Identification of Dietary Molecules as Therapeutic Agents to Combat COVID-19 Using Molecular Docking Studies

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Abstract
Recently, a new and fatal strain of coronavirus named as SARS-CoV-2 (Disease: COVID-19) appeared in Wuhan, China in December of 2019. Due to its fast growing human to human transmission and confirmed cases in nearly every country, it has been declared as pandemic by World Health Organisation (WHO) on 11 March 2020. Till now, there is no therapy such as vaccines and specific therapeutic agents available globally. Inspite of this, some protease inhibitors and antiviral agents namely lopinavir, ritonavir, remdisivir and chloroquine are under investigation and also implemented in several countries as therapeutic agents for the treatment of COVID-19. Seeing the health crisis across the world, it was our aim to find out a suitable drug candidate which could target SARS-CoV-2. For this purpose, molecular docking of 7 proteins of SARS-CoV-2 was done with 18 active constituents that have previously been reported to be antiviral or anti-SARS-CoV agents. The docking results of these 18 compounds were compared with 2 FDA approved drugs that have are currently being used in COVID-19, namely Remdesivir and Chloroquine. Our result revealed that among all, epigallocatechin gallate (EGCG), a major constituent of green tea, is the lead compound that could fit well into the binding sites of docked proteins of SARS-CoV-2. EGCG showed very strong molecular interactions with binding energies -9.30, -8.66, -8.38, -7.57, -7.26, -6.99 and -4.90 kcal/mole for 6y2e, 6vw1, 6vww, 6lxt, 6vsb, 6lu7 and 6lvn proteins of SARS-CoV-2, respectively. Therefore, EGCG as per our results, should be explored as a drug candidate for the treatment of COVID-19.

1. Introduction
The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV–2) has emerged as a virus of grave concern due to its ability to cause the severe and life-threatening disease called coronavirus disease 2019 (COVID-19) with high mortality rate worldwide [1]. World Health Organization (WHO) declared COVID-19 as a pandemic disease on 11 March 2020 [2]. As per “situation report–63” released by WHO on 23 March 2020, more than 300,000 cases and 14510 deaths have been confirmed globally. By January 12, 2020 the Chinese authorities had released the whole genome sequence of SARS-CoV-2 which has been hallmark for researchers worldwide to quickly identify and develop the
potential candidates by using computational methods and other therapeutic techniques [3]. First publication along with other recent studies on current outbreak revealed that SARS-CoV–2 is a member of the coronavirus family and shared 96% similarity with previously identified genome of SARS-CoV that had emerged in China in November, 2002 [4].

Based on recent studies, this virus has a complex genomic organization consisting of single stranded-positive sense RNA which codes for several structural and non-structural proteins (nsps) including envelope protein (E) gene, spike protein (S) gene, membrane protein (M) gene, nucleocapsid protein (N) gene, replicase complex (orf1ab) gene along with 3’ and 5’-untranslated region (UTR) [5, 6]. As per study carried out by K. Anand et al. in 2003, coronaviruses make small polypeptide chains during transcription by proteolytic enzymes such as papain-like protease (PLpro) and 3-chymotrypsin-like protease (3CLpro) to form several types of non-structural proteins which are responsible for viral replication [7]. Additionally, unique spike protein (S) has also been found to have a strong affinity with the human ACE2 receptor [8]. Thus, both main protease and spike protein complexed with human ACE2 receptor might be important targets to discover and develop vaccines and other therapeutic agents to control this new CoV.

