Furie, B. C. Vitamin K-dependent biosynthesis of γ -carboxyglutamic acid. *Blood* **93**, 1798–808 (1999).
14. Miller, J. M. et al. Curcumin: A double hit on malignant mesothelioma. *Cancer Prev. Res. (Phila)*. **7**, 330–40 (2014).
15. Anand, P. et al. Curcumin and cancer: An “old-age” disease with an “age-old” solution. *Cancer Lett.* **267**, 133–164 (2008).
16. Kunnumakkara, A. B., Anand, P., & Aggarwal, B. B. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signalling proteins. *Cancer Lett.* **269**, 199–225 (2008).
17. Paramasivam, M. et al. High-performance thin layer chromatographic method for quantitative determination of curcuminoids in *Curcuma longa* germplasm. *Food Chem.* **113**, 640–644 (2009).
18. Zhongfa, L. et al. Enhancement of curcumin oral absorption and pharmacokinetics of curcuminoids and curcumin metabolites in mice. *Cancer Chemother. Pharmacol.* **69**, 679–689 (2012).
19. Khaerunnisa, S. Potential inhibitor of COVID-19 main protease (M^{pro}) from several medicinal plant compounds by molecular docking study. Preprints 2020030226 (2020). doi: 10.20944/preprints202003.0226.v1.
20. Xu, Z. et al. Nelfinavir was predicted to be a potential inhibitor of 2019-nCov main protease by an integrative approach combining homology modelling, molecular docking and binding free energy calculation. *bioRxiv* **1201**, 0–2 (2020). <https://doi.org/10.1101/2020.01.27.921627>

21. Liu, X., Zhang, B., Jin, Z., Yang, H., Rao, Z., “The crystal structure of 2019-nCoV main protease in complex with an inhibitor N3,” 2020. DOI:10.2210/pdb6LU7/pdb.
22. Lee, P.I., Hsueh, P.R. Emerging threats from zoonotic coronaviruses—from SARS and MERS to 2019-nCoV. *J Microbiol Immunol Infect.* S1684-1182(20)30011-6(2020) (2020).
23. Rodríguez-Morales, A.J., MacGregor, K., Kanagarajah, S., Patel, D., Schlagenhauf, P. Going global - Travel and the 2019 novel coronavirus. *Travel Med Infect Dis.* Epub 2020 doi: 10.1016/j.tmaid.2020.101578 (2020).
24. Lu, H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). *Biosci Trends.* 14(1):69-71 (2020).
25. Holshue, M.L., DeBolt, C., Lindquist, S. et al. First case of 2019 novel coronavirus in the United States. *N Engl J Med.* doi.org/10.1056/nejmoa2001191(2020).
26. Centers for Disease Control (3 February 2020). Coronavirus Disease 2019 (COVID-19): Prevention & Treatment (<https://www.cdc.gov/coronavirus/about/prevention.html>). Archived (<https://web.archive.org/web/20191215193934/https://www.cdc.gov/coronavirus/about/prevention.html>) from the original on 15 December 2019. Retrieved 10 February 2020.
27. Hemilä, H. Vitamin C and Infections. *Nutrients.* 29;9(4 (2017).
28. Praditya, D., Kirchhoff, L., Brüning, J., Rachmawati, H., Steinmann, J., & Steinmann, E. Anti-infective Properties of the Golden Spice Curcumin. *Front. Microbiol.* 10:912. (2019).
29. Momtazi-Borojeni, A.A., Haftcheshmeh, S.M., Esmaeili, S.A., Johnston, T.P., Abdollahi E., Sahebkar, A. Curcumin: A natural modulator of immune cells in systemic lupus erythematosus. *Autoimmun. Rev.* 17:125–135 (2018).
30. Heath, D.D., Pruitt, M.A., Brenner, D.E., Begum, A.N., Frautschy, S.A., Rock, C.L. Tetrahydrocurcumin in plasma and urine: quantitation by high performance liquid chromatography. *J Chromatogr B Analyt Technol Biomed Life Sci.* 824(1-2):206-12 (2005).

