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Tea flavonoids inhibiting multiple proteins related to SARS-CoV-2 judged from molecular docking

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Abstract

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has caused Coronavirus Disease 2019 (COVID-19) pandemic. Flavonoids-derived Chinese patent medicines have outstanding curative effects for the improvement and treatment of COVID-19. Numerous studies were suggesting that flavonoid-rich tea has antiviral effects. In vitro studies demonstrated that bioactive compounds of tea flavonoids could inhibit the activity of SARS-CoV-2 main protease (Mpro). However, bioactive compounds from tea flavonoids with antiviral effect, and the potential molecular mechanisms are unclear. In this study, we performed a molecular docking of 468 tea flavonoids and their derivatives with Mpro, RNA-dependent RNA polymerase (RdRp), angiotensin-converting enzyme 2 (ACE2), compared with the positive clinical drugs of each target. The results suggest that ACE2 and RdRp are the main targets inhibited by tea flavonoids according to the binding affinity. Quercetin 3-glycosides (Q3G), Isovitexin, and 4',5,7-Trihydroxyflavanone 7-O-Fructoside (S)-form (TF) would be considered as the potential candidate compounds of RdRp and ACE2. Our study provides a theoretical basis for further drug design of anti-COVID-19 bioactive compounds.

Introduction

Coronavirus Disease 2019 (COVID-19) has rapidly spread around the world, causing a pandemic of the infectious pneumonia and enormous damage to the social economy. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the causative pathogen of COVID-19, which could be transmitted through droplets expelled during talking, coughing, or sneezing [1,2]. To date (29 June 2021), cumulative numbers of COVID-19 confirmed cases have already exceeded 0.18 billion according to the report of the World Health Organization. According to the Science's COVID-19 reporting, Delta variant would trigger dangerous new phase in the pandemic. Systematic autopsy and percutaneous multiple organ biopy discovered that SARS-CoV-2 might cause injuries including multiple organs and tissues [3]. Among them, heart failure and acute kidney injury were major complications except for pulmonary lesions, even leading to diabetes [4]. Therefore, it is essential to investigate potential components to prevent or treat the multiple organic failures caused by COVID-19.

Currently, no specific anti-virus drugs are available for the treatment of COVID-19. Although people are being vaccines against COVID-19, the number of confirmed cases and deaths has been still soaring. Additionally, the safety and effectiveness of vaccines are still needed to evaluate [5]. Surprisingly, greater than 85% of SARS-CoV-2 infected patients in China had received Traditional Chinese Medicine (TCM) treatment [6]. China had successfully controlled the domestic epidemic through the strict policy and integrative medicine especially traditional Chinese medicine, such as Lianhua Qingwen capsule. Six active compounds of Lianhua Qingwen capsule, belong to flavonoids including quercetin, luteolin, naringenin, kaempferol, wogonin, were identified for treatment of COVID-19 [7]. Early in 1985, naturally occurring flavonoids, in which quercetin reduced intracellular replication of virus, had been reported to possess a variable spectrum of antiviral activity against certain RNA (RSV, Pf-3, polio) and DNA (HSV-1) viruses acting to inhibit infectivity and/or replication [8]. Shenfu injection was also the recommended Chinese patent medicine for the patients with critical illness of COVID-19. Research suggested that flavonoids derived from Shenfu injection showed favorable binding energy with RNA-dependent RNA polymerase (RdRp) and main protease (Mpro, also known as 3CLpro) [9]. SARS-CoV-2 is an RNA virus with a Mpro which plays an essential role in the production of infectious virions and the replication of SARS-CoV-2 [10]. Besides, RdRp is also the central component of coronaviral replication and transcription machinery [11]. Baicalein and quercetin from the flavonoids of Huashi Baidu formula, an auxiliary medicine for the treatment of patients with severe COVID-19, may regulate multiple signaling pathways like TNF signaling pathway through angiotensin-converting enzyme 2 (ACE2) [12]. SARS-CoV-2 entries into target cells through the viral structural spike protein binding to the ACE2 receptor [13]. In vitro studies indicated that caflanone, one of the flavonoids, could inhibit SARS-CoV-2 infection [14]. Hence, cumulative pieces of evidence suggest that it is a promising approach to select the inhibitors of proteins related to SARS-CoV-2 from the natural flavonoids based on traditional Chinese medicine (TCM). Meanwhile, Mpro, RdRp, ACE2 have been considered as the potential molecular target for the treatment of COVID-19 and anti-SARS-CoV-2 drug discovery.

