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Phytoconstituents of *Zingiber officinale* Targeting Host-viral Protein Interaction at Entry Point of SARS-CoV-2: A Molecular Docking Study

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ABSTRACT

Current COVID 19 outbreak is a critical issue in safeguarding public health worldwide. The lack of prophylactic drugs, vaccine and effective antiviral and other supporting therapies has prompted researchers to look for promising leads against the virus. Metabolic pathways and biochemicals involved in pathophysiology of SARS-CoV-2 can be targeted to find out effective inhibitor molecules acting at the entry point of infection. SARS-CoV-2 uses their Spike protein to dock at ACE2 and the serine protease, TMPRSS2 of host cell for Spike protein priming to get entry into the host cell. In the present study phytochemicals from *Zingiber officinale* were evaluated to find their binding with these proteins by conducting ligand-receptor binding docking study with AutoDockVina. The structures were observed by visualizing softwares Pymol to determine unique amino acids of receptor proteins. Physicochemical properties of phytochemicals and chemotherapeutic markers were assessed with Molinspiration tool. Docking study revealed that Gingerenone (-5.87 kcal/mol) and Zingiberene (-5.77 kcal/mol) have shown effective binding affinity towards ACE2. Shoagol (-5.72 kcal/mol), Zingerone (-5.79 kcal/mol) and Zingiberene (-5.52 kcal/mol) have shown higher binding with extracellular domain of serine protease TMPRSS2. Zingiberene scored significant binding energy of -6.23 kcal/mol with Spike protein of SARS-CoV-2. This study provides an evidence base to the experiential learning about use of *Zingiber officinale* in microbial infections. Once further validated, it may lead to development of herbal based anti-viral adjuvants.

Keywords: COVID-19; SARS-CoV-2; ACE2; TMPRSS2; S protein; *Zingiber officinale*

1. INTRODUCTION

COVID-19 is a coronavirus disease caused by 2019 novel corona virus now called as SARS-CoV-2[1]. SARS-CoV-2 is very significant and dreadful virus of *Coronavirinae* subfamily from *Coronaviridae* family[2,3]. *Coronaviridae* have been drawing attention globally since last two decades as its important members severe acute respiratory syndrome (SARS-CoV) (2002-2004) and middle east respiratory syndrome (MERS-CoV) (2012, 2015 and 2018), are intermittently causing pneumonia a respiratory syndrome[4]. SARS-CoV-2 confirmed by Chinese health authorities as an etiological agent for cluster of pneumonia cases in Wuhan, China in December 2019[5]. The bushfire effect of COVID-19 compelled World Health Organisation (WHO) to declare it a Pandemic on 11th March 2020[6]. The epidemic, which started out from Wuhan, China now spread to 214 Countries and Territories around the world with a total of 3,60,41,783 confirmed cases and a death toll of 10,54,604 deaths as on 7th October 2020[7-9]. Fever, non-productive cough, dyspnea, myalgia, fatigue, imbalance in leukocyte counts and radiographic evidence of pneumonia are the important clinical symptoms of COVID-19[10]. In worsening dyspnea ventilator support is required. This may result in another threat of secondary nosocomial infections, such as ventilator-associated pneumonia[11]. Combination of antibacterial and antiviral therapy is being given to the COVID patients[12]. WHO has initially approved the drug chloroquine and hydroxychloroquine trial in "Solidarity trial" for the management of COVID-19[13].

There is a need to identify novel potential inhibitor for SARS-CoV-2 that can control the pathology by targeting its mechanism of infection. SARS-CoV-2 utilises its Spike protein as a significant part of its envelop that participate in the interaction with its cellular receptor angiotensin converting enzyme 2(ACE2)[14]. Consequently, the spike protein is cleaved by extracellular catalytic domain of Transmembrane protease Serine 2 (TMPRSS2) also called as Serine protease or Hepsin[15] leading to entry of virus into the host cell[16]. Therefore, the cascade involved in the attachment and entry of SARS-CoV-2 virus is the most crucial step of pathogenesis mediated by Spike protein, ACE2 and further assisted by extracellular catalytic domain of TMPRSS2 on cell membrane. Inhibition of these steps may lead to the design of promising drug targets for COVID-19.Chloroquine has its root in herbal medicine as it is an analogue of quinine isolated from bark extract of *Cinchona officinalis*[17]. Mother nature treasures many such molecules that can be used as prophylactic, and adjunct to therapeutic approaches. The exploration of herbals for potential prophylactic and therapeutic utility requires a logical interface, that is, *in silico* study for screening or selection of

