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RESEARCH ARTICLE

Matrix metalloproteinase inhibitors identified from *Camellia sinensis* for COVID-19 prophylaxis: an in silico approach

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Abstract

To respond to the public panic, government and private research organizations of every country keep working on the COVID-19 pandemic, even though still there is a lack of more efficacious medicine for the choice of Coronavirus disease treatment. To counteract on this situation several approved drugs including anti-malarial (hydroxychloroquine and chloroquine), and few anti-viral (remdesvir) agents are choice of treatment for COVID-19. However, these agents suffer from certain limitation in their uses and pointed that there is no specific treatment or vaccine available to counter this contagious disease. Hence, there is urgent requirement to find a specific cure for the disease. In this view, there are several ongoing clinical trials of both western and traditional medicines. In present study, phytochemicals from *Camellia sinensis* were retrieved from the database and identified based on their ability to inhibit matrix metalloproteinase (MMPs) against SARS-CoV-2 main protease. *Camellia sinensis* entails of a massive number of phytochemicals with a good source of polyphenols such as Catechin, Epicatechin, Epigallocatechin and (–)-Epigallocatechin gallate. Molecular docking was performed using the GLIDE docking module of Schrodinger Suite software. The analysis displayed docking score for the five polyphenols i.e. theaflavin (− 8.701), 1-O-caffeoylquinic acid (− 7.795), Genistein (− 7.168), Epigallocatechin 3-gallate (− 6.282) and Ethyl trans-caffeate (− 5.356). Interestingly, theaflavin and Epigallocatechin 3-gallate have not revealed any side effects. These polyphenolic compounds had a strong binding affinity with hydrogen bonds and a good drug-likeness score. Therefore, *Camellia sinensis* could be the beneficial option in the prophylaxis of the COVID-19 outbreak.

Keywords *Camellia sinensis* · COVID-19 · *In silico* · Matrix metalloproteinase · Polyphenols

Abbreviations

ADMET	Absorption, distribution, metabolism, excretion and toxicity
ChEBI	Chemical entities of biological interest
ECM	Extracellular matrix
KEGG	Kyoto encyclopedia of genes and genomes
MMPs	Matrix metalloprotease
MERS	Cov—middle east respiratory syndrome coronavirus
PCIDB	Phytochemical Interactions DB
PDB	Protein data bank
RCSB	Research collaboratory for structural bioinformatics
RNA	Ribonucleic acid
SARS-Cov	Severe acute respiratory syndrome coronavirus
SMILES	Simplified molecular-input line-entry system
STRING	Search tool for the retrieval of interacting genes/proteins
WHO	World Health Organization
NHBA	Number of hydrogen bond acceptor
NHBD	Number of hydrogen bond donor
DLS	Drug likeness score

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Introduction

Ongoing COVID-19 epidemic, a novel viral disease invaded 216 countries all over the world. According to the WHO (World Health Organization), 4,589,526 + cases of Coronavirus disease have been confirmed to date and 310,391 people had lost their lives (https://www.who.int/emergencies/diseases/novel-coronavirus-2019) (WHO, May 2020a). Coronavirus crisis caused emotional and mental distress in public due to fear of 'End of Life'(Lima et al. 2020). Social distancing and home quarantine had started psychological changes in the public. To respond to this panic situation, government and private research organizations of every country start working on the COVID-19 epidemic, although there is still lack of more efficacious medicine for the cure of Coronavirus.

COVID-19 has been documnted for two types: (1) Severe Acute Respiratory Syndrome Coronavirus (SARS-Cov) and (2) the Middle East Respiratory Syndrome Coronavirus (MERS-Cov). Both are RNA viruses with glycoprotein spikes on surface, The family *Coronaviridae* causes severe respiratory tract dysfunction with symptoms such as cold, fever, body ache, and difficulty in breathing. The first outbreak occurred at the Wuhan China sea food market and has now spread globaly (Liu and Wang 2020).

This disaster had compelled the government to take stringent measures to save lives such as national and international lockdown, social distancing, the extension of vacations, patient hospitalization and quarantine, and many other changes to safe guard their countries (Lin et al. 2020). To counteract this situation anti-malarial drugs are used i.e. Hydroxychloroquine and Chloroquine (Frie and Gbinigie 2020; WHO, April 2020b) and few anti-viral drugs such as Ritonavir, Tipranavir and Lopinavir has been tested in patients with COVID-19 but still, no specific vaccine or anti-corona virus drug/s are available (Nukoolkarn et al. 2008).

Indian Traditional medicine plays an important role in many viral diseases. *Camellia sinensis* commonly refered as 'TEA' belongs to family '*Theaceae*'. It consists of a huge number of phytochemicals, along with a good source of polyphenols i.e. Catechin, Epicatechin, Epigallocatechin and Epigallocatechin gallate. Among them, Epigallocatechin gallate (constitutes 59%) is a major source of polyphenol (Kaur and Saraf 2011). According to published literature, polyphenols have been previously reported for its strong potency in the treatment of viral diseases. *Camellia sinensis* has been documented for antioxidant (Chan et al. 2007), Chemoprotective (Kaur and Saraf 2011), Wound healing (Hajiaghaalipour et al. 2013), Anti-diarrheal (Besra et al. 2003), antimicrobial (Farooqui et al. 2015) and numerous anti-viral activities (Xu et al. 2017). Above cited studies suggests that phytochemicals identified from *Camellia sinensis* could have ability to inhibit MMPs (enzyme belongs to family *Proteases*), which is associated with chemokine activation and contributes significantly in the degradation of myelin proteins and generation of auto-antigens. MMPs and their inhibitors are involved in remodeling of the extracellular matrix (ECM) during normal physiological conditions (Marten and Zhou 2005; Gupta 2016).

Therefore, this study was planned to analyse one of very prominent, economical, and popular beverage source, *Camellia sinensis* for the prophylaxis of COVID-19. *Camellia sinensis* has been reported for more than hundred phytochemicals and can be a potential candidate for the COVID-19 prophylaxis. Thus, with the aid of molecular doking, this study aimed to analyse *Camellia sinensis* for its possible therapeutic efficacy as per available phytochemicals in data base.