Tea (Camellia sinensis) as a traditional Chinese medicine contains abundant bioactive compounds especially flavonoids, which has been reported to possess various beneficial effects including cardiovascular-protective, anti-diabetic, immune-regulatory, antiviral effects [15,16]. Tea flavonoids like epigallocatechin gallate (EGCG) have been tested for their antiviral activity against several viruses, which is recognized as a multi-functional bioactive molecule exhibiting anti-inflammatory, antioxidative, antibacterial, antiviral effects [17,18]. One previous study showed inhibition of SARS-CoV 3C-like protease activity by theaflavin-3, 3'-digallate [19]. Recently, epigallocatechin-3-gallate and theaflavin-3,3'-digallate derived from tea flavonoids had a significant interaction with the receptors of SARS-CoV-2, which suggested the use of tea flavonoids as potential candidates in prophylaxis and treatment of COVID-19 [18,20]. In vitro study demonstrated epigallocatechin-3-gallate (IC50: 7.58 μg·mL-1) and theaflavin (IC50: 8.44 μg·mL-1) showed inhibitory activity against the SARS-CoV-2 Mpro in a dose-dependent manner. Moreover, different flavonoids have been investigated for their potential antiviral activities, and several of them have shown significant antiviral properties in vitro and in vivo [21].

Network pharmacology is a promising approach to identify potential novel drugs or targets based on the interaction between multi-compounds and multi-targets [22,23]. Molecular docking, a reliable method for drug discovery, is widely used to the investigation of novel compounds against disease to predict ligand-protein interactions pose and molecular mechanism [24,25]. To select new inhibitors of the relevant proteins in SARS-CoV-2 infection and unveil the mechanism of compounds-targets interaction, we performed molecular docking to investigate the tea flavonoids against Mpro, RdRp, ACE2 and elucidate the molecular mechanism.

Materials and methods

Collection of tea flavonoids and targets

Four hundred and sixty-eight tea flavonoids and their derivatives were retrieved from Tea Metabolome Database (TMDB, http://pcsb.ahau.edu.cn:8080/TCDB/f) [26]. One hundred and nineteen small molecules from 468 tea flavonoids were identified based on their molecular weight (< 500g/mol). The structures of these compounds were sketched in the mol format using the ChemDraw. One hundred and nineteen compounds were subjected to optimization and energy minimization under AMBER 10 force field in MOE, saved as the selected compounds for further research.

The information of protein targets and corresponding clinical drugs for the treatment of COVID-19 (Table 2) was obtained from DrugBank (https://go.drugbank.com/). The X-ray crystal structures of candidate protein targets with their embedded ligands were downloaded from the Protein Data Bank (http://www.rcsb.org/pdb).

Molecular docking

Molecular docking analysis was performed using Molecular Operating Environment. The binding site was identified based on the embedded ligands site of the crystal structure of each target. Each target was protonated 3D at physiological pH and removed water for subsequent virtual screening [27]. The docking poses generated from compounds-targets interaction were sorted based on binding energy (also called docking score, DS). The DS function is calculated by the interactions between ligands and amino acids in the binding site, such as hydrogen bonds, arene-arene, interactions distance, etc. The London dG scoring function estimates the free energy of binding of the ligand from a given pose. Value of docking score was used to evaluate binding ability: the lower the DS, the more stable the ligand-protein complex. The best conformation with a lower DS will be retained for the next analysis.

Construction of compounds-targets interaction network

A network interaction model of compounds-targets was constructed and visualized by Cytoscape 3.8.1 software. Network analysis represents large biological datasets in an easily interpretable manner. Compounds and targets were shown by different colored square nodes in the network model. The compounds and targets will be connected if the DS absolute value (|DS|) is more than 7. The red edge denotes a strong binding capacity (|DS| ≥8), while the black edge denotes a good binding capacity (8 ≥ |DS| ≥7) [26]. A network analyzer was employed to calculate the degree, topological parameters for demonstrating the importance of compounds and targets in the network interaction. Meanwhile, the significant difference of |DS| of tea flavonoids for different targets was tested pairwise. t. test (p. adjust. Method = "fdr"). The boxplot and heatmap were generated by ggplot2 and pheatmap packages in R-3.6.2, respectively.