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active phytoconstituents. The natural plant products provide an excellent resource for discovering novel antiviral agents with the help of shape based superposing docking. Current progress in computational methods can be helpful in selection of probable agents or repurposing licensed drugs[18]. Drug repurposing, meant drug discovery procedure from existing medications, could altogether abbreviate the time and diminish the expense contrasted with a new drug revelation and randomised clinical preliminaries[18]. However the drug repurposing is costly and time-consuming. Computational methodologies offer novel testable theories for methodical medication repositioning[19].

The *Zingiber officinale* is reported to be effective against respiratory ailments. *Z. officinale* has been proved to be loaded with ethnopharmalogical properties including the inhibition of ACE[20]. Also, it is reported to exhibit antibacterial, anti-biofilm and cell permeability activities in case of pneumonia induced by *Pseudomonas aeruginosa*bacteria[21], which is a major cause of ventilator-associated pneumonia[21]. The fresh and dried *Z. officinale* extract have also been shown to possess anti-viral activity against human respiratory syncytial virus and Chikungunya virus as tested in different cell lines[22,23]. In majority of the herbal drugs, the crude or semipurified extracts are generally superior to the isolated phytochemicals in terms of bioactivity as the phytochemical constituents act synergistically. However, for establishing the molecular mechanism of action, studies are carried out on isolated moieties. In the present study it is planned to explore the point of action of major constituents of *Z. officinale* against SARS-CoV-2. Major phytochemicals of Ginger showing following activities have been selected for the ligand-receptor binding docking study. Zingiberene, Shoagol, Gingerdione and Gingerol, are known to obstruct reverse transcriptase enzyme and thereby inhibits viral replication[24]. Zingerone improves cellular and humoral immune response in viral infection[25]. Gingerenone is known to possess anti-hypercholesteremic effect and has been included as the patients with familial hypercholesterolemia (FH) are at very high risk of cardiovascular disease, which is associated with poor outcomes from coronavirus infections[26,27]. The present *in silico* study was performed mainly to find out potential inhibitors for entry of the SARS-CoV-2 virus into the host cell by targeting ACE2, Spike protein, and extracellular domain of hepsin as components of virus-host protein interaction. The binding score were compared with the selected chemotherapeutic marker drugs like chloroquine and hydroxychloroquineas that are reported to be a potent inhibitor of SARS coronavirus infection by binding with ACE2 receptor[11,12]. The aim is to explore the major phytochemicals of *Z. officinale* to select the promising ones that can work holistically at entry point of the virus. Another objective was also to assess the drug-likeness properties of each ligand.

2. MATERIALS AND METHODS

2.1 Softwares

The present *in silico* study was a combination of different web servers and operating system that were used to accomplish individual step including Pubchem(http://pubchem.ncbi.nlm.nih.gov/)[22], RCSB Protein Data Bank (https://www.rcsb.org/)[23], Protein Data Bank Japan (https://www.pdbj.org/)[28], Open Babel (https://protein.plus)[29] Molinspiration (https://www.molinspiration.com/)[30], online SMILES translator and structure file generator (https://cactus.nci.nih.gov/translate/)[31], MGL tool 1.5.6[32], Autodock Vina[32], and Pymol 2.3.4[32].

2.2 Host-Viral Proteins, Phytochemicals and Chemotherapeutic Marker Drugs

Angiotensin converting enzyme 2 (PDB ID: 1R42; native human angiotensin enzyme-related carboxypeptidase)[33] were studied *in silico* by downloading their structures from RCSB Protein Data Bank, Serine protease hepsin (TMPRSS2) 2-{5-[Amino(Iminio)Methyl]-1H-Benzimidazol-2-Yl}Benzenolate (PDB ID: 1P57; Extracellular Domain of Hepsin) was downloaded from Protein Data Bank Japan[34], SARS-CoV-2 Spike ectodomain structure (PDB ID: 6VYB) was retrieved from RCSB Protein Data Bank[35]. Structures of the phytochemicals of *Z. officinale* namely Zingiberene (PubChem CID: 92776), Zingerone (PubChem CID: 31211), Shoagol (PubChem CID: 5281794), Gingerenone (PubChem CID: 5281775), 1-Dehydro- 6-gingerdione (PubChem CID: 139031793), and Gingerol (PubChem CID: 442793) were obtained from Pubchem. Chloroquine(PubChem CID: 2719), hydroxychloroquine (PubChem CID: 3652) and Camostat mesylate (PubChem CID: 5284360) were selected from the list of WHO "Solidarity" clinical trial programme as chemotherapeutic markers[13] and their structures were taken from Pubchem.