Materials and methods

Phytochemicals identification

The phytochemicals of *Camellia sinensis* were retrieved from ChEBI online tool (https://www.ebi.ac.uk/chebi/), and molecular weight, molecular formula, PubChem CID and Canonical SMILE of phytochemicals were recorded (Kanbarkar et al. 2020).

Prediction for matrix metalloproteinase inhibitor

All the identified phytochemicals were predicted for their Matrix Metalloproteinase inhibition activity by submitting the Canonical SMILE with the help of an online tool—Swiss Target Prediction http://www.swisstargetprediction.ch/ (Gfeller et al. 2014).

Estimation of drug likeness

The drug-likeness properties of the identified phytochemicals were determined from Molsoft online tool https://molsoft.com/mprop/ (Khanal et al. 2019). As per Lipinski's rule of five, molecular weight; lipophilicity (MolLogP); number of hydrogen bond acceptor; number of hydrogen bond donor; and drug-likeness score were noted.

Toxicity study

The side effects of the identified phytochemicals were calculated using the ADVERPred online tool http://www.way2drug.com/adverpred/ (Ivanov et al. 2008). It predicted probable

activity and inactivity values for each compound along with their side effects.

Gene enrichment analysis

The gene set data obtained for each compound from DIGEPpred. http://www.way2drug.com/GE/ (Lagunin et al. 2013) were submitted to STRING online tool https://string-db.org/ (Szklarczyk et al. 2017) and the KEGG pathway was downloaded. The pathway predicts possible mechanism of action which could be followed by the identified phytochemicals.

Ligand preparation

All the selected polyphenolic compounds of *Camellia sinensis* were downloaded from PubChem and prepared using the LigPrep version 4.8 (Schrodinger LCC) (Adnan et al. 2020). LigPrep generates energy minimized structure with multiple tautomer and stereoisomer's, which was further used as input to molecular docking.

Target/receptor preparation

The phytochemicals were subjected to molecular docking to explore its conformational space and orientation of substituents in the binding pocket of the target proteins. The crystal structure of SARS-CoV-2 main protease (PDB ID: 6LU7) in complex with a peptide for the present study was downloaded from the RCSB protein data bank (Berman et al. 2002) database. For protein preparation, the standard protocol of protein preparation wizard (Schrodinger, LLC) was followed and minimized the protein structure until the RMS gradient for heavy atom reached 0.3 A°.

Receptor grid generation and molecular docking

The crystal bound ligand was selected to enumerate a binding site grid with a scaling factor of 1.0 and partial charge cutoff of 0.25 for the Van Der Waals radius. Molecular docking simulations were performed using the GLIDE docking module of Schrodinger Suite software (Adnan et al. 2020). The glide approximates a complete systemic search of the conformational, orientational and positional space of the ligand in the protein binding pocket. The glide docking produces different poses for each input ligand, and each pose was scored and ranked by the glide docking scores (kcal/mol).

Results

Phytochemicals identification

By using keyword '*Camellia sinensis*' in data base, total 122 phytochemicals were retrieved and their canonical SMILES were recorded for generating data in the further steps.

Prediction for matrix metalloproteinase inhibitor

All the retrieved phytochemicals predicted for MMPs property and out of 122 phytochemicals, twelve phytochemicals were identified based on their inhibition potential of MMPs (Table 1). Theaflavin was predicted to inhibit eight MMPs, being the highest inhibitor in the listed polyphenolic compounds.

Determination of drug-likeness

The drug-like properties or physicochemical properties such as molecular weight, lipophilicity (MolLogP), number of hydrogen bond acceptor (NHBA), number of hydrogen bond donors (NHBD) and drug-likeness score (DLS) were calculated for the tweleve identified compounds (Table 2). The ranking order of DLS was perceived as follows: 2-(4-hydroxybenzyl) quinazolin-4(3H)-one > Genistein > 1-O-caffeoylquinic acid > Theaflavin > Epigallocatechin 3-gallate > Cordysinin A > Vanillic acid > Ethyl trans-caffeate > Gedunin > Inflatin E > Inflatin D > Inflatin f. All these compounds follows the Lipinski's rule, except epigallocatechin 3-gallate and 1-O-caffeoylquinic acid.

Table 1 Compounds from *Camellia sinensis* having MMPs inhibition activity

S. No.	Compound Name	Matrix Metalloproteinase Inhibitors
1.	Theaflavin	MMPs—1, 2, 7, 8, 9, 12, 13, 14
2.	(–)-Epigallocatechin 3-gallate	MMPs—2, 9, 12, 13, 14
3.	Cordysinin A	MMPs—1, 2
4.	1-O-caffeoylquinic acid	MMPs—2, 12
5.	Genistein	MMPs—2, 9, 12
6.	Inflatin E	MMPs—1, 2, 3, 7, 8, 9, 13
7.	Inflatin F	MMPs—1, 2, 3, 7, 8, 9, 13
8.	Inflatin D	MMPs—1, 2, 3, 7, 8, 9, 13
9.	2-(4-hydroxybenzyl) quinazolin-4(3H)-one	MMPs—1, 9
10.	Vanillic acid	MMPs—2, 8, 9, 12
11.	Ethyl trans-caffeate	MMPs—1, 2, 9
12.	Gedunin	MMPs—1, 3, 9

Table 2 Drug likeness of bioactive compounds from *Camellia sinensis*

S. No.	Compound Name	PubChem CID	Molecular formula	Molecular weight (g/mol)	NHBA (< 10)	NHBD (≤ 5)	MolLogP (≤ 5)	DLS
1.	Theaflavin	135403798	$C_{15}H_{15}NO_3$	257.11	3	1	2.68	0.29
2.	Epigallocatechin 3-gallate	65064	$C_{22}H_{18}O_{11}$	458.08	11	8	1.44	0.23
3.	Cordysinin A	54671997	$C_{11}H_{18}N_2O_3$	226.13	3	2	−0.03	−0.10
4.	1-O-caffeoylquinic acid	10155076	$C_{16}H_{18}O_9$	354.10	9	6	−0.93	0.37
5.	Genistein	5280961	$C_{15}H_{10}O_5$	270.05	5	3	1.92	0.44
6.	Inflatin E	53493989	$C_{22}H_{26}O_9$	434.16	9	0	1.42	−1.08
7.	Inflatin F	53494114	$C_{22}H_{26}O_9$	434.16	9	0	1.42	−1.08
8.	Inflatin D	53493988	$C_{22}H_{26}O_9$	434.16	9	0	1.42	−1.08
9.	2-(4-hydroxybenzyl) quinazolin-4(3H)-one	136026468	$C_{15}H_{12}N_2O_2$	252.09	3	2	1.96	1.09
10.	Vanillic acid	8468	$C_8H_8O_4$	168.04	4	2	1.20	−0.18
11.	Ethyl trans-caffeate	5317238	$C_{11}H_{12}O_4$	208.07	4	2	2.21	−0.31
12.	Gedunin	12004512	$C_{28}H_{34}O_7$	482.23	7	0	3.71	−0.44