Prediction of ADMET properties

ADME refers to the absorption, distribution, metabolism and excretion of the compounds, which are important parameters to evaluate pharmacological effects. According to the favorable level, drug-like score (DL) ≥ 0.18 and bioavailability score (BS) ≥ 0.17 are often assigned as the criteria to evaluate active compounds. DL and BS were calculated by the molsoft website (https://www.molsoft.com/mprop/) and SwissADME online tool (http://www.swissdock.ch/), respectively.

Results and discussion

Docking score of compounds-targets interaction

Small molecules could prevent the spreading of infection by targeting specific vital compounds of the viral genome [28]. In the 468 tea flavonoids, 119 small molecules with a molecular weight below 500 $g \cdot mol^{-1}$ were collected for molecular docking. The ligand-protein complex will be more stable when higher the docking score (DS) absolute value (|DS|) in that the DS was negative and it refers to the binding affinity of the ligand-protein complex. |DS| of the compounds-targets interaction was shown in (Figure 1). The higher |DS| was observed in RdRp (mean ± sd, 7.31 ± 1.18), while lower |DS| was shown in Mpro (mean ± sd, 6.63 ± 0.72). The RdRp and ACE2 (mean ± sd, 7.51 ± 0.98) were significantly higher than Mpro in |DS| of compounds-proteins interaction. There was no significant difference between RdRp and ACE2 in |DS|. Therefore, preliminary evidence indicated RdRp

Table 1: The features of the ligands-targets interaction network

Network parameters	Value
Number of nodes	90
Number of edges	192
Network density	0.024
Network heterogeneity	2.687
Average number of neighbors	4.267
Characteristic path length	2.038
Network centralization	0.882

Table 2. *Clinical drugs and protein targets involved in SARS-CoV-2 infection*

Protein targets	PDB ID	Clinical drugs	degree	DS (kcal·mol-1)
Angiotensin-converting enzyme 2	1r4l	Hydroxychloroquine	82	-7.8583
RNA-dependent RNA polymerase from SARS-CoV-2	7bv2	Remdesivir	68	-9.1084
Main protease from SARS-CoV-2	6lu7	Lopinavir	45	-8.7147

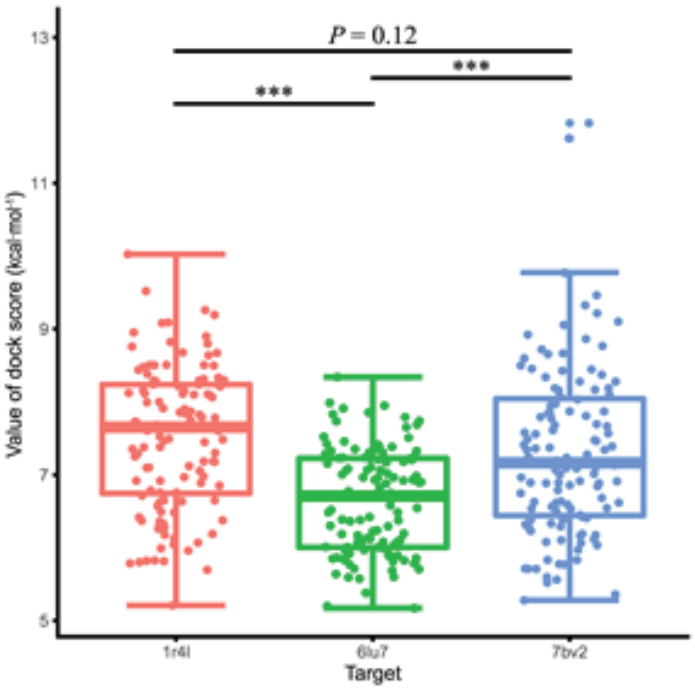


*Figure 1: DS absolute value boxplot. The minimum and maximum values are directly observed from the boxplot; the boxplot center is the median; the boxplot edges represent the 25th and 75th percentiles. Pairwise. t. test (p. adjust. method = "fdr"). *: p < 0.05; **: p < 0.01; ***: p < 0.001.*