Since the first reported case of COVID 19 on 31 December 2019, no specific medication is available to prevent or kill the SARS-CoV–2 so far. Preliminary treatment of COVID–19 depends upon the severity of infection which ranges from mild to strong including, if necessary administration of oxygen, maintaining the body fluids and administration of antibiotics and antiviral drugs to combat co-infections because of numerous types of bacteria and virus [9]. Recent studies suggested the use of remdisivir and chloroquine along with HIV–1 protease inhibitors like lopinavir and ritonavir as therapeutic agents for the treatment of COVID–19 [10]. Moreover, Xu et al. identified four tested drugs nelfinavir, praziquantel, perampanel and pitavestatin as potential candidates against SARS-CoV–2 using computational methods. Therefore, three approaches need to be urgently pursued, namely vaccines, post exposure prophylaxis and therapeutic agents that target virus-encoded functions, replication, infection as well as the respiratory symptoms in humans that exacerbate the disease.
In the last decade, dietary molecules from edible herbs and vegetables have of great interest among researchers worldwide because of their diversified and complex structures having health benefits with no or minimal side-effects [11]. These dietary molecules may be developed as herbal medicines or therapeutic agents in the prevention and treatment of current COVID-19 disease. In previous studies, numerous dietary molecules such as curcumin, savinin and betulinic acid have been found to show inhibition of SARS-CoV in the range of 3–10 μM concentrations [12]. Recently, kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, and epicatechin-gallate have been identified as significant anti-COVID-19 agents with the help of molecular docking study [13]. Seeing this terrible and deadly crisis, as yet, it is urgent and timely need to evaluate and develop more potent and reliable anti-COVID-19 agents which are easy to reach us. In this study, we evaluated 18 dietary molecules namely epigallocatechin gallate (EGCG), piperine, apigenin, curcumin, gingerol-[6], beta glucan, resveratrol, myricetin, quercetin, genistein, diadzein, alliin, allicin, sulphoraphane, phycocyanobilin, ferulic acid and alpha lipoic acid by using molecular docking study. Our findings will provide valuable information to explore and develop dietary molecules as novel anti-COVID-19 agents in the future.

2. Material And Methods
To obtain molecular interactions of selected dietary molecules with the binding pockets of different types of proteins of COVID-19, molecular docking analysis was carried out by using computer cluster system provided by Gigabyte Technology co., LTD, model-B365M DS3H running Intel Core i5–9400F CPU @2.90GHz Processor, 16 GB RAM, 1TB hard disk, and Intel HD Graphic card. The crystal structures of seven types of newly released proteins of COVID-19 were retrieved from protein data bank (PDB) site whose PDB IDs were 6lu7, 6lvn, 6lxt, 6vsb, 6vw1, 6www and 6y2e. Prior to docking study, the retrieval of target protein binding sites was necessary to find the best docking result. Binding site retrieval was performed with the help of Discovery Studio 3.0 Visualizer by removing Hetatm and adding hydrogen atom to the protein. The top binding sites were used for the docking analysis. The chemical structures of selected dietary molecules and reference drugs were retrieved from the PubChem site with their PubChem IDs: 650336, 87310, 5280443, 439262, 969516, 5281708,
The geometries of all compounds were optimized with Discovery Studio 3.0 visualizer by using clean geometry option and applied the Dreiding force field on ligand molecule. The preparation of target proteins was performed on AutoDock tool 4.2.6, by addition of polar hydrogen atoms and Kollman charges and their PDBQT files were saved. Ligand preparation was done by detecting root, set number of torsion and aromaticity criterion. Preparation of grid maps for each protein was performed by inputting binding site coordinates which were retrieved by Discovery Studio 3.0 visualizer and Grid Box X, Y, and Z dimensions changed from default to 50×50×50. Docking was performed by Lamarckian genetic algorithm and empirical scoring function by using flexible method. All docking results were analyzed with the help of AD4 analyze option to find out the binding energy (BE) and inhibitory constant (Ki) of the ligand with a particular target protein. Visualization of structural complex of ligand and protein was done with the help of Discovery Studio 3.0 Client [14, 15].

3. Result And Discussion
In the light of recent pandemic situation, there are two questions raised: first of which protein molecule of SARS-CoV-2 is responsible for their high virulence and replication processes while second is that which therapeutic agent can prevent or kill the SARS-CoV-2. For the answer of the first question, we searched the literature and found out recently released structural and non-structural proteins of SARS-CoV-2 which are structured and repositioned on Protein Data Bank (PDB) site (https://www.rcsb.org/). Thus, based on database of PDB, we have selected seven different types of protein macromolecules which play a pivotal role in propagating the SARS-CoV-2 (table 1). Our intriguing protein targets include main protease covid-19 (6lu7), structure of the 2019-nCoV HR2 Domain (6lvn), structure of post fusion core of 2019-nCoV S2 subunit (6lxt), prefusion 2019-nCoV spike glycoprotein (6vsb), structure of 2019-nCoV chimeric receptor-binding domain complexed with its receptor human ACE2 (6vw1), crystal structure of NSP15 endoribonuclease from SARS CoV-2 (6vww) and crystal structure of the free enzyme of the SARS-CoV-2 (2019-nCoV) main protease (6y2e).
Due to technical limitations, Table 1 is provided in the Supplementary Files section.