Table 3 Side effects of bioactive compounds from *Camellia sinensis*

S. No.	Compound name	*Pa*	*Pi*	Side effects
1.	Theaflavin	–	–	–
2.	Epigallocatechin 3-gallate	–	–	–
3.	Cordysinin A	0.328	0.147	Myocardial infraction
4.	1-O-caffeoylquinic acid	0.3	0.157	Nephrotoxicity
		0.273	0.199	Cardiac failure
5.	Genistein	0.342	0.308	Hepatotoxicity
6.	Inflatin E	0.391	0.192	Arrhythmia
		0.277	0.182	Nephrotoxicity
		0.238	0.235	Cardiac failure
7.	Inflatin F	0.391	0.192	Arrhythmia
		0.277	0.182	Nephrotoxicity
		0.238	0.235	Cardiac failure
8.	Inflatin D	0.391	0.192	Arrhythmia
		0.277	0.182	Nephrotoxicity
		0.238	0.235	Cardiac failure
9.	2-(4-hydroxybenzyl) quinazolin-4(3H)-one	0.67	0.112	Hepatotoxicity
10.	Vanillic acid	0.424	0.241	Hepatotoxicity
		0.329	0.129	Nephrotoxicity
		0.303	0.3	Arrhythmia
		0.272	0.201	Cardiac failure
11.	Ethyl trans-caffeate	0.607	0.027	Myocardial infraction
		0.405	0.255	Hepatotoxicity
		0.326	0.132	Nephrotoxicity
12.	Gedunin	–	–	–

Pa probable activity; *Pi* probable inactivity

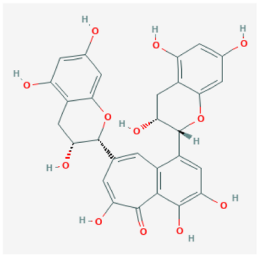
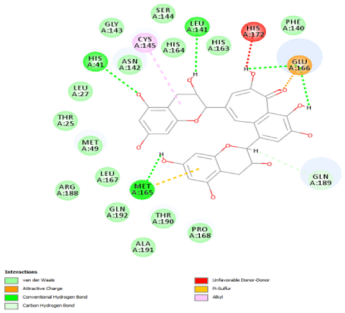
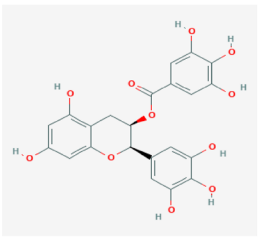
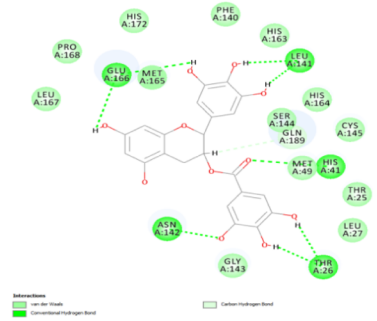
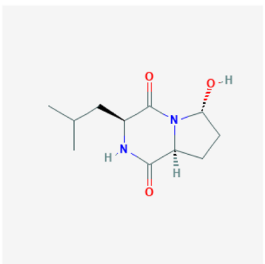
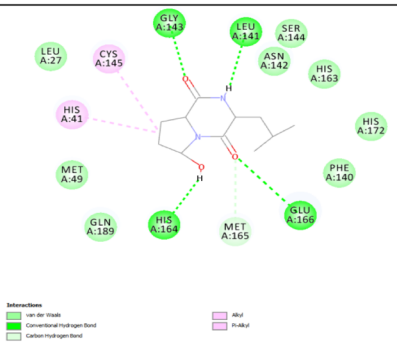
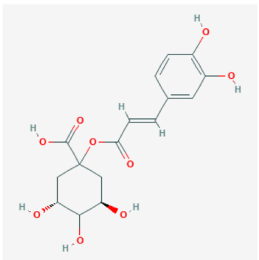
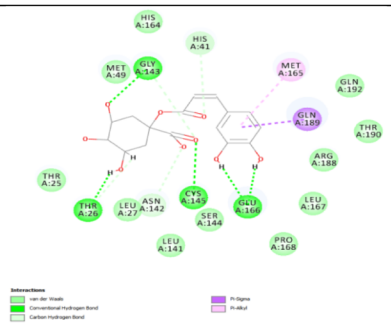
Toxicity study

The possible side effects of selected phytochemicals are listed in Table 3. The Theaflavin, Epigallocatechin 3-gallate, and Gedunin displayed no side effects, whereas vanillic acid indicated four major side effects such as hepatotoxicity, nephrotoxicity, arrhythmia, and cardiac failure with their probable activity and in-activity.

Molecular docking

The molecular docking study was performed for twelve identified phytoconstituents that have been predicted for Matrix Metalloproteinase enzyme inhibition potential against SARS-CoV-2 main protease. We observed that Theaflavin had maximum and Gedunin had minimum docking score (−8.401 to −3.169 kcal/mol respectively). Based on docking score, the ranking of all compounds were: Theaflavin > 1-O-caffeoylquinic acid > Genistein > Epigallocatechin 3-gallate > Ethyl trans-caffeate > 2-(4-hydroxybenzyl) quinazolin-4(3H)-one > Cordysinin A > Inflatin D > Inflatin E > Vanillic acid > Inflatin F > Gedunin (Table 4). The binding interactions of each compound with SARS-CoV-2 main protease protein were represented in the form of several hydrogen bonds and interaction residue analysis revealed that most of the compounds formed interaction with conserved catalytic dyad (Cys145 and His41) amino acid residue (Characteristic features from SARS-CoV-2 main protease). The analysis of docked poses of Theaflavin revealed that this compound occupies the catalytic site of SARS-CoV-2 main protease and interacts with catalytic His41 and Cys145 amino acid residues. This compound also interacted with His41, Leu141, Glu166, Met165 side chain amino acid residues, and formed several H-bond interactions (Fig. 1a). Gedunin a steroid compound, in the binding pocket obtained a U-shaped conformation forming H-bond with His41, Asn142 has the lowest docking score (Fig. 1b).