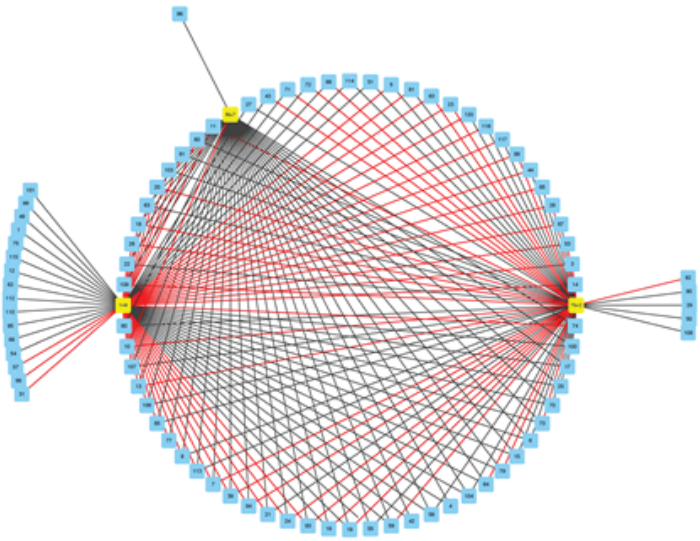


Figure 2: Network model (B) of the compounds-targets interaction. The network model of the compounds-targets interaction. The blue square nodes represent the tea flavonoids, the yellow square nodes represent the protein targets. The red edge denotes a strong binding capacity (|DS| ≥8), while the black edge denotes a good binding capacity (8≥ |DS| ≥7).

Table 3: Top 10 tea flavonoids for each target

Protein targets	TMDB ID	DS (kcal·mol-1)	Degree
6lu7	TMDB-00167	-8.34	3
	TMDB-00198	-7.99	3
	TMDB-00228	-7.95	3
	TMDB-00211	-7.91	3
	TMDB-00229	-7.86	3
	TMDB-00033	-7.83	3
	TMDB-00205	-7.79	3
	TMDB-01317	-7.74	3
	TMDB-01285	-7.74	3
	TMDB-00001	-7.69	3
7bv2	TMDB-00229	-11.83	3
	TMDB-00228	-11.62	3
	TMDB-01430	-9.77	3
	TMDB-00185	-9.76	2
	TMDB-00196	-9.46	3
	TMDB-00285	-9.33	2
	TMDB-01238	-9.22	2
	TMDB-00213	-9.10	3
	TMDB-00202	-9.06	2
	TMDB-01388	-8.92	3
1r4l	TMDB-00174	-10.03	3
	TMDB-00172	-9.52	1
	TMDB-01309	-9.26	3
	TMDB-00185	-9.19	2
	TMDB-01238	-9.09	2
	TMDB-01317	-9.08	3
	TMDB-01268	-8.95	2
	TMDB-00030	-8.90	3
	TMDB-00196	-8.82	3
	TMDB-01387	-8.80	3