2.3 Assessment of Ligands for Drug Likeliness

Virtual screening of ligands by using Molinspirationan online property calculation toolkitfor drug likeliness was performed check violation from 'Lipinski rule of 5' on the basis of physicochemical properties including MiLog P, molecular weight, number of atoms, number of hydrogen bond donors and acceptors and number of rotatable bonds. Ligands were loaded in the Molinspiration software with SMILES as an input and the calculation of their physicochemical properties were conducted as per 'Lipinski rule of 5'[38].

2.4 *In silico* Screening

2.4.1 Preparation of Receptors and Ligands

The pdb structure of ACE2, SARS-CoV-2 Spike ectodomain structure, and extracellular domain of Hepsin protein/Serine protease TMPRSS2 were retrieved from RCSB PDB or other databanks as applicable. The pdb structure was than converted into pdbqt readable file format in the AutoDock Tools 1.5.6[32].

The ligands first converted into SMILES file format from sdf file format by using OpenBabel GUI. The SMILES file format for each ligand than converted into pdb structure by using online SMILES translator and structure file generator (https://cactus.nci.nih.gov/translate/)[31]. The pdb file format then converted into pdbqt readable file format in the AutoDockTools(ADT)4.2[32].

The pdbqt file format of receptors and ligands further converted into grid and docking parameter file (a.gpf and a.dpf) using ADT4.2[32].

4.2.2 Molecular Docking

Molecular docking was carried out by using AutoDock Vina[32]. Three different set of docking studies were performed with six phytoligands from *Z. officinale* respectively: the first set for ACE2; the second set for SARS-CoV-2 Spike ectodomain structure and the third set was for extracellular domain of Hepsin protein/Serine protease TMPRSS2. The chemotherapeutic agonists were also docked as positive control set. The receptor grid generation was done by using receptor grid generation panel for all the three receptors. Grid box spacing was0.889A°, 1.000A° and 0.497A° for ACE2, Spike protein and Serine protease hepsin, respectively in order to cover almost whole binding pocket and its adjacent residues. Lamarckian Genetic Algorithm (GA) in combination of grid based energy evaluation method was used for docking. The program was run for a total number of 10 Genetic algorithm runs. The ligand moved around the rigid protein 25,000,000 energy evaluations for each cycle. Other parameters were set as default. The visualizing was done with the Pymol 2.3.4 software.

3. RESULTS

3.1 Ligands Scanning for Drug Likeliness

Gingerol, Zingiberene, Zingerone, Gingerenone, 1-dehydro,6-gingerdione, Shoagol, Chloroquine, and Hydroxychloroquine had molecular weights in a range of 194.23D to 335.88D, number of hydrogen acceptor lying in a range of 0 to 5, while number of hydrogen donor was scored in a scale of 0 to 2. The ligands, Gingerol, Zingerone, Gingerenone, 1-dehydro,6-gingerdione, Shoagol, and Hydroxychloroquine have shown the partition coefficient value of <5 while Zingiberene and Chloroquine have shown violation with MiLogP, partition coefficient as depicted in Table 1.

3.2 *In silico* Screening

Molecular docking study revealed Zingiberene has the highest estimated binding energy score of -6.23 kcal/mol to Spike protein of SARS-CoV-2. Chloroquine showed binding energy of -5.52 kcal/mol towards ACE2 while Gingerenone and Zingiberene have shown binding energy values of -5.87 and -5.77 kcal/mol respectively. Hydroxychloroquine was found to have the binding energy of -6.95 kcal/mol. Shoagol, Zingerone and Zingiberene showed higher values of binding energy as compared to their agonist Camostat mesylate against extracellular domain of Hepsin protein/Serine protease TMPRSS2 with the binding energy -5.72 kcal/mol, -5.79 kcal/mol and -5.52kcal/mol, respectively. The Camostat mesylate showed the interaction value of -5.24 kcal/mol. The details of the binding energy of each ligand and involved amino acid positions in receptor protein are shown in Tables 2, 3 and 4.