Table 4 Molecular docking score and binding interaction of compounds

S. No.	Compound Name	2D Interaction of ligand with Target	Docking score (kcal/mol)	NHB	Amino acid Residue
1.	Theaflavin 		-8.701	4	His41 Leu141 Met165 Glu166
2.	(-)-Epigallocatechin 3-gallate 		-6.282	5	Thr26 His41 Leu141 Asn142 Glu166
3.	Cordysinin A 		-4.688	4	Leu141 Glu143 His164 Glu166
4.	1-O-caffeoylquinic acid 		-7.795	4	Thr26 Glu143 Cys145 Gly166

Comparing the number of hydrogen bonds formed between all the docked compounds and binding site residues, Epigallocatechin-3-gallate showedthe maximum number of hydrogen bonds with the following amino acid residue: Thr26, His41, Leu141, Asn142, and Glu166.

Table 4 (continued)

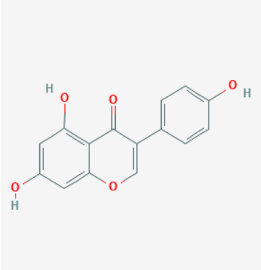
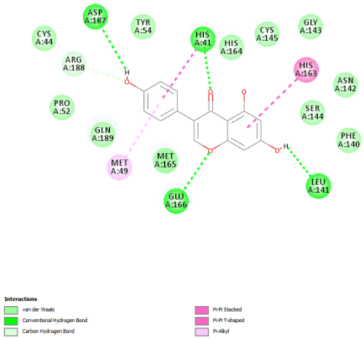
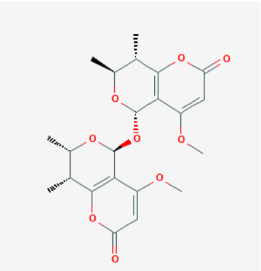
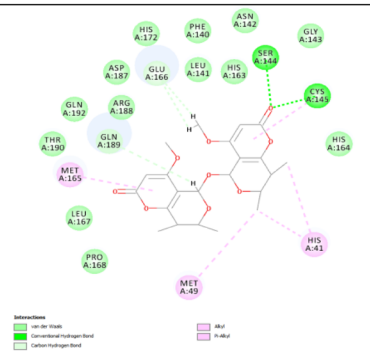
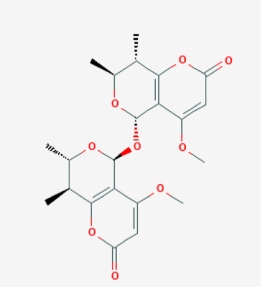
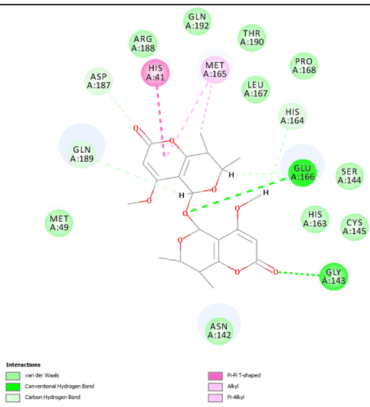
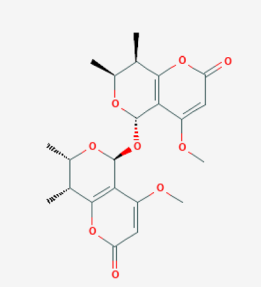
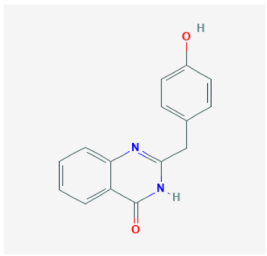
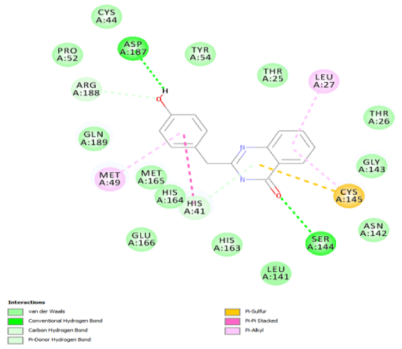
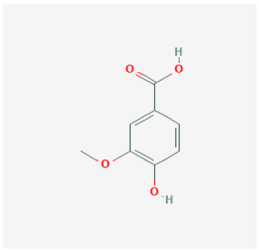
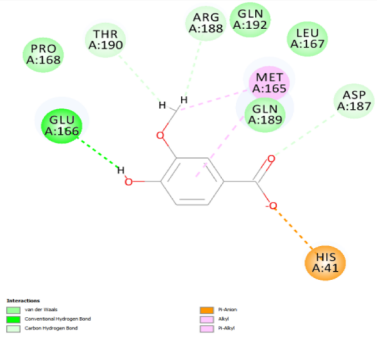
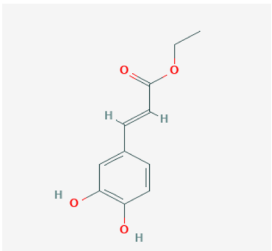
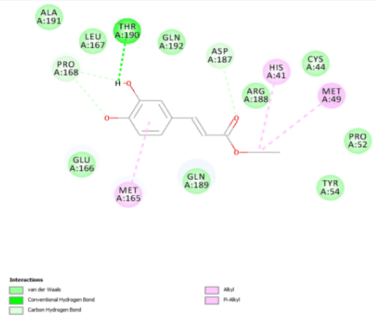
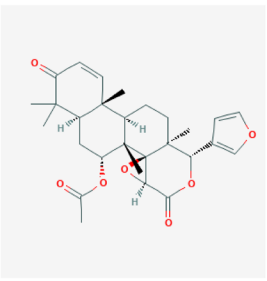
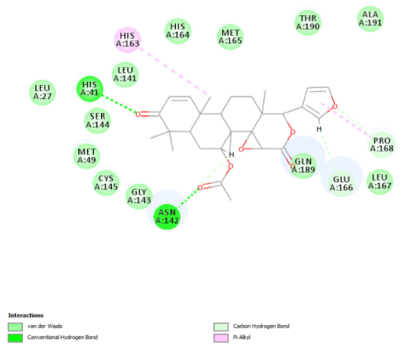
S. No.	Compound Name	2D Interaction of ligand with Target	Docking score (kcal/mol)	NHB	Amino acid Residue
5.	Genistein 		-7.168	4	His41 Leu141 Glu166 Asp187
6.	Inflatin E 		-4.395	2	Ser144 Cys145
7.	Inflatin F 		-3.774	2	Glu143 Glu166
8.	Inflatin D 		-4.434	2	Ser144 Cys145

