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A study on natural phytochemicals and antiviral drugs to combat the deadly covid-19- an *in silico* approach

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Abstract- Novel coronavirus (COVID-19) cases were first reported in Wuhan, Hubei province of China and have since spread all over the world. The virus is spreading rapidly by human to human transmission despite serious precautions, threatening a pandemic that will affect billions of people. Currently there are no vaccines, monoclonal antibodies or drugs available for SARS-CoV-2. There is an urgent need to identify antiviral compounds that can combat the effects of this deadly virus. In this review, an effort is taken to perform molecular docking of some natural phytochemicals to 2019-nCoV spike receptor-binding domain. The docking studies were carried out in Autodock 4.2.6 and the drug likeness properties were predicted using SwissADME webserver. The results revealed that quercetin (-8.71 Kcal/mol) and theaflavin (-7.36 Kcal/mol) from *Camellia sinensis* had best binding scores with 2019-nCoV spike receptor-binding domain.

***Keywords*:** Coronavirus, SARS-CoV-19, Docking, Phytochemicals, COVID-19

I. INTRODUCTION

Coronaviruses belongs to the Coronaviridae family in the order of Nidovirales. Corona viruses are named so because they have a characteristic corona like spikes on the outer surface. Coronaviruses range from 65-125 nm in diameter and they contain a single-stranded RNA as a nucleic material, size ranging from 26 to 32kbs in length [1]. Coronaviruses are known to infect a wide range of hosts including humans, other mammals and birds. The infected hosts often exhibit different clinical symptoms ranging from asymptomatic to severe [2]. There are six known coronaviruses that cause infection in humans. Among these, coronavirus 229E, OC43, NL63, and HKU1 generally cause mild cold-like symptoms, whereas Severe Acute respiratory syndrome-coronavirus (SARS-CoV) and Middle East respiratory syndrome-coronavirus (MERS-CoV) cause severe respiratory diseases such as pneumonia and death [3].

An outbreak of novel coronavirus (SARS-CoV-19) infection that emerged in Wuhan, China has progressed rapidly and led to more than 66 lakh cases and 3.9 lakh deaths worldwide as of June 6, 2020 and has evolved as a major threat. The disease caused by the novel coronavirus, called as COVID-19 is characterized by fever, cough, shortness of breath, pneumonia, fatigue and in many cases leads to death [4]. To date, there are no SARS-CoV-2-specific antiviral agents. Researchers have been racing to find possible treatments to save lives and produce vaccines for future prevention.

Medicinal plants have been used to treat a variety of infectious and non-infectious diseases since ancient times. They synthesize a variety of chemical compounds that perform important functions to defend against pathogenic microorganisms [5]. *Camellia sinensis* (tea) and *Azadiratcha indica* (neem) are the most commonly found plants in India with a wide range of pharmaceutical properties including antioxidant, antiviral and antibacterial activities [6] [7].

Thus the present study is aimed to perform a comparative docking analysis of some of the phytochemicals that are present in *Camellia sinensis*, *Azadiratcha indica* namely, Catechin, Chlorogenic acid, Quercetin, Theaflavin, Nimbin and Azadirachtin to 2019-nCoV spike receptor-binding domain using Autodock 4.2.6.

II. METHODOLOGY

Protein preparation

The 3D structure 2019-nCoV spike receptor-binding domain (PDB ID: 6M0J) was downloaded from the Protein Data Bank. The ACE2 domain was removed from the spike receptor binding domain. The docking calculations were performed using Autodock 4.2.6.

Ligand preparation

A total of 6 compounds namely Catechin, Chlorogenic acid, Quercetin, Theaflavin from *Camellia sinensis* and Nimbin, Azadirachtin from *Azadiratcha indica* were selected from literature study to carry out docking. Three antiviral drugs that are currently used in treatment namely Hydroxy chloroquine, Oseltamavir and Ritonavir were also subjected to docking with the spike protein of Covid-19. (T- 1). The structures of selected compounds to be docked with target protein were obtained from the PubChem

database of the National Centre for Biotechnological Information (NCBI) and converted to PDB file format using CORINA classic.