4. DISCUSSION

ACE2 a trans-membrane protein that diverge from ACE in being a carboxypeptidase, is mainly involved in vasodilation and thus, is an important target for controlling hypertension[37]. It is majorly expressed in pneumocyte II and, is a main entry point for SARSCoV2[38]. The Spike protein of SARS-CoV-2 of virus recognises and binds to ACE2 followed by entry of virus into the cell. The progression comes into action via extracellular domain of cellular protease, Hepsin protein/Serine protease/TMPRSS2 that split spike protein of SARS-CoV-2 resulting in fusion of viral and cellular membrane[2]. Splitting of Spike protein is crucial for SARS-CoV-2 infection. Thus, ACE2, spike protein, and Hepsin protein/Serine protease/(TMPRSS2) provides insight into viral transmission and reveals therapeutic targets. Similar drug targets were used by Wu[38], *et al.,* for discovery of potential drugs by computational methods by considering SARS-CoV-2 spike protein, ACE2, and Hepsin protein/Serine protease/TMPRSS2 as the therapeutic targets for SARS-CoV-2.

The Lipinski rule of 5 restricted a molecule to be developed as an orally active drug candidate with not more than one violation of the following four criteria[34]

(i) The value of hydrogen bond donors should not be more than five,
(ii) Hydrogen bond acceptors should be under the value of 10,
(iii) Molecular weight should remain under 500 Da, and
(iv) Octanol–water partition coefficient should be less than or equals to 5.

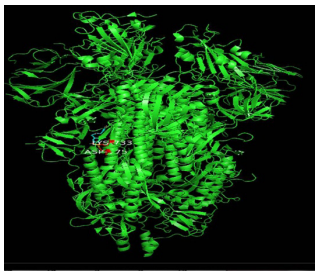
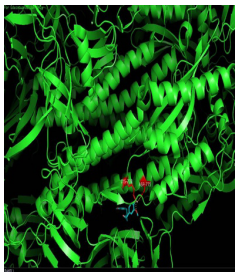
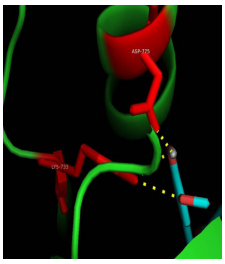
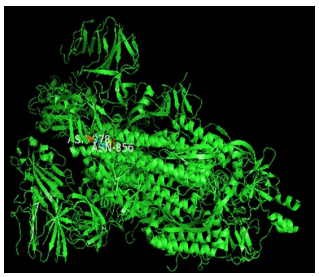
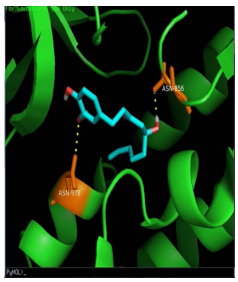
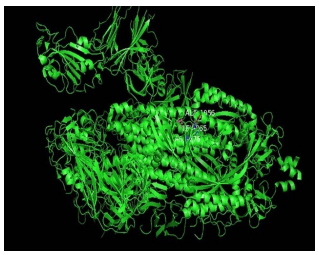
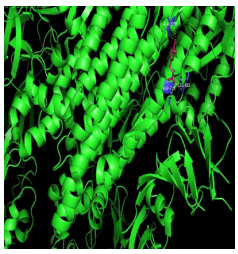
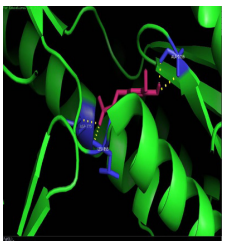
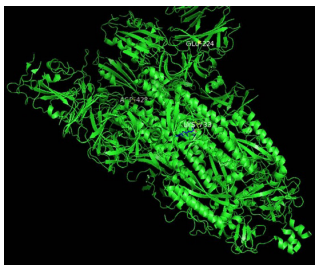
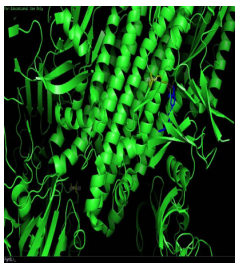
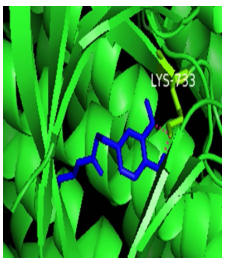
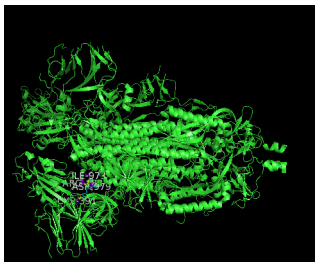
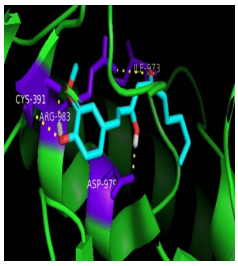
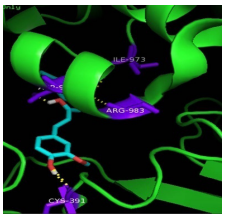
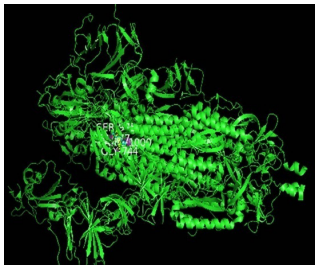
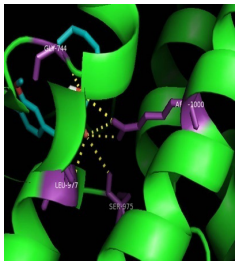
A druggable molecule must lie in the range of 5 Lipinski rule[34]. Molecules are considered as poor therapeutic modality, if there is > 5 H-bond donors and >10 H-bond acceptors and