Table 4 (continued)

S. No.	Compound Name	2D Interaction of ligand with Target	Docking score (kcal/mol)	NHB	Amino acid Residue
9.	2-(4-hydroxybenzyl) quinazolin-4(3H)-one 		-4.784	2	Ser144 Asp187
10.	Vanillic acid 		-3.862	1	Glu166
11.	Ethyl trans-caffeate 		-5.356	1	Thr190
12.	Gedunin 		-3.169	2	His41 Asn142

NHB number of hydrogen bonds

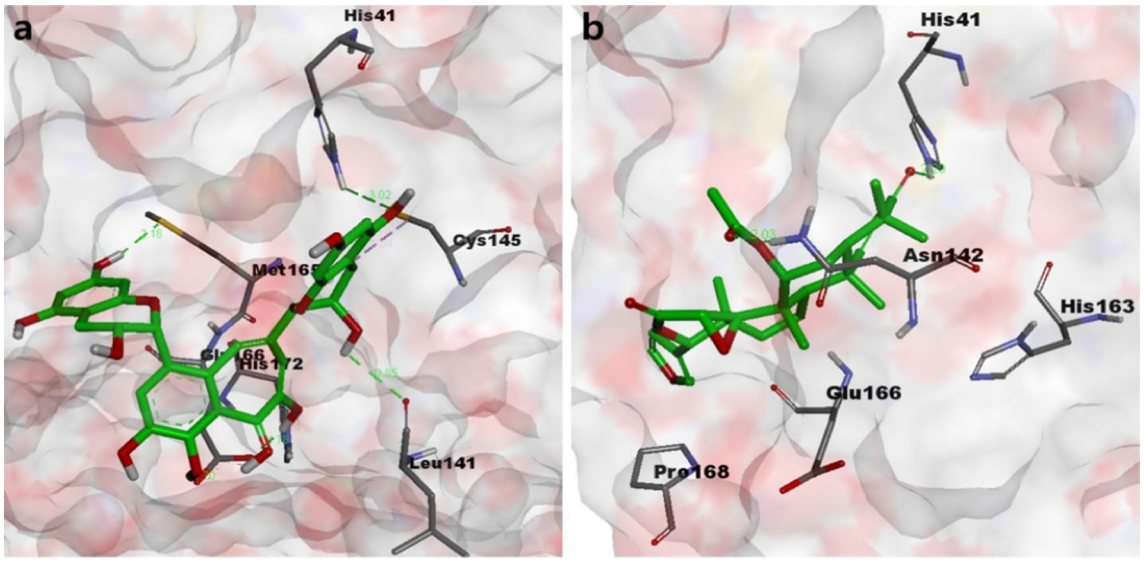


Fig. 1 Ligand binding interactions of compound. **a**Theaflavin, **b** Gedunin within the binding pocket of SARS-CoV-2 main protease enzyme

Gene enrichment analysis

The gene set data has described the KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway followed by the compounds to display the possible molecular mechanism (Table 5). It was detected that all compounds followed more than one pathway to hit the target, but all compounds displayed one common pathway that is cancer pathway. It could be believed that naturally occurrring compounds may follow single and multiple pathways may have an anti-viral mechanism at the end. Table 5 displayed the list of pathways, gene counts, and modulated proteins.

Discussion

COVID-19 is a viral infection and emerging with increasing prevalence. It has cought the attention of researchers, doctors, and health care professionals worldwide. Owing to countless deaths and a limitations in available drugs, it has caused the terrible human condition to eradicate the virus. Therefore, potential and cost-effective medicine/s is warrented for best prophylactic (pre and post COVID-19) effect. The present study aimed to investigate the possible effect of *Camellia sinensis* using in silico approach in the management of COVID-19. Numerous research projects are ongoing over the globe and several has been conducted to identify the potential medicine candidate for the COVID-19 crisis. In this life-threatening situation, traditional medicine/s might be effective for treatment of COVID-19.

Warm water decoction made by using various species in Ayurveda called '*Kashay'* is generally in practice in the prevention of fever, headache, common cold, and inflammation (Tillu et al. 2020). Similarly, the warm decoction of dry or fresh leaves of *Camellia sinensis* with or without sugar is also used in daily life style to overcome stress and has been documented for anti-inflammatory, analgesic (De Lima MotaI et al. 2015) and CNS stimulant activity (Rubab et al. 2020).

In the present study with the help of in silico approach, we predicted potential phytochemicals of *Camellia sinensis* for the inhibition of Matrix Metalloprotease (MMPs). MMPs play an important role in immunity, inflammation, cell growth, organ morphogenesis, wound healing, angiogenesis, apoptosis, and embryonic development. Overexpression of MMPs was also observed in various pathological conditions such as cancer, corneal endogens, skin ulceration, neurological diseases, arthritis, and fibrotic lung diseases, etc. (Gupta 2016).