Molceular docking

The molecular docking approach can be used to study the interaction between a small molecule and a protein at the atomic level, which allow us to understand the behaviour of small molecules in the binding site of target proteins [8]. Molecular docking is routinely used for understanding drug-receptor interactions in modern drug designing [9]. The use of computational methods in the early stages of target identification and drug discovery becomes more attractive to solve the pressing need of combating the pathogens [10].

Molecular docking was carried out using Autodock 4.2.6. The docking results were visualized using PyMOL and the type of the interactions involved was visualized using Discovery studio.

Druglikeness properties

SwissADME, a free web tool was used to analyse the pharmacokinetics and druglikeness properties of these compounds. Lipinski's rule was analysed to evaluate the druglikeness of the compounds [11].

III. RESULTS AND DISCUSSION

Coronaviruses (CoVs) belong to a group of viruses that can infect humans and vertebrate animals. Coronavirus infections affect the respiratory, digestive, liver, and central nervous systems of humans and animals [12]. The present study focussed on docking some natural phytochemicals with 2019-nCoV spike receptor-binding domain. Medicinal plants have been used in traditional health care systems since ancient times and are still the most important health care source for a vast majority of the population around the world. About 25% of the commonly used antiviral medicines contain compounds isolated from plants [13].

The target protein 2019-nCoV spike receptor-binding domain was docked with Catechin, Chlorogenic acid, Quercetin, Theaflavin, Nimbin and Azadirachtin by Autodock 4.2.6. The antiviral drugs, Hydroxy chloroquine, Oseltamavir and Ritonavir were also included in the docking study. The energy values and the amino acids involved in interactions between protein and ligands are presented in T- 1.

The energy values of binding affinities of Catechin, Chlorogenic acid, Quercetin, Theaflavin, Nimbin and Azadirachtin obtained by Autodock 4.2.6 were -6.93, -5.34, -8.71, -7.36, -7.4, -6.24 Kcal/mol respectively. The binding energy of antiviral drugs Hydroxy chloroquine, Oseltamavir and Ritonavir were found to be -7.16, -8.9, -5.6 Kcal/mol respectively. The docking poses were analyzed and the amino acid residues involved in the various interactions were studied. The binding energies of the phytochemicals were significantly similar to those that of the antiviral drugs.

The free energy of binding was found to be best for Quercetin followed by other ligands in the order Quercetin (-8.71) > Nimbin (-7.4) > Theaflavin (-7.36) > Catechin (-6.93) > Azadirachtin (-6.24) > Chlorogenic acid (-5.34).

Many studies have been conducted to test the antiviral potential of phytochemicals. Quercetin, Chlorogenic acid, Theaflavin and Catechin has been shown to act as an antiviral agent against many viruses including Influenza A virus, herpes simplex virus type 1 and respiratory syntical virus. They also act as antioxidants that protect the cells against free radicals [14] [15] [16] [17]. Quercetin is present in abundance in plants and it diminishes the replication of many viruses like the highly pathogenic influenza virus, rhinovirus, dengue virus type-2, HSV-1, poliovirus, adenovirus, Epstein-Barr virus, Mayaro virus, Japanese encephalitis virus, respiratory syncytial virus, and HCV [18]. In, a similar study Nimbin and Azadirachtin were docked against NS2B-NS3 protease of dengue virus. The results revealed that both phytochemicals were potent inhibitors of the viral protease [19].

In the present study, an attempt was made to dock the bioactive phytochemicals of tea and neem by *in silico* methods. The results revealed that the phytochemicals showed good binding affinity with the 2019-nCoV spike receptor-binding domain.

Lead-likeliness properties

Absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties play important roles in the development of a drug candidate and in clinical trials [20]. The pharmacokinetic properties and druglikeness of the selected ligands were predicted using SwissADME and are illustrated in Table 2. Catechin, Quercetin and Nimbin has high gastro-intestinal absorption whereas Chlorogenic acid, Theaflavin and Azadirachtin has low absorption.