31. Niemeyer, H.B., Honig, D.M., Kulling, S.E., Metzler, M. "Studies on the metabolism of the plant lignans secoisolariciresinol and matairesinol". *J. Agric. Food Chem.* 51 (21): 6317–25 (2003).
32. Bultosa G. Functional Foods: Overview, in Reference Module in Food Science, Elsevier, ISBN 9780081005965 (2016).
33. Milder, I.E., Arts, I.C., van de Putte, B., Venema, D.P., Hollman, P.C. Lignan contents of Dutch plant foods: a database including lariciresinol, pinoresinol, secoisolariciresinol and matairesinol. *Br. J. Nutr.* 93 (3): 393–402 (2005).
34. Iyon, E. J et al. Intake of the Plant Lignans Secoisolariciresinol, Matairesinol, Lariciresinol, and Pinoresinol in Dutch Men and Women, *The Journal of Nutrition* 135: 1202–1207 (2005).

Fig. 1. World epidemic curve of confirmed COVID-19 cases and mortality rate
Source: WHO March 2020

Fig.2a: Ligplot showing active site of SARS coronavirus main peptidase inhibited by an aza-peptide epoxide

Fig. 3(a): SARS coronavirus main peptidase in complex with an inhibitor Vitamin K2-7

Fig. 3(b): SARS coronavirus main peptidase in complex with an inhibitor Tetrahydrocurcumin

Fig. 3(c): SARS coronavirus main peptidase in complex with an inhibitor matairesinol

Fig. 4(a): COVID-19 main protease in complex with an inhibitor VitaminK 2-7

Fig. 4(b): COVID-19 main protease in complex with an inhibitor Tetrahydrocurcumin.

Fig. 4(c): COVID-19 main protease in complex with an inhibitor matairesinol

Table 1.1: Amino acids of active site of Covid19 main protease(6lu7) which form H-bonds with native ligands

S. No.	Atom Type	Amino Acid	Hydrogen bond Distance
1	O	PHE 140 (A)	3.19
2	N	GLY 143 (A)	2.87
3	NE2	HIS 163 (A)	2.37
4	O	HIS 164 (A)	2.8
5	N	GLU 166 (A)	2.98
6	O	GLU 166 (A)	2.83
7	OE1	GLN 189 (A)	2.89
8	O	THR 190 (A)	2.85

Table 1.2: Amino acids of active site of SARS coronavirus main peptidase(2gtb) which form H-bonds with native ligands

S. No.	Atom Type	Amino Acid	Hydrogen bond Distance
1	OD1	ASN 142(A)	3.21
2	N	GLY 143(A)	2.79
3	N	CYS 145(A)	3.18
4	NE2	HIS 163(A)	2.74
5	O	HIS 164(A)	2.65
6	N	GLU 166(A)	2.83
7	O	GLU 166(A)	3.14
8	OE2	GLU 166(A)	2.91
9	OE1	GLN 189(A)	3.09

Table 2: The binding energy and inhibition constant for different drugs with target

Protein	Molecules	Binding Energy	Inhibition Constant
2GBT	AZ401(native ligand)	-4.96	22.40uM
	Tetrahydrocurcumin	-8.08	1.2uM
	Vitamin K2-7	-6.92	8.48uM
	Matairesinol	-8.67	444.88nM
6LU7	N3(native ligand)	-7.59	2.72uM
	Tetrahydrocurcumin	-7.69	2.32uM
	Vitamin K2-7	-6.54	16.24uM
	Matairesinol	-9.03	241.7nM

Table 1. Countries, territories or areas with reported laboratory-confirmed

[illegible]

Western Pacific Region

China	82545
Republic of Korea	9786
Australia	4359
Malaysia	2626
Japan	1953
Philippines	1546
Singapore	879
New Zealand	600
Viet Nam	203
Brunei Darussalam	127
Cambodia	107
Mongolia	12

Lao People's Democratic Republic	
Lao People's Democratic Republic	
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Lao People's Democratic Republic	
Lao People's Democratic Republic	
Lao People's Democratic Republic	
Lao People's Democratic Republic	
Lao People's Democratic Republic	8
Fiji	5
Papua New Guinea	1
Territories**	
Guam	58
French Polynesia	36
New Caledonia	15
Northern Mariana Islands (Commonwealth of the)	
Northern Mariana Islands (Commonwealth of the)	
Northern Mariana Islands (Commonwealth of the)	
Northern Mariana Islands (Commonwealth of the)	
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Northern Mariana Islands (Commonwealth of the)	
Northern Mariana Islands (Commonwealth of the)	
Northern Mariana Islands (Commonwealth of the)	2
European Region	
Italy	101739
Spain	85195
Germany	61913
France	43977
The United Kingdom	22145
Switzerland	15412
Belgium	11899
Netherlands	11750
Turkey	10827
Austria	9618
Portugal	6408
Israel	4831
Norway	4226
Sweden	4028