Table 1. Physicochemical properties of phytochemicals in comparison with the marker chemotherapeutic drugs

Ligands	Physicochemical properties					
	N violation	N atoms	MilogP<5	MW<500D	Noh<10	Nohn<5
Gingerol	0	21	3.22	294.39	4	2
Zingiberene	1	15	5.12	204.36	0	0
Zingerone	0	14	1.52	194.23	3	1
Gingerenone	0	26	3.22	356.42	5	2
1-dehydro,6-gingerdione	0	21	3.06	290.36	4	1
Shoagol	0	20	4.35	276.38	3	1
Chloroquine	1	22	5.00	319.88	3	1
Hydroxychloroquine	0	23	4.00	335.88	4	2
Camostat mesylate	0	29	1.56	398.42	9	4

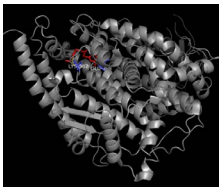
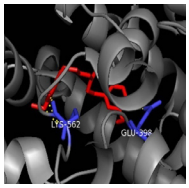
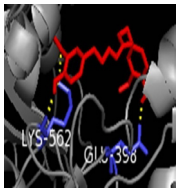
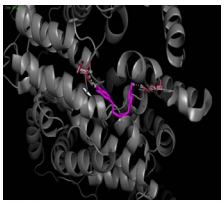
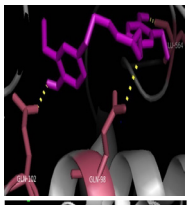
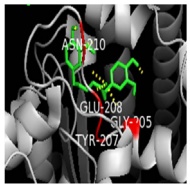
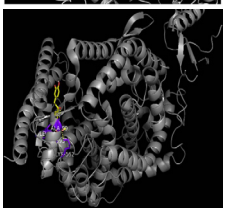
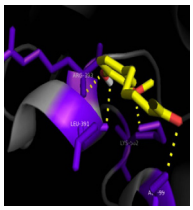
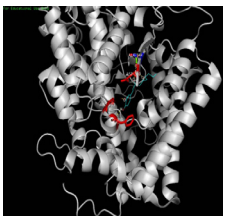
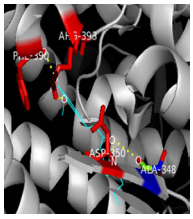
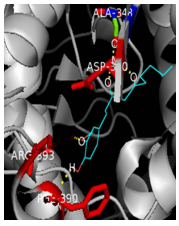
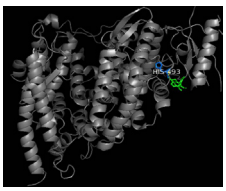
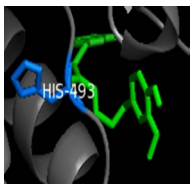
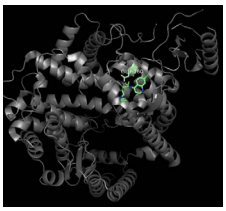
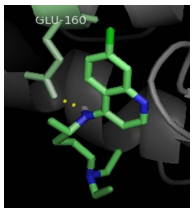
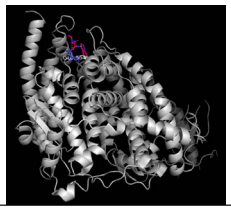
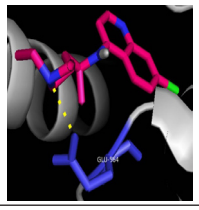
*Shaded values have shown the violation from Lipinski rule of 5