IV. CONCLUSION AND FUTURE SCOPE

SARS-CoV-19 virus has emerged as a serious threat with its alarming levels of spread and severity. Molecular docking is a promising tool for the creation of more effective and potential drugs through ligand-based drug designing approaches. Based on the obtained docking results in the present study, the ligands could be a good target for the spike protein that may inhibit the growth of the virus. Of the selected ligands, quercetin and theaflavin showed best binding with the 2019-nCoV spike receptor-binding domain with a score of -8.71 and -7.36 Kcal/mol respectively. These phytochemicals should be further explored through *in vitro* and *in vivo* studies.

Figures and Tables

Table-1 Results of docking analysis performed on Autodock 4.2.6 software between ligands and 2019-nCoV spike receptor-binding domain

Ligand	Estimated free energy of binding (kcal/mol)	Aminoacids involved in interactions
Catechin	-6.93	Phe 390, Asp 350, Ala 348, Asp 382, Arg 393
Chlorogenic acid	-5.34	Asp 206, Lys 562, Gly 395, Asn 394, Phe 400, His 401, Arg 514
Quercetin	-8.71	Leu 91, Leu 95, Glu 208, Val 209, Asn 210, Val 212, Ala 396, Ser 563, Pro 565
Theaflavin	-7.36	Phe 40, Trp 69, Ala 348, Asp 350, Asp 382, Phe 390, Arg 393
Nimbin	-7.4	Ala 99, Tyr 385, Phe 390, Leu 391, Arg 393, Asn 394, His 401
Azadirachtin	-6.24	Phe 40, Trp 69, Ala 348, Trp 349, Asp 350, His 378, Asp 382, Tyr 385
Hydroxychloroquine	-7.16	Phe 40, Ala 348, Asp 350, Asp 382, Phe 390, Leu 391, Arg 393, His 401
Oseltamavir	-8.9	Phe 40, Ala 348, Trp 349, Asp 350, Asp 382
Ritonavir	-5.6	Ser 47, Thr 347, Ala 348, Trp 349, Asp 350

Table 2- Druglikeness of the ligands

(GI: Gastrointestinal, TPSA: Topological polar surface area)

Ligand	SwissADME filters							
	H donor	H acceptor	Molar mass (g/mol)	Log P	Water solubility	GI absorption	TPSA (Å²)	Drug likeness
Catechin	5	6	290.27	1.54	Soluble	High	110.38	Yes
Chlorogenic Acid	6	9	354.31	-0.64	Soluble	Low	164.75	Yes
Quercetin	5	7	302.24	2.01	Soluble	High	131.36	Yes
Theaflavin	9	12	564.49	2.34	Moderately Soluble	Low	217.60	No
Nimbin	0	9	540.60	3.9	Moderately Soluble	High	118.34	Yes
Azadirachtin	3	16	720.71	-0.2	Soluble	Low	215.34	Yes