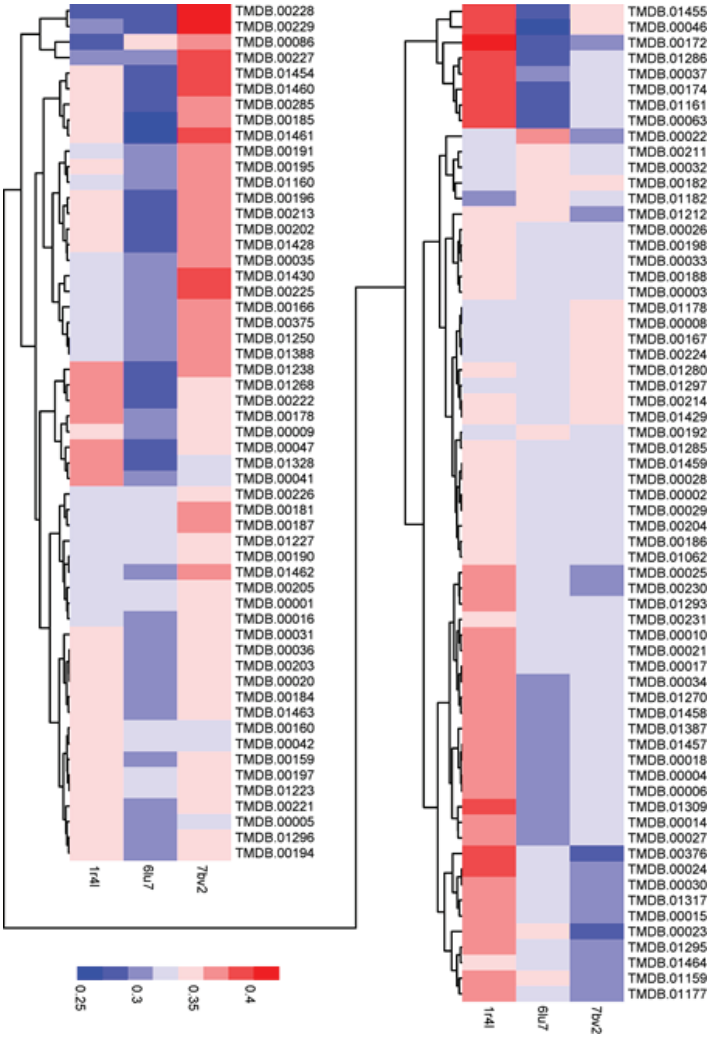


Figure 3: Heatmap of the relative value of |DS| of the compounds-targets interaction

and ACE2 could be considered as the main potential targets for tea flavonoids against COVID-19.

Network analysis of compounds-targets interaction

To further investigate the interaction between tea flavonoids and targets, we established a network model of compounds-targets interaction. The compounds-targets interaction network was shown in (Figure 2). Analyze tool in Cytoscape was employed to manifest the degree, topological parameters, etc. The node degree of a node n is the number of edges linked to n. It indicated the node was more critical when the node with a higher degree. Ninety nodes (87 compounds and 3 targets) and 192 edges were contained in the network model of compounds-targets interaction (Table 1), which suggested that tea flavonoids against COVID-19 may be attributed to a synergistic effect.

ACE2 had a relatively higher degree of 82, followed by RdRp and Mpro with 68 and 45, respectively (Table 2). It could be speculated that ACE2 might be a main potential target of tea flavonoids, followed by RdRp, consistent with the previous result (Figure 1). In contrast, some tea flavonoids were shown outside the circle, which had a lower degree (S1 Table in S1 File). ACE2 is the target of inhibitor hydroxychloroquine. Remdesivir is considered as the inhibitor of RdRp. We could predict that the effect of tea flavonoids was similar to hydroxychloroquine and remdesivir.

The blue square nodes in the network model represent the tea flavonoids. Among them, 40 tea flavonoids with a degree of 3 (S2 Table in S1 File) were collected, and the top 10 tea flavonoids for each target were also collected (Table 3). Although nine compounds of the top 10 tea flavonoids in Mpro had a higher degree, the DS of these compounds was higher than the positive control lopinavir (Tables 2,3). Hence, the binding affinity of compounds-Mpro was not superior to the clinical drug lopinavir. The relative values of |DS| in the compounds-targets interaction were shown in (Figure 3). Mpro had relatively low |DS|, which demonstrated that Mpro could not be the main target of tea flavonoids again (Figure 3). Therefore, ACE2 and RdRp would be used for the subsequent analysis.

In the top 10 compounds of RdRp, six compounds had the degree of 3 and DS of 5 compounds were lower than the clinical drug remdesivir (S2 Table in S1 File, Tables 2 and 3). For ACE2, 6 tea flavonoids had a higher degree and DS lower than the clinical drug hydroxychloroquine (S2 Table in S1 File, Tables 2 and 3). Moreover, by taking an intersection of the top 10 compounds in ACE2 and RdRp Quercetin 3-glycosides (Q3G), 4',5,7-trihydroxyflavanone 7-O-fructoside (S)-form (TF) and isovitexin were obtained for further analysis (S1 Figure in S1 File, Tables 3,4). Meanwhile, TMDB-00229 and TMDB-00174 with the lowest DS in RdRp and ACE2, respectively, would also be used for the following analysis (Table 3, Figure 3).