Table 2. Docking of SARS-CoV-2 Spike ectodomain structure with ligands (Phytochemicals and chemotherapeutic agonist): Binding site including hydrogen bond, amino acids and binding energy

Docking	Docking complex	One slant of binding Site including hydrogen bond	One slant of Binding Site including hydrogen bond	Amino acids of receptor form H-bond with ligand	Binding energy (-kcal/mol)
1. Spike protein-Gingerenone				LYS 733 ASP775	-4.21
2. Spike protein-Zingiberene				ASN856 ASN978	-6.23
3. Spike protein-Zingerone				ASP775 LEU865 ALA1056	-5.96
4. Spike protein – Shoagol				LYS733	-3.93
5. Spike protein- 1 Dehydro 6Gingerdione				CYS391 ILE973 ASP979ARG983	- 6.02
6. Spike protein – Gingerol				GLY744 SER975 LEU977 ARG1000	-5.16

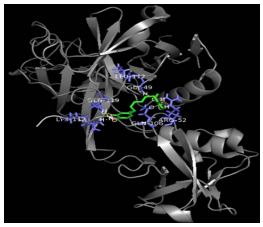
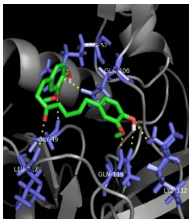
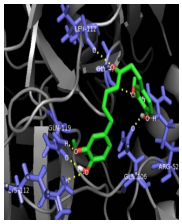
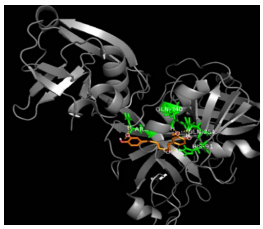
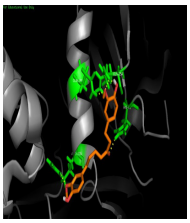
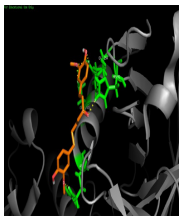
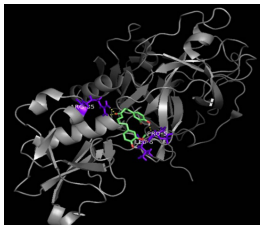
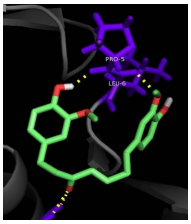
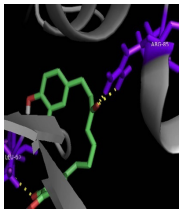
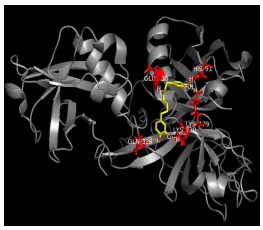
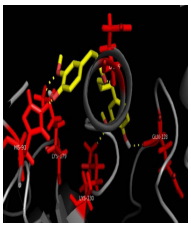
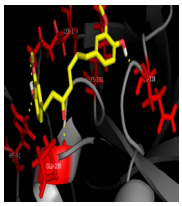
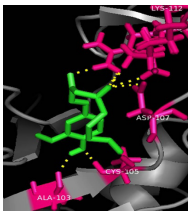
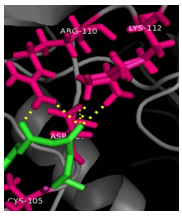
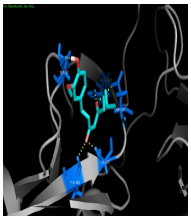
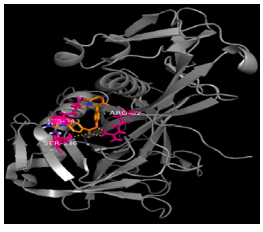
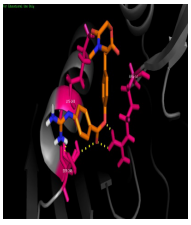
*Shaded scores are the highest with respect to each case