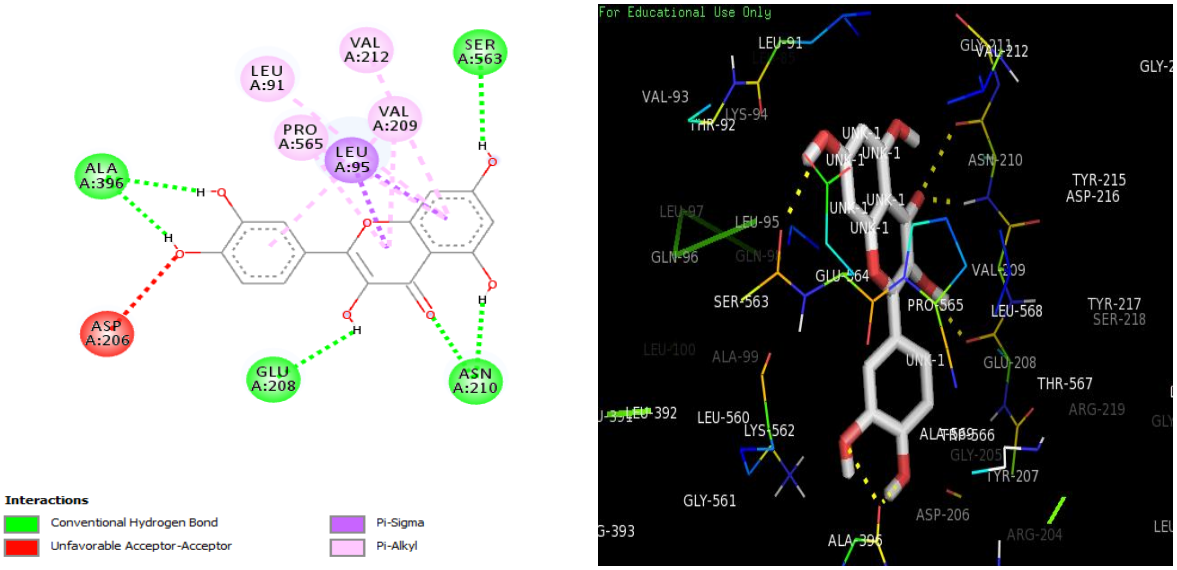

Figure-1 Visualization of Quercetin docked with *2019-nCoV spike receptor-binding domain using PyMOL and Discovery studio*

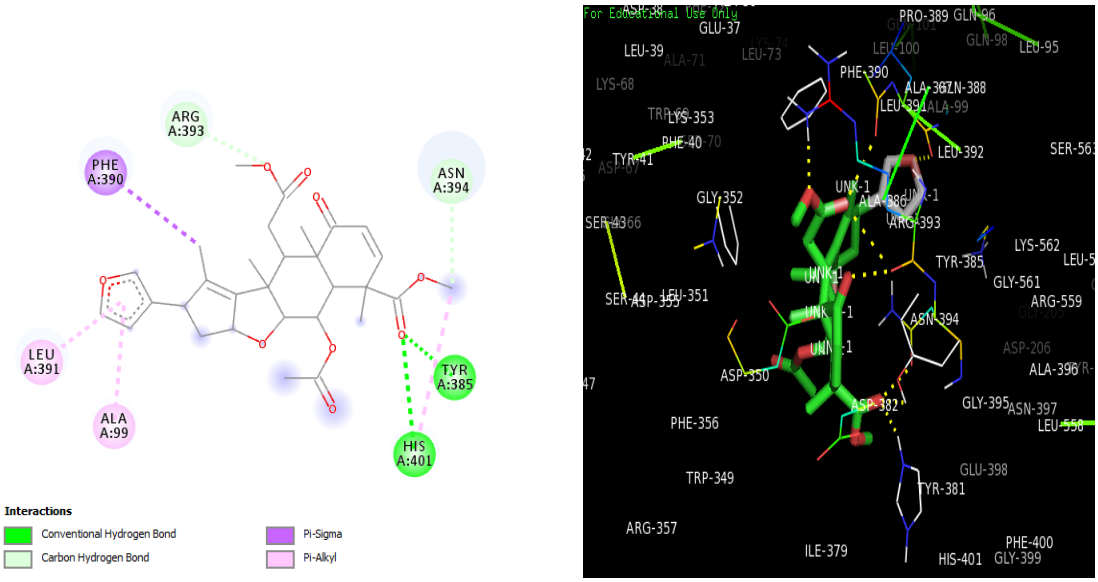

Figure-2 Visualization of Nimbin docked with *2019-nCoV spike receptor-binding domain using PyMOL and Discovery studio*