The twelve identified phytochemicals from *Camellia sinensis* were predicted as MMPs inhibitors in Swiss Target Prediction data base, namely: Theaflavin, (–)-epigallocatechin 3-gallate, cordysinin A, 1-O-caffeoylquinic acid, genistein, inflatin E, inflatin F, inflatin D, 2-(4-hydroxybenzyl) quinazolin-4(3H)-one, vanillic acid, ethyl trans-caffeate, and gedunin with MMPs: − 1, − 2, − 3, − 7, − 8, − 9, − 12, − 13 and − 14 (Table 1). Overexpression of these MMPs initiates various diseases. MMP-1 originate breast cancer growth, metastasis, cardiac hypertrophy and heart attack (Marten and Zhou 2005), MMP-2: involved in chronic lung diseases (Kong et al. 2009), MMP-3: participates in rheumatoid arthritis and ankylosing spondylitis (Sun et al. 2014), MMP-7: degraded natural immunity of lung and intestine (Burke 2004), MMP-8: activates Interleukin and

Table 5 Pathways followed by the compounds targeting SARS-CoV-2 Main protease

Compounds name	Term ID	Pathway description	Gene count	False discovery rate	Targeted proteins
Theaflavin	hsa05200	Pathways in cancer	23	0.002	ARNT, CKS1B, ERBB2, FGF23, FOXO1, GNAI1, HES1, IL15, IL4R, ITGA6, ITGAV, KRAS, MAPK8, NCOA1, NOTCH1, PLCG2, PTGER3, RALA, RARB, ROCK1, ROCK2, WNT11, WNT7A
	hsa04919	Thyroid hormone signaling pathway	9	0.0136	FOXO1, ITGAV, KAT2B, KRAS, MYH6, NCOA1, NOTCH1, PFKFB2, PLCG2
	hsa04360	Axon guidance	10	0.0388	EFNB2, GNAI1, KRAS, L1CAM, NTN4, PLCG2, RASA1, ROCK1, ROCK2, SEMA3G
	hsa05224	Breast cancer	9	0.0388	ERBB2, FGF23, HES1, KRAS, NCOA1, NOTCH1, PGR, WNT11, WNT7A
(–) Epigallocatechin 3-gallate	hsa05200	Pathways in cancer	17	0.0016	ARNT, CKS1B, ERBB2, FGF23, HES1, ITGA6, ITGAV, KRAS, NCOA1, NOTCH1, PTGER3, RARA, RBX1, ROCK2, TRAF5, WNT11, WNT7A
	hsa05224	Breast cancer	8	0.0089	ERBB2, FGF23, HES1, KRAS, NCOA1, NOTCH1, WNT11, WNT7A
Cordysinin A	hsa04915	Estrogen signaling pathway	13	0.0037	CREB3L2, CTSD, EBAG9, GNAI1, HSPA6, KCNJ5, KRAS, KRT17, KRT23, NCOA1, PGR, PRKCD, TFF1
	hsa05200	Pathways in cancer	27	0.0051	ARNT, CKS1B, EP300, ERBB2, FOXO1, GNAI1, HES1, IL15, IL4R, ITGA6, ITGAV, KRAS, MAPK8, MET, MITF, NCOA1, NOTCH1, NQO1, PLCG2, PTGER3, RALA, RARB, ROCK1, ROCK2, TGFB2, WNT11, WNT7A
	hsa05206	MicroRNAs in cancer	13	0.0051	CYP1B1, DNMT1, EP300, ERBB2, FOXP1, KRAS, MET, NOTCH1, PLCG2, ROCK1, SOX4, STMN1, TGFB2
	hsa00790	Folate biosynthesis	5	0.0294	ALPPL2, CBR1, DHFR, GGH, PAH

Table 5 (continued)

Compounds name	Term ID	Pathway description	Gene count	False discovery rate	Targeted proteins
1-O-caffeoylquinic acid	hsa04668	TNF signaling pathway	6	0.0013	CCL5, CREB3L1, CXCL10, CXCL2, MAPK8, TRAF5
	hsa04657	IL-17 signaling pathway	5	0.0042	CXCL10, CXCL2, MAPK8, S100A9, TRAF5
	hsa04217	Necroptosis	5	0.029	FTL, MAPK8, SMPD1, TNFRSF10B, TRAF5
	hsa04216	Ferroptosis	3	0.0294	FTL, GCLM, GSS
	hsa04621	NOD-like receptor signaling pathway	5	0.0294	CCL5, CXCL2, MAPK8, RNASEL, TRAF5
	hsa05164	Influenza A	5	0.0294	CCL5, CXCL10, MAPK8, RNASEL, TNFRSF10B
	hsa05168	Herpes simplex infection	5	0.0294	CCL5, MAPK8, RNASEL, SRSF2, TRAF5
	hsa05215	Prostate cancer	4	0.0294	CREB3L1, ERBB2, FGFR1, FOXO1
	hsa04210	Apoptosis	4	0.0483	CASP2, CTSV, MAPK8, TNFRSF10B
	hsa05230	Central carbon metabolism in cancer	3	0.0483	ERBB2, FGFR1, HK2
Genistein	hsa04915	Estrogen signaling pathway	13	0.0036	CREB3L2, CTSD, EBAG9, GNAI1, HSPA6, KCNJ5, KRAS, KRT17, KRT23, NCOA1, PGR, PRKCD, TFF1
	hsa05200	Pathways in cancer	28	0.0036	ARNT, CKS1B, EP300, ERBB2, FOXO, GNAI1, HES1, IL15, IL4R, ITGA6, ITGAV, KRAS, LRP6, MAPK8, MET, MITF, NCOA1, NOTCH1, NQO1, PLCG2, PTGER3, RALA, RARB, ROCK, ROCK2, TGFB2, WNT11, WNT7A
	hsa05206	MicroRNAs in cancer	14	0.0036	CYP1B1, DNMT1, EFNA3, EP300, ERBB2, FOXP1, KRAS, MET, NOTCH1, PLCG2, ROCK1, SOX4, STMN1, TGFB2
	hsa00790	Folate biosynthesis	5	0.0336	ALPPL2, CBR1, DHFR, GGH, PAH
	hsa04360	Axon guidance	12	0.0403	EFNA3, EFNB2, GNAI1, KRAS, L1CAM, MET, NTN4, PLCG2, RASA1, ROCK1, ROCK2, SEMA3G
	hsa04068	FoxO signaling pathway	10	0.0439	EP300, FOXO1, KRAS, MAPK13, MAPK8, PLK3, PLK4, PRKAB2, SGK2, TGFB2
Inflatin E	hsa04068	FoxO signaling pathway	5	0.0061	FOXO4, MAPK8, PLK3, PLK4, SGK2
Inflatin F	hsa04068	FoxO signaling pathway	5	0.0056	FOXO4, MAPK8, PLK3, PLK4, SGK2
Inflatin D	hsa04068	FoxO signaling pathway	5	0.0061	FOXO4, MAPK8, PLK3, PLK4, SGK2
2-(4-hydroxybenzyl) quinazolin-4(3H)-one	hsa04920	Adipocytokine signaling pathway	4	0.022	ADIPOQ, PPARGC1A, PRKAB2, SLC2A4