In search of the answer for the second question, we selected 18 dietary molecules namely allicin, alliin, apigenin, beta-glucan, curcumin, diadzein, EGCG, ferullic acid, genistein, gingerol-[6], glucosamine, alpha-lipoic acid, myricetin, phycocyanobilin, piperine, quercetin, resveratrol and sulphoraphane that are abundantly present in commonly used herbs, spices, fruits and vegetables. All the dietary molecules exhibited either antiviral or anti-SARS-CoV activities as reported in previous studies (table 2). Recent studies revealed that some drugs like remdisivir, chloroquine, lopinavir and ritonavir could be repurposed and studied to treat COVID-19. All these dietary molecules as well as selected drugs remdisivir and chloroquine as control to verify and compare our results were docked against SARS-CoV-2 3CL homology model. Based on our docking analysis, we recommend that the ligands with the highest binding affinity and lowest inhibition constant be considered for further investigation.

Due to technical limitations, Table 2 is provided in the Supplementary Files section.

Among these dietary molecules, epigallocatechin gallate (EGCG) which is found abundantly in green tea, was found as most active agent against COVID-19. EGCG showed highest binding affinity (-9.30 kcal/mole) and lowest inhibition constant (0.152 µM) for 6y2e protein. Moreover, EGCG exhibited a strong molecular interaction with 6vw1 which is an important target of this new CoV. It showed highest binding affinity and lowest inhibition constant with -8.66 kcal/mole and 0.152 µM values respectively. Further, EGCG displayed excellent interactions with 6vww wherein it showed highest binding affinity (-8.38 kcal/mole) with lowest inhibition constant at 0.724 µM concentration. Additionally, EGCG also exhibited good molecular interactions with SARS-CoV-2 proteins 6lu7, 6lnv, 6lxt, and 6vsb with the values of binding energies and inhibition constant as -6.99, -4.90, -7.57, -7.26 kcal/mole and 7.57, 255.95, 2.84, 4.75 µM concentrations. The computed activity of EGCG was found to be higher than that of both reference drugs, Remdesivir and Chloroquine. All docked poses are depicted in figure 1 and 2 which show strong interactions of EGCG with selected protein residues.

It has been established that the molecules having hydroxyl (-OH) and carbonyl (C = O) functionalities showed strong intermolecular interactions with amino acid residues at active sites of proteins through
physical forces such as hydrogen bonds and hydrophobic bonds. Due to amount and types of these intermolecular interactions, they show druggable and druglikeness properties. In this study, we also identified eight more active phytochemicals namely curcumin, apigenin, beta-glucan, myricetin, piperine, genistein, diadzein and quercetin. Apigenin, myricetin, and quercetin are flavonoids while genistein and diadzein are isoflavonoids. On the other hand curcumin and piperine are phenolic compounds whereas beta-glucan is a polymer of sugar. They all have hydroxyl (−OH) and carbonyl (C = O) functionalities in their core structures and hence exhibited strong molecular interaction with all protein macromolecules chosen under this study. All values of binding affinities and inhibition constant of these dietary molecules are listed in table 3.

Table 3: Molecular docking values of phytochemicals against target protein macromolecules