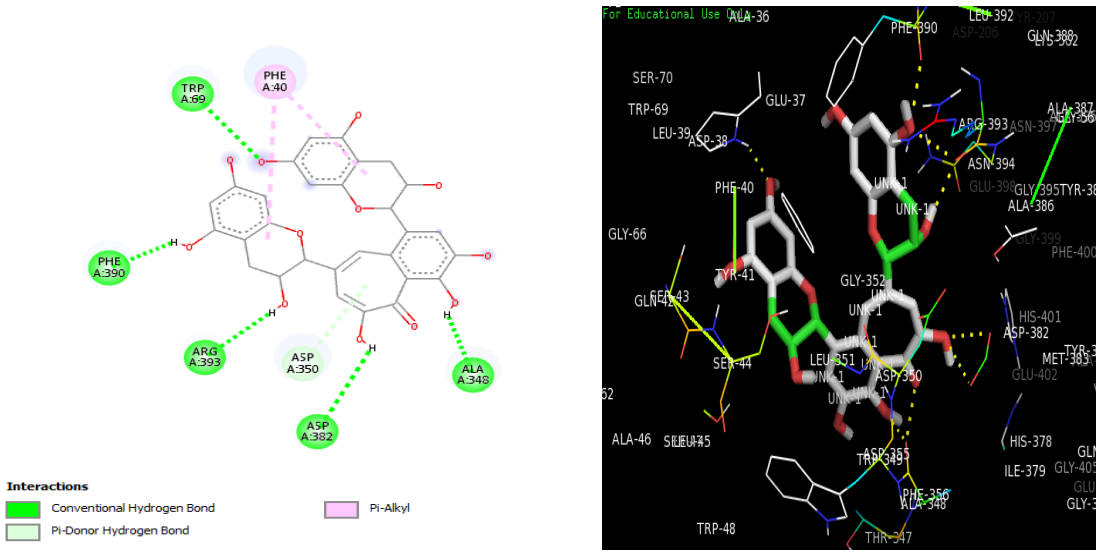

Figure-3 Visualization of Theaflavin docked with *2019-nCoV spike receptor-binding domain using PyMOL and Discovery studio*

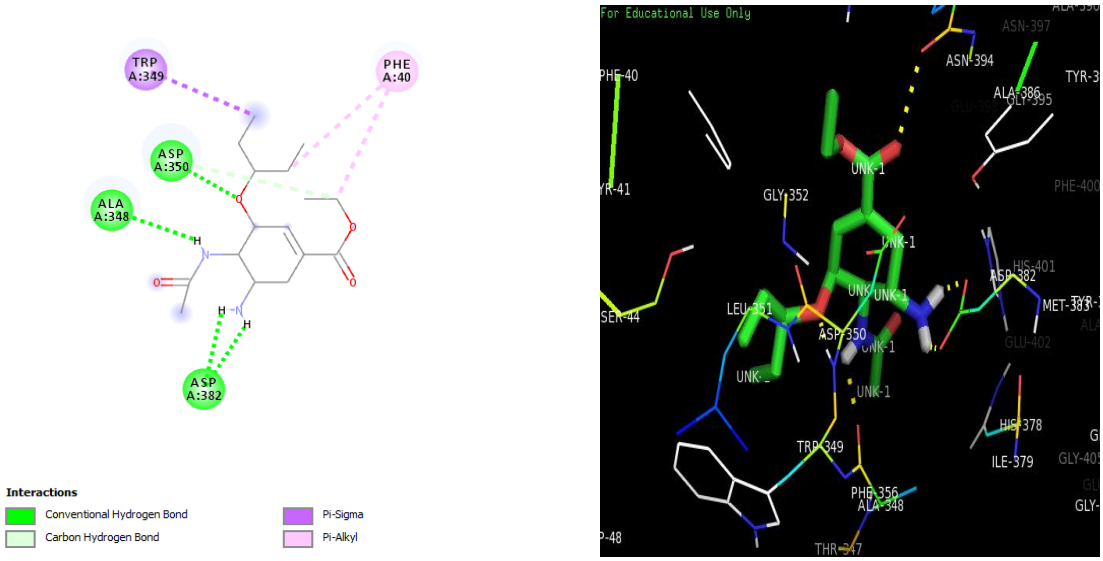

Figure-4 Visualization of *Oseltamavir* docked with *2019-nCoV spike receptor-binding domain using PyMOL and Discovery stud*

REFERENCES

[1] N. Zhong, B. Zheng, Y Li, L. Poon, Z.Xie, K. Chan *et al*, "Epidemology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's republic of China, in February, 2003". *The Lancet*. 362 (9393) (2003), pp. 1353-1358.