Table 5 (continued)

Compounds name	Term ID	Pathway description	Gene count	False discovery rate	Targeted proteins
Vanillic acid	hsa04216	Ferroptosis	5	0.0022	ACSL3, FTL, GCLC, GCLM, GSS
	hsa00480	Glutathione metabolism	5	0.003	GCLC, GCLM, GSS, MGST1, PGD
	hsa05200	Pathways in cancer	12	0.0115	CKS1B, EP300, ERBB2, ITGA6, ITGAV, KRAS, MGST1, NQO1, PRKACB, STAT5B, TRAF5, TXNRD2
	hsa04512	ECM-receptor interaction	5	0.0129	HMMR, ITGA6, ITGAV, ITGB8, SDC4
	hsa05203	Viral carcinogenesis	7	0.0129	CDC20, EGR3, EP300, KRAS, PRKACB, STAT5B, TRAF5
	hsa05418	Fluid shear stress and atherosclerosis	6	0.0129	IL1R1, ITGAV, MGST1, NQO1, SDC4, SUMO1
	hsa04213	Longevity regulating pathway - multiple species	4	0.0258	HSPA1L, KRAS, PRKACB, SOD1
	hsa05152	Tuberculosis	6	0.0288	CD74, CEBPG, CORO1A, EP300, IL10RB, PLK3
	hsa00051	Fructose and mannose metabolism	3	0.0329	AKR1B1, AKR1B10, TPI1
	hsa04110	Cell cycle	5	0.0329	CDC20, E2F5, EP300, MCM6, MCM7
	hsa04120	Ubiquitin mediated proteolysis	5	0.0329	CDC20, SIAH1, UBE2C, UBE2M, WWP2
	hsa04915	Estrogen signaling pathway	5	0.0329	FKBP5, HSPA1L, KRAS, KRT17, PRKACB
	hsa05020	Prion diseases	3	0.0329	CCL5, PRKACB, SOD1
	hsa05168	Herpes simplex infection	6	0.0329	CCL5, CD74, EP300, POLR2A, SRSF2, TRAF5
	hsa05169	Epstein-Barr virus infection	6	0.0329	EP300, HSPA1L, IL10RB, POLR2A, PRKACB, TRAF5
	hsa04514	Cell adhesion molecules (CAMs)	5	0.0332	ITGA6, ITGAV, ITGB8, OCLN, SDC4
	hsa05414	Dilated cardiomyopathy (DCM)	4	0.0383	ITGA6, ITGAV, ITGB8, PRKACB
	hsa00270	Cysteine and methionine metabolism	3	0.042	GCLC, GCLM, GSS
	hsa04217	Necroptosis	5	0.042	FTL, SMPD1, STAT5B, TNFRSF10B, TRAF5
	hsa05222	Small cell lung cancer	4	0.042	CKS1B, ITGA6, ITGAV, TRAF5
	hsa04913	Ovarian steroidogenesis	3	0.0479	ACOT2, CYP1B1, PRKACB

Table 5 (continued)

Compounds name	Term ID	Pathway description	Gene count	False discovery rate	Targeted proteins
Ethyl trans-caffeate	hsa05200	Pathways in cancer	11	0.0024	EP300, ERBB2, FGFR1, FOXO1, ITGA6, KRAS, MET, MGST1, NQO1, RARB, TXNRD2
	hsa00480	Glutathione metabolism	4	0.0067	GCLC, GCLM, MGST1, PGD
	hsa05215	Prostate cancer	5	0.0067	EP300, ERBB2, FGFR1, FOXO1, KRAS
	hsa05230	Central carbon metabolism in cancer	4	0.0097	ERBB2, FGFR1, KRAS, MET
	hsa04520	Adherens junction	4	0.0107	EP300, ERBB2, FGFR1, MET
	hsa01521	EGFR tyrosine kinase inhibitor resistance	4	0.0125	ERBB2, GAS6, KRAS, MET
	hsa04216	Ferroptosis	3	0.0194	FTL, GCLC, GCLM
	hsa05225	Hepatocellular carcinoma	5	0.0194	KRAS, MET, MGST1, NQO1, TXNRD2
	hsa04015	Rap1 signaling pathway	5	0.0328	FGFR1, KRAS, MAPK13, MET, VASP
	hsa04510	Focal adhesion	5	0.0328	ERBB2, ITGA6, ITGB8, MET, VASP
	hsa05205	Proteoglycans in cancer	5	0.0328	ERBB2, FGFR1, KRAS, MAPK13, MET
	hsa04014	Rassignaling pathway	5	0.0388	FGFR1, KRAS, MET, PLA2G6, REL
	hsa04068	FoxOsignaling pathway	4	0.0388	EP300, FOXO1, KRAS, MAPK13
	hsa04151	PI3K-Akt signaling pathway	6	0.0388	ERBB2, FGFR1, ITGA6, ITGB8, KRAS, MET
	hsa04213	Longevity regulating pathway—multiple species	3	0.0388	FOXO1, KRAS, SOD1
	hsa04218	Cellular senescence	4	0.0388	E2F5, FOXO1, KRAS, MAPK13
	hsa04910	Insulin signaling pathway	4	0.0388	FOXO1, KRAS, PRKAR2A, SOCS2
	hsa04917	Prolactin signaling pathway	3	0.0388	KRAS, MAPK13, SOCS2
	hsa05206	MicroRNAs in cancer	4	0.0388	EP300, ERBB2, KRAS, MET
	hsa05211	Renal cell carcinoma	3	0.0388	EP300, KRAS, MET
	hsa05218	Melanoma	3	0.0388	FGFR1, KRAS, MET
	hsa05223	Non-small cell lung cancer	3	0.0388	ERBB2, KRAS, RARB
	hsa05226	Gastric cancer	4	0.0388	ERBB2, KRAS, MET, RARB
	hsa04060	Cytokine-cytokine receptor interaction	5	0.0431	CXCL10, CXCL2, IL10RB, MET, TNFRSF10B
	hsa05164	Influenza A	4	0.0453	CXCL10, EP300, MAPK13, TNFRSF10B
Gedunin	hsa00270	Cysteine and methionine metabolism	2	0.0343	GCLM, GSS
	hsa00480	Glutathione metabolism	2	0.0343	GCLM, GSS
	hsa03030	DNA replication	2	0.0343	MCM6, MCM7
	hsa04110	Cell cycle	3	0.0343	CDC20, MCM6, MCM7
	hsa04216	Ferroptosis	2	0.0343	GCLM, GSS