| Phytochemicals | Targets Proteins; binding energy in kcal/mole (inhibition constant in µM) |
|----------------|--------------------------------------------------------------------------|
|                | 6lu7          | 6lvn          | 6lxt          | 6vsb          |
| 1              | EGCG         | -6.99 (7.57)  | -4.90 (255.95)| -7.57 (2.84)  | -7.26 (4.75)  |
| 2              | Curcumin     | -6.04 (37.57) | -4.73 (340.89)| -5.50 (92.90)| -5.05 (197.96)|
| 3              | Apigenin     | -5.96 (43.03) | -3.71 (1.9x10^-5)| -5.13 (1.74x10^-5)| -5.98 (4.1x10^-5)|
| 4              | Beta Glucan  | -5.96 (42.79) | -4.16 (889.95)| -5.06 (195.39)| -3.20 (4.4x10^-5)|
| 5              | Myricetin    | -5.38 (114.10)| -3.70 (1.96x10^-5)| -5.74 (62.01)| -6.14 (313.2)|
| 6              | Quercetin    | -5.29 (132.27)| -3.68 (2.02x10^-5)| -5.73 (63.52)| -6.14 (313.2)|
| 7              | Piperine     | -5.16 (165.72)| -4.08 (1.02x10^-5)| -5.40 (109.87)| -6.05 (36.85)|
| 8              | Genistein    | -5.03 (204.91)| -3.97 (1.24x10^-5)| -5.68 (69.09)| -6.54 (16.04)|
| 9              | Diadzein     | -4.86 (275.53)| -3.72 (1.89x10^-5)| -5.21 (151.77)| -6.16 (30.34)|
| 10             | Ferulic acid | -4.76 (322.26)| -2.79 (9.00x10^-5)| -3.75 (1.80x10^-5)| -5.44 (103.05)|
| 11             | Alliin       | -4.66 (385.74)| -3.90 (1.37x10^-5)| -5.02 (210.26)| -4.57 (447.67)|
| 12             | Lipoic acid  | -4.58 (439.80)| -1.90 (40.6x10^-5)| -3.25 (4.16x10^-5)| -4.93 (243.6)|
| 13             | Resveratrol  | -4.20 (832.91)| -3.58 (2.38x10^-5)| -4.32 (685.04)| -5.57 (82.09)|
| 14             | Glucosamine  | -4.06 (1.06x10^-5)| -3.59 (2.32x10^-5)| -5.26 (138.93)| -4.89 (262.36)|
| 15             | Gingerol-6   | -4.00 (1.16)  | -2.23 (23.38)  | -3.08 (50.56)  | -4.46 (537.58)|
| 16             | Sulforaphane | -3.74 (1.81x10^-5)| -2.25 (22.3x10^-5)| -3.11 (5.22x10^-5)| -3.43 (3.0x10^-5)|
| 17             | Allicin      | -3.46 (2.89x10^-5)| -2.09 (29.4x10^-5)| -3.20 (4.49x10^-5)| -3.46 (2.92)|
| 18             | PCB          | +0.16, (Nil)  | -3.12 (5.14x10^-5)| -4.63 (4.05x10^-5)| +11.3 (Nil)|
| 19             | Remdesvir    | -2.47 (15.4x10^-5)| -2.68 (10.7x10^-5)| -4.84 (281.48)| -4.27 (745.64)|
| 20             | Chloroquine  | -3.62 (2.2x10^-5)| -3.26 (4.0x10^-5)| -4.35 (65.15)| -4.79 (309.3)|

6lu7: Main protease of covid-19; 6lvn: Structure of the 2019-nCoV-HR2 Domain; 6lxt: Structure of
From docking results as well as analysis of binding affinity with binding pockets within active sites of proteins, we prepared a decreasing order of their potency against SARS-CoV–2.

Order of activity against main protease (6lu7) of SARS-CoV-2 is EGCG > curcumin > apigenin > beta-glucan > myricetin.

Order of activity against HR2 domain of spike glycoprotein (6lvn) of SARS-CoV-2 is EGCG > curcumin > glucosamine > quercetin > myricetin.

Order of activity against chimeric receptor-binding domain of spike glycoprotein (6vw1) of SARS-CoV-2 is EGCG > curcumin > myricetin > glucosamine.

Order of activity against single receptor binding domain of spike glycoprotein (6vsb) of SARS-CoV-2 is EGCG > genistein > myricetin > quercetin > curcumin.

Order of activity against NSP15 endoribonuclease (6vww) of SARS-CoV-2 is EGCG > curcumin > genistein > myricetin.

Order of activity against post fusion core S2 subunit (6lxt) of SARS-CoV-2 is EGCG > myricetin > quercetin.

Order of activity against free enzyme of SARS-CoV-2 main protease is EGCG > curcumin > apigenin > myricetin > beta-glucan.

We, thus, found EGCG, curcumin, myricetin, genistein, myricetin, beta-glucan, quercetin and diadzein as recommended compounds for the treatment of COVID–19 (figure 3). Finally, as a result of our study, we have discovered EGCG as potent SARS-CoV–2 inhibitor which might be a drug candidate in future to treat this dreadful disease.

**Diet Suggestions**

In light of current findings, intake of the suggested foods (Table 4) as supplements in adequate doses could be helpful to prevent and control COVID–19 infection by suppression of propagation and pathogenesis of SARS-CoV–2. Since green tea is a rich source of EGCG, it may have a major role in combating the SARS-CoV–2. Our careful and extensive analysis revealed that other promising molecules that can be easily available to us, might also be expected to suppress the pathogenicity of this coronavirus. It might be helpful to include the suggested food substances in the diet of COVID 19 patients and healthcare workers to control and avoid the infection. Doing so may also prevent secondary infections, since these compounds have previously been reported to have antimicrobial activity. Hence, these dietary suggestions may also be implemented in case of influenza and common
flu.