[2] J Cui, F Li, ZL Shi, "Origin and evolution of pathogenic coronaviruses", *Nature Reviews Microbiology*, 2019;17(3):181–92.

[3] Kim JM, Chung YS, Jo HJ, et al. "Identification of Coronavirus Isolated from a Patient in Korea with COVID-19", *Osong Public Health and Research Perspectives*. 2020; 11(1):3–7.

[4] "Situation Report – 138". *World Health Organization,* World Health Organization, 27 March. 2020.

[5] Chitra, P and Salupriya, NS, "Comparative Study of Phytochemical Analysis of Leaves And Roots of Persea Americana". *International Journal for Science and Advance Research in Technology* 4(3).

[6] Friedman, M. (2007), "Overview of antibacterial, antitoxin, antiviral, and antifungal activities of tea flavonoids and teas". *Molecular Nutrition & Food Research*. 51: 116-134.

[7] Atawodi, S.E., Atawodi, J.C. "*Azadirachta indica* (neem): a plant of multiple biological and pharmacological activites". *Phytochemistry Reviews* 8, 601-620 (2009).

[8] Meng XY, Zhang HX, Mezei M, Cui M. "Molecular docking: a powerful approach for structure-based drug discovery". *Current Computer Aided Drug Design*. 2011;7(2):146–157.

[9] A.M. Vijesh, Arun M. Isloor, Sandeep Telkar, T. Arulmoli, Hoong-Kun Fun, "Molecular docking studies of some new imidazole derivatives for antimicrobial properties", *Arabian Journal of Chemistry*, Volume 6, Issue 2, 2013, Pages 197-204.

[10] Suguna L and Chitra P, "Exploring biological networks for finding potential drug targets in methicillin resistant staphylococcus aureus", *International Journal of Pharma and Bio Sciences* 2(4).

[11] Lipinski CA. "Lead and drug like compounds: the rule of five revolutions". *Drug Discovery Today Technologies*. 2004;1(4):337–41.

[12] Gautam, Pankaj. (2013). "Antiviral potential of medicinal plants: an overview". *International Research Journal of Pharmacy*. 4. 8-16. 10.7897/2230-8407.04603.

[13] Yang, P., Wang, X. "COVID-19: a new challenge for human beings". *Cellular & Molecular Immunology* (2020).

[14] Wu W, Li R, Li X, et al. "Quercetin as an Antiviral Agent Inhibits Influenza A Virus (IAV) Entry". *Viruses*. 2015;8(1):6. Published 2015 Dec 25. doi:10.3390/v8010006

[15] Kaul, T.N., Middleton, E., Jr. and Ogra, P.L. (1985), Antiviral effect of flavonoids on human viruses. *Journal of Medical Virology*., 15: 71-79.

[16] Ding Y, Cao Z, Cao L, Ding G, Wang Z, Xiao W. "Antiviral activity of Chlorogenic acid against influenza A (H1N1/H3N2) virus and its inhibition of neuraminidase". *Scientific Reports*. 2017;7:45723.

[17] Chowdhury P, Sahuc ME, Rouillé Y, et al. "Theaflavins, polyphenols of black tea, inhibit entry of hepatitis C virus in cell culture". *PLoS One*. 2018;13(11):e0198226..

[18] Ben-Shabat S, Yarmolinsky L, Porat D, Dahan A. "Antiviral effect of phytochemicals from medicinal plants: Applications and drug delivery strategies". *Drug Delivery and Transational Research*. 2020; 10(2):354–367.

[19] Dwivedi, Vivek&Tripathi, Indra& Mishra, Sarad. (2016). "Insilico evaluation of inhibitory potential of triterpenoids from Azadirachta indica against therapeutic target of dengue virus, NS2B-NS3 protease". *Journal of vector borne diseases*. 53. 156-161.

[20] Kolita B, Jyoti Bora A and Hazarik P, "A Search of COVID-19 main Protease Inhibitor from Plant Derived Alkaloids using Chloroquine and Hydroxychloroquine as Reference: An *In-silico* Approach". International Journal of Scientific Research in Biological Sciences Vol.7, Issue.2, pp.51-61

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