Table 3. Docking of ACE2 with ligands (Phytochemicals and chemotherapeutic agonist): Binding site including hydrogen bond, amino acids and binding energy

Docking	Docking complex	One slant of binding site including hydrogen bond	One slant of binding site including hydrogen bond	Amino acids of receptor form H-bond with ligand	Binding energy (-kcal/mol)
1. ACE2-Gingerenone				LYS562 GLU398	-5.87
2. ACE2-Zingiberene				GLN98 GLN102 GLU564	-5.77
3. ACE2-Zingerone				GLY205 TYR207 GLU208 ASN210	-4.56
4. ACE2-Shoagol				ALA99 LYS562 ARG393 LEU391	-5.22
5. ACE2-1 - Dehydro, 6- Gingerdione				ARG393 PHE390 ASP350 ALA348	-3.75
6. ACE2-Gingerol				HIS493	-2.5
7. ACE2-Chloroquine				GLU160	-5.52
8. ACE2-Hydroxychloroquine				GLU564	-7.16

*Shaded scores are the highest with respect to each case

Table 4. Docking of Transmembrane serine protease (TMPRSS2) with ligands (Phytochemicals and chemotherapeutic agonist): Binding site including hydrogen bond, Amino acids and Binding Energy

Docking	Docking complex	One slant of binding site including hydrogen bond	One slant of binding site including hydrogen bond	Amino acids of receptor form H-bond with ligand	Binding energy (kcal/mol)
1. TMPRSS2-Gingerenone				LEU112 GLN119 GLY49 ARG52 GLN56 LYS112	-4.73
2. TMPRSS2-Zingiberene				ARG35 GLN240 GLN254 HIS91	-5.52
3. TMPRSS2-Zingerone				ARG85 LEU6 PRO5	-5.79
4. TMPRSS2 – Shoagol				HIS9 GLN12 LYS179 LYS230 GLU236	-5.72
5. TMPRSS2 – 1 Dehydro 6Gingerdione				ALA103 CYS105 ASP107 ARG110 LYS112	- 4.89
6. TMPRSS2 – Gingerol				CYS105 ALA103 SER13 ASP107 ARG208 GLN106 LYS112	-4.99
7. TMPRSS2-Camostat mesylate				ARG52 LYS243 SER246	-5.24

*Shaded scores are the highest with respect to each case

when the molecular weight is > 500 and calculated partition coefficient is greater than 5. As shown in Table 1, the six tested phytochemical showing the score within the range thus are druggable molecules. The molecules with increasing lipophilicity tend to increase its blood brain barrier (BBB) permeability and shows druggability[34].

Ministry of Ayush, Government of India, has proposed Ayurveda's immunity boosting measures for self care during COVID 19 crisis that includes dry ginger (*Zingiber officinale*) as one of the constituents in immunity promoting measures. *Z. officinale* is treasured with medicinal properties that are found to be accountable for antibacterial, antioxidant, anti-inflammatory, anti-diabetic and anti-tumour effect[39]. *Z. officinale* is a spicy herb, augmented with the phytochemicals which contributes to its medicinal value[40]. Since ages, ginger has been used to give flavour to food and has achieved important position in the list of folk remedies against common cold, sore throat *etc*[41].Even though, ginger is regarded to be safe, yet its mechanism of action is not fully elucidated and a careful evaluation is essential before considering its phytochemicals for any therapy[42]. COVID-19, the disease the SARS-CoV-2 causes, can spread to the lungs, causing pneumonia. Furthermore, ventilator acquired pneumonia is a common nosocomial infection in such patients. We have earlier reported the antibacterial effect of *Zingiber officinale* against multi-drug resistant strain of *P. aeruginosa*.