Table 4: Daily dose based diet suggestion for prevention and treatment of COVID-19

| Dietary Molecules (DM) | Recommended Daily Intake | Amount of DM present in Food Source (per 100g) | Suggested Dose of Food Source Per Day (gm) | t1/2(h) | Suggested Frequency | Suggested Preparation |
|-----------------------|--------------------------|-----------------------------------------------|------------------------------------------|--------|---------------------|----------------------|
| EGCG                  | 800 mg                   | 7.38 gin Green Tea                            | 16.67*                                   | 4.5    | 3-4 times a day after every 4.5 h | Brewed for 3 minutes in boiling water |
| Curcumin              | 500 mg                   | 3.2 gin Turmeric                              | 15.625                                   | 6-7    | 3 times a day every 6.5 h | Mix with lukewarm milk |
| Apigenin              | 3-10 mg                  | 1.2 gin Chamomile Tea                         | 1.08**                                   | 12     | 2 times a day every 12 h | Brewed in water      |
|                       |                          | 300 mg in Parsley                             | 2.16                                     |        |                     |                      |
| Beta-Glucan           | 3-10 g                   | 5.5 g in Whole Grain Oats#                    | 118.18                                   | 19.5-27.3 | Once a day | Boil in milk |
|                       |                          | 11 g in Whole Grain Barley##                 | 59                                       |        |                     |                      |

#average based on range 3-8%; ##average based on range 2-20%; *assuming 65% yield; **assuming 50% yield. All values of dietary molecules are taken from USDA databases (https://doi.org/10.15482/USDA.ADC/1178142)

4. Conclusion

In concluding remark, COVID–19 has become a global health concern. Causalities are increasing day by day throughout the globe. Researchers and medical practitioners are unable to search out new therapeutic agents so far to treat this disease except some already FDA-approved drugs which act on the main protease of SARS-CoV. Thus, the aim of our study was to screen the antiviral and anti-SARS dietary molecules that are easily available with the help of computational methods. For this, we screened 18 bioactive dietary molecules by molecular docking study against recently released proteins of SARS-CoV–2. We have taken two drugs remdesvir and chloroquine to compare the computed activity of selected dietary molecules. Among them, EGCG, curcumin, myricetin, genistein, myricetin, beta-glucan, quercetin and diadzein were found as active agents against COVID–19. EGCG exhibited the strongest molecular interactions within pockets at active sites of all the proteins of SARS-CoV–2 which were taken under this study. EGCG was also far more active than the standard drugs remdesvir and chloroquine. Therefore, in our study we suggest EGCG as a potential inhibitor of...
SARS-CoV-2. However, further research is needed to investigate the mechanism and mode of action of these phytochemicals in future.

Declarations

Conflict of interests

The author(s) declared no conflict of interest

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Figures
Figure 1

Depiction of molecular docking of EGCG with different types of protein related to SARS-CoV-2. (A) Molecular interaction of EGCG to SARS-CoV-2 main protease. (B) Molecular interaction of EGCG to SARS-CoV-2 HR2 Domain. (C) Molecular interaction of EGCG to post fusion core of SARS-CoV-2 S2 subunit. (D) Molecular interaction of EGCG to prefusion SARS-CoV-2 spike glycoprotein with a single receptor-binding domain up. In this depiction, all oxygen atoms in the molecules are shown in red whereas hydrogen atoms are in blue lines. Hydrogen bonds are indicated in dotted green lines.
Figure 2
Depiction of molecular docking of EGCG with different types of protein related to SARS-CoV-2
(A) Molecular interaction of EGCG to SARS-CoV-2 chimeric receptor-binding domain
complexed with its receptor human ACE2 (B) Molecular interaction of EGCG to NSP15
Endoribonuclease from SARS-CoV-2. (C) Molecular interaction of EGCG to free enzyme of the
SARS-CoV-2 main protease. In this depiction, all oxygen atoms in the molecules are shown
in red whereas hydrogen atoms are in blue lines. Hydrogen bonds are indicated in dotted
green lines.
Figure 3

An illustrative view showing structural and functional proteins of SARS-CoV-2. On the basis of molecular docking, red boxes are showing suggested dietary phytochemicals which are useful to prevent the propagation of SARS-CoV-2. In red boxes, phytochemicals are arranged in decreasing order of their activity. EGCG is the most active against all the target proteins and may have the ability to kill SARS-CoV-2.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.
Tables 1-2.pdf