Interaction analysis of compounds-targets

To further elucidate the binding modes of the above selected representative compounds, 3D active pockets and 2D docking interaction of those selected tea flavonoids and clinical drugs with ACE2 and RdRp were compared. RdRp is essential for the replication and transcription of SARS-CoV-2, which is mainly inhibited by antiviral drug remdesivir [29]. Remdesivir is covalently incorporated into the primer strand at the first replicated base pair and terminates chain elongation [30]. TMDB-00229 (Figure 4B), isovitexin (Figure 4C), Q3G (Figure 4D), TF (Figure 4F) and the clinical drug remdesivir (Figure 4A) with RdRp was shown in (Figure 4). The 3D interaction poses of compounds-RdRp are similar but remdesivir only moderately entry into active pockets. The moiety of 4 tea flavonoids could deeply intercalate at the active site of RdRp. Moreover, DS of 4 tea flavonoids with RdRp was lower than remdesivir (Tables 2-4). Therefore, the interaction poses of compounds-targets would result in the improvement of binding affinity.

2D interactions of compounds-RdRp exhibited similar interaction, i.e., the similar hydrophobic interaction with ArgA55, AspA618 (Figure 4). TMDB-00229 with the lowest DS (DS = -11.83 kcal·mol^{-1}) was the optimum compound in all tea flavonoids (Table 3), whose hydroxyl oxygen atoms could form 4 metal bonds with Mg^{2+} (Figure 4B). Unlike TMDB-00229, remdesivir and isovitexin might form hydrogen bonds with the same residue of Tyr619 (Figure 4A,4C). Additionally, the hydrogen bonding interaction was also observed between Asp618 and the corresponding hydroxyl oxygen atoms in isovitexin, Q3C, TF (Figure 4C-4E). TF also formed a hydrogen bond with Asp760 (Figure 4E). In summary, four tea flavonoids and remdesivir with RdRp could form similar chemical bonds. These tea flavonoids could be considered as the potential inhibitors of RdRp for the prevention and treatment of COVID-19.

ACE2 is widely expressed in multiple human organs such as lungs, cardiovascular system, kidneys, etc [31]. SARS-CoV-2 uses the homotrimeric spike glycoprotein on the envelope to bind to

Table 4: Overlapping components in top 10 tea flavonoids of ACE2 and RdRp

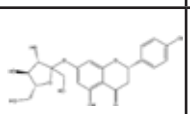
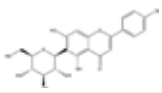
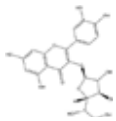
TMDB ID	Structure	Name	Degree	DS (kcal/mol)	DL	BS
TMDB- 01238		4',5,7-Trihydroxyflavanone 7-O-Fructoside (S)-form	2	7bv2: -9.22 1r4l: -9.09	0.98	0.55
TMDB-00185		Isovitexin	2	7bv2: -9.76 1r4l: -9.09	0.59	0.55
TMDB-00196		Quercetin 3-glycosides	3	7bv2: -9.46 1r4l: -8.82 6lu7: -7.30	0.70	0.17

Figure 4: 3D active pocket and 2D interaction of identified optimum conformation against RdRp (7bv2). (A) Remdesivir (B) TMDB-00229 (C) Isovitexin (D) Q3G (E) TF

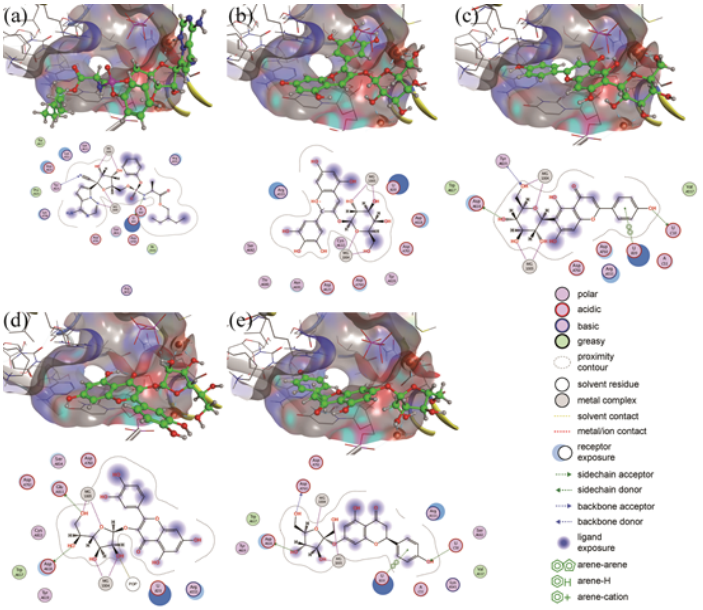