The camostat mesylate was taken as a potent inhibitor of TMPRSS2 and reported to block the SARS-2 entry into the lung cells[43].The molecular docking between ligands and ACE2 revealed that Gingerenoneone and Zingiberene phytoconstituent of *Z. officinale* has the binding energy value -5.87 kcal/mol and -5.77 kcal/mol that lies between the binding energy values of Chloroqine (-5.52 kcal/mol) and Hydroxychloroquine (-6.95kcal/mol). Both the chemotherapeutic marker drugs also have *in vitro* activity against SARS-CoV-2 and may possess immunomodulating properties[41,42]. Mechanisms may include ACE2 cellular receptor inhibition, acidification at the surface of the cell membrane inhibiting fusion of the virus, and immunomodulation of cytokine release[41,42]. Other mechanisms may contain inhibition of viral enzymes such as viral DNA and RNA polymerase, viral protein glycosylation, virus assembly, new virus particle transport and virus release[41,42]. We also explored the binding of ligands with the extracellular domain of serine protease/hepsin/TMPRSS2 by considering the fact that these host cellular protease prime Spike protein of SARS-CoV-2 after viral-host cell attachment to facilitate the viral infection. Finding a serine protease inhibitor may block the SARS-CoV-2 Zingerone (-5.79 kcal/mol), Shoagol (-5.72 kcal/mol) and Zingiberene (-5.52 kcal/mol) have shown significantly higher binding score as compared to chemotherapeutic counterpart, Camostat mesylate (-5.24 kcal/mol). The docking results revealed that binding energy value of phytochemicals with Spike protein have shown a significant range from -3.93 kcal/mol to -6.23 kcal/mol, which can be considered as a basis for further testing of these phytochemicals against coronavirus. Our finding proved that *Z.officinale* is competent to assail entry of the virus due to efficacy of its phytoconstituents to bind viral and host protein (schematically depicted in Fig. 1). Further *in vitro* and *in vivo* studies are warranted including investigations to further define the underlying mechanisms.

5. CONCLUSION

The present study shows the inhibitory effect of *Z. officinale* constituents as entry inhibitor of SARS-CoV-2 virus by using all the protein of host and virus origin. We found Gingerenone and Zingiberene had remarkable effective binding activity with ACE2 in terms of docking score compared to Chloroquine. Significant quality binding activity against serine protease was found with respect to Shoagol, Zingerone and Zingiberene as compared with Camostat mesylate. Also, the phytochemicals were found to effectively bind with the Spike protein. The drug likeliness assessment of all the phytochemicals revealed acceptable results with their scores satisfying the Lipinski rule of 5.

Z. officinale (Ginger), a natural immunity promoting supplements, is a constituent ingredient of a herbal formulation recommended by Ministry of Ayush, Government of India, as a preventive measure to enhance body's immunity in the wake of COVID-19 outbreak. It is concluded that *Z. officinale* found

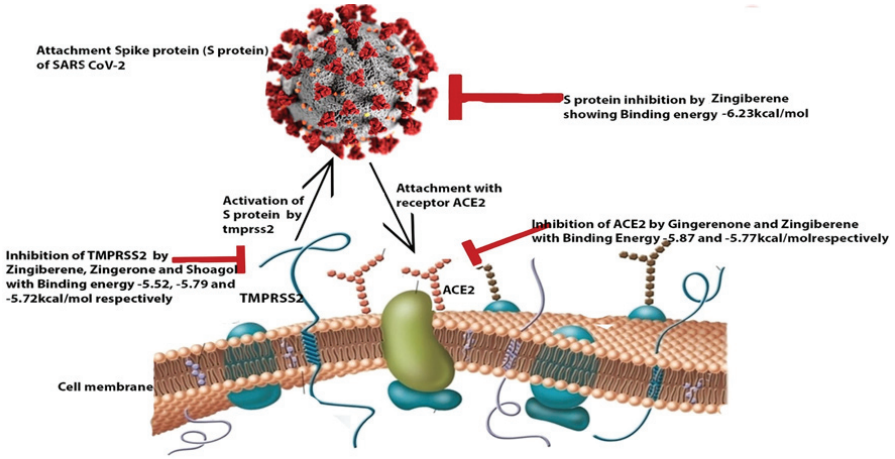


Figure 1. Interaction of host and viral proteins at entry point the site of action of phytochemicals.

as entry inhibitor of SARS-CoV-2 in present study, could be a safe and reliable adjuvant for mitigating COVID-19 to reduce infectivity as it also possesses antibacterial and immunity booster activity. While there is no specific prophylactic or therapeutic modality against SARS-CoV-2 as of now, our study indicated that *Z. officinale* can be a valuable preventive measure for COVID-19. Additional investigations on reduction of viral load in experimental models of COVID are warranted. The promising outcomes of this study can also be further extrapolated to Ginger preparations as muco-adhesive mouthwash, gargling agents, throat lozenges, syrups and nasal/ eye drops for the preclusion /mitigation of COVID-19.

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