Czechia	3002
Ireland	2910
Denmark	2577
Poland	2055
Luxembourg	1988
Romania	1952
Russian Federation	1837
Finland	1313
Greece	1212
Iceland	1086
Croatia	790
Serbia	785
Slovenia	763
Estonia	715
Ukraine	549
Lithuania	484
Armenia	482
Hungary	447
Latvia	376
Andorra	370
Bosnia and Herzegovina	
Bosnia and Herzegovina	
Bosnia and Herzegovina	
Bosnia and Herzegovina	
Bosnia and Herzegovina	
Bosnia and Herzegovina	
Bosnia and Herzegovina	
Bosnia and Herzegovina	
Bosnia and Herzegovina	
Bosnia and Herzegovina	359
Bulgaria	359
Slovakia	336
Kazakhstan	312
Republic of Moldova	298
North Macedonia	285
Azerbaijan	273
Cyprus	230
San Marino	230
Albania	223
Malta	156
Belarus	152
Uzbekistan	149
Kyrgyzstan	107
Georgia	103
Montenegro	91
Liechtenstein	64

Monaco	49
Holy See	6
Territories**	
Faroe Islands	168
Kosovo[1]	106
Gibraltar	69
Jersey	63
Guernsey	45
Isle of Man	42
Greenland	10
South-East Asia Region	
Thailand	1524
Indonesia	1414
India	1071
Sri Lanka	120
Bangladesh	49
Maldives	17
Myanmar	10
Nepal	5
Bhutan	4
Timor-Leste	1
Eastern Mediterranean Region	
Iran (Islamic Republic of)	41495
Iran (Islamic Republic of)	
Iran (Islamic Republic of)	
Iran (Islamic Republic of)	
Iran (Islamic Republic of)	
Iran (Islamic Republic of)	
Iran (Islamic Republic of)	
Pakistan	1865
Saudi Arabia	1453
Qatar	693
Egypt	656
Iraq	630
United Arab Emirates	611
Morocco	574
Bahrain	515
Lebanon	446
Tunisia	362
Jordan	268
Kuwait	266
Oman	179
Afghanistan	166
Djibouti	26
Syrian Arab Republic	10
Libya	8

Sudan	6
Somalia	3
Territories**	
occupied Palestinian	
territoryoccupied Palestinian	
territoryoccupied Palestinian	
territoryoccupied Palestinian	
territoryoccupied Palestinian	
territoryoccupied Palestinian	
territoryoccupied Palestinian	
territory	117
Region of the Americas	
United States of	
AmericaUnited States of	
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AmericaUnited States of	
AmericaUnited States of	
America	140640
Canada	6317
Brazil	4256
Chile	2449
Ecuador	1962
Mexico	993
Panama	989
Dominican Republic	901
Peru	852
Argentina	820
Colombia	702
Costa Rica	314
Uruguay	309
Cuba	170
Honduras	139
Venezuela (Bolivarian	
Republic of)Venezuela (Bolivarian	
Republic of)Venezuela (Bolivarian	
Republic of)Venezuela (Bolivarian	
Republic of)Venezuela (Bolivarian	
Republic of)	129
Bolivia (Plurinational	
State of)Bolivia (Plurinational	
State of)Bolivia (Plurinational	
State of)Bolivia (Plurinational	
State of)Bolivia (Plurinational	
State of)	97
Trinidad and Tobago	82
Paraguay	64

Guatemala	36
Jamaica	36
Barbados	33
El Salvador	30
Haiti	15
Bahamas	14
Cayman Islands	12
Grenada	9
Saint Lucia	9
Guyana	8
Suriname	8
Antigua and Barbuda	7
Nicaragua	4
Belize	3
Saint Kitts and Nevis	2
Saint Vincent and the GrenadinesSaint Vincent and the GrenadinesSaint Vincent and the GrenadinesSaint Vincent and the GrenadinesSaint Vincent and the Grenadines	1
Territories**	
Puerto Rico	174
Martinique	111
Guadeloupe	106
Aruba	50
French Guiana	43
United States Virgin IslandsUnited States Virgin IslandsUnited States Virgin IslandsUnited States Virgin Islands	30
Bermuda	22
Saint Martin	18
Curaçao	11
Dominica	11
Saint Barthélemy	6
Sint Maarten	6
Montserrat	5
Turks and Caicos IslandsTurks and Caicos IslandsTurks and Caicos IslandsTurks and Caicos Islands	5
Anguilla	2
British Virgin Islands	2
African Region	
South Africa	1326