Fig. 2 Anti-viral potential of polyphenols from *Camellia sinensis* along with their mechanism

contribute in wound healing and tissue remodeling during inflammation (Djuric and Zivkovic 2017), MMP-9: activates viral lung or pulmonary infections, angiogenesis, and metastasis (Dabo et al. 2015), MMP-12: participates in the aneurysm, atherosclerosis, and emphysema (Chen 2004), MMP-13: osteoarthritis and rheumatoid arthritis (Takaishi et al. 2008) and MMP-14: promote hepatocellular carcinoma and metastasis (Chen et al. 2011; Murugan et al. 2009). The above-mentioned MMPs play a vital role in the rapid development of viral infections. Thus, inhibition of over-expressed MMPs possibly arrests the expansion of several diseases. Compound theaflavin (Bedran et al. 2015), EGCG (Demeule et al. 2002), 1-O-caffeoylquinic acid (Jin et al. 2005) and genistein (Kousidou et al. 2005) were identified as inhibitors of MMPs involved in various disease conditions such as cancer and lung diseases. Furthermore, by using the STRING online tool, study predicted probable pathways that could be followed by the compounds to identify the possible mechanism. All phytochemicals were observed to for their common pathway (Cancer pathways). Table 5 displays the modulated pathways and their gene counts.

The various studies revealed that catechins present in the *Camellia sinensis*, are the major polyphenols and have a potential role in several viral diseases namely: (HBV) Hepatitis B Virus (Zhong et al. 2015), (HSV) Herpes Simplex Virus (Colpitts and Schang 2014), (EBV) Epstein–Barr Virus (Liu et al. 2018), Adenovirus (Weber et al. 2003), (HIV) Human Immunodeficiency Virus (Yamaguchi et al. 2002), (HCV) Hepatitis C Virus (Ciesek et al. 2011), (DENV) Dengue Virus (Ismail and Jusoh 2017), (JEV) Japanese encephalitis Virus (Ismail and Jusoh 2017), (ZIKV) Zika virus (Carneiro et al. 2016), (TBEV) Tick Borne Encephalitis Virus (Ismail and Jusoh 2017), (CHIKV) Chikungunya Virus (Weber et al. 2015), (HTLV-1) Human T cell Leukaemia Virus Type -1 (Harakeh et al. 2014), (EV71) Enterovirus 71 (Ho et al. 2009), (EBOV) Ebola Virus (Shurtleff et al. 2014), (PRRSV) Porcine Reproductive and Respiratory Syndrome Virus (Zhao et al. 2014), (VHSV) Hemorrhagic Septicaemia Virus (Estepa 2005), (IHNV) Hematopoietic Necrosis Virus (Estepa 2005), (SVCV) Spring Viremia Carp virus (Estepa 2005) and (GCRV) Grass Carp Reo Virus (Wang et al. 2016) (Fig. 2). Considering the above mentioned anti-viral research on the tea polyphenols and its easy availability, this study was planned to perform the in silico molecular docking of predicted phytochemicals against SARA-CoV-2 main protease.

The main reason behind the compounds selection having MMPs inhibition activity for the targeting SARS-CoV-2 main protease was that both, drug and target belong to the same family '*protease*'. The proteases have been

earlier documented for their role in several biological pathways. The dysfunction of this enzyme may result in an exhaustive range of diseases. Recently used anti-viral drugs for COVID-19 managemnt: Ritonavir, Tipranavir, and Lopinavir are belongs to the class of 'protease inhibitors'. There are mainly five classes of protease namely: Metalloproteases, Aspartic acid protease, Serine protease, Cysteine protease, and Threonine protease. Metalloproteases and aspartic acid protease act through a 'peptide bond hydrolysis' mechanism whereas Serine, Cysteine, and Threonine protease act through 'peptide bond cleavage' mechanism (Drag and Salvesen 2015).

The polyphenols such as epicatechin, epicatechingallate, epigallocatechin, and epigallocatechingallate are previously reported in the tea and inhibits MMPs-2, and -9. Further, also directed to have a chemoprotective effect against various cancers. In addition, Genistein inhibits a wide variety of cancer cells by inhibiting MMPs -2 and -9. Polyphenols such as Theaflavin, 1-O-caffeoylquinic acid, genistein, (–)-epigallocatechin 3-gallate, and ethyl trans-caffeate displayed the higher docking score against SARS-CoV-2 main protease enzyme. Therefore, in silico molecular docking investigations suggests that *Camellia sinensis* could target SARS-Cov-2 main protease in the management of COVID-19.

Conclusion

In the view of previous reported anti-viral activities of *Camellia sinensis* and in silico study data in present study supports the beneficial effect of traditional Ayurvedic/herbal medicine in the management of COVID-19 crisis by targeting SARA-CoV-2 main protease. Significantly the anti-viral potential is evident from the predicted docking score of polyphenols such as theaflavin, (–)-epigallocatechin 3-gallate, Genistein, 1-O-caffeoylquinic acid, and Ethyl trans-caffeate. Drug likeness characteristics and no or less side effects of theaflavin, (–)-epigallocatechin 3-gallate directs the future scope of these polyphenols. Hence it is concluded that *Camellia sinensis* could be the an option in the prophylaxis of the COVID-19 outbreak.

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Compliance with ethical standards

Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest Authors has no conflict of interest.

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