Algeria	511
Burkina Faso	246
Cote d'Ivoire	169
Senegal	162
Ghana	152
Cameroon	139
Nigeria	111
Mauritius	107
Democratic Republic of the CongoDemocratic Republic of the CongoDemocratic Republic of the Congo	98
Rwanda	70
Madagascar	46
Kenya	38
Zambia	35
Togo	34
Uganda	33
Ethiopia	23
Niger	20
Congo	19
United Republic of TanzaniaUnited Republic of Tanzania	19
Mali	18
Guinea	16
Equatorial Guinea	14
Namibia	11
Eswatini	9
Mozambique	8
Seychelles	8
Gabon	7
Benin	6
Central African RepublicCentral African Republic	6
Eritrea	6
Cabo Verde	5
Chad	5
Mauritania	5
Zimbabwe	5
Gambia	3
Liberia	3
Angola	2
Guinea-Bissau	2
Territories**	
Réunion	207
Mayotte	82

Subtotal for all regions	750178
International conveyance (Diamond Princess)	712
Grand total	750890

98	3314	4
125	162	4
393	18	2
156	37	3
87	56	2
128	78	7
35	3	0
48	1	0
15	0	0
1	1	0
4	0	0
0	0	0

0	0	0
0	0	0
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4050	11591	810
6398	7340	812
4615	583	128
4335	3017	415
2619	1408	180
1138	295	38
1063	513	82
884	864	93
1556	168	37
805	108	22
446	140	21
584	17	2
124	26	4
328	146	36

173	24	8
295	54	8
182	77	5
193	31	9
38	22	1
192	44	4
303	9	0
95	13	2
56	43	5
66	2	0
77	6	0
44	13	0
33	11	0
36	3	0
69	13	2
0	7	0
0	3	0
0	15	0
0	0	0
29	8	2

34	9	3
13	8	0
0	0	0
18	1	0
35	2	0
26	7	1
83	4	0
16	7	1
1	25	1
0	11	1
5	0	0
0	0	0
4	2	0
23	0	0
5	0	0
6	1	0
2	0	0

3	0	0
0	0	0
9	0	0
12	1	0
4	0	0
0	2	0
6	0	0
0	0	0
0	0	0
0	9	0
129	122	8
0	29	0
0	1	0
0	5	0
0	0	0
2	0	0
0	0	0
0	0	0
0	0	0

3186	2757	117
240	25	7
154	8	0
59	1	0
47	41	1
83	46	4
41	5	2
58	33	6
0	4	0
8	11	1
50	9	1
9	5	2
11	0	0
12	0	0
52	4	0
7	0	0
1	2	1
0	0	0

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2	1	0
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17987	2398	286
662	66	5
352	136	22
540	8	2
127	60	12
145	20	4
88	24	7
320	42	22
181	11	0
75	20	1
94	10	4
19	2	0
6	0	0
51	4	1
29	2	0

16	3	1
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23	5	5
6	3	0
5	3	0

2	1	0
4	1	0
7	0	0
6	0	0
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4	0	0
4	1	0
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3	1	0
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110	6	4
6	2	0
10	4	2
4	0	0
12	0	0

8	0	0
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57	31	2
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17	8	0
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Local transmission

Figures

Figure 1

World epidemic curve of confirmed COVID-19 cases and mortality rate Source: WHO March 2020

Figure 3

A. SARS coronavirus main peptidase in complex with an inhibitor Vitamin K2-7. B. SARS coronavirus main peptidase in complex with an inhibitor Tetrahydrocurcumin. C. SARS coronavirus main peptidase in complex with an inhibitor matairesinol.

Figure 4

A. COVID-19 main protease in complex with an inhibitor VitaminK 2-7. B. COVID-19 main protease in complex with an inhibitor Tetrahydrocurcumin. C. COVID-19 main protease in complex with an inhibitor matairesinol.

Supplementary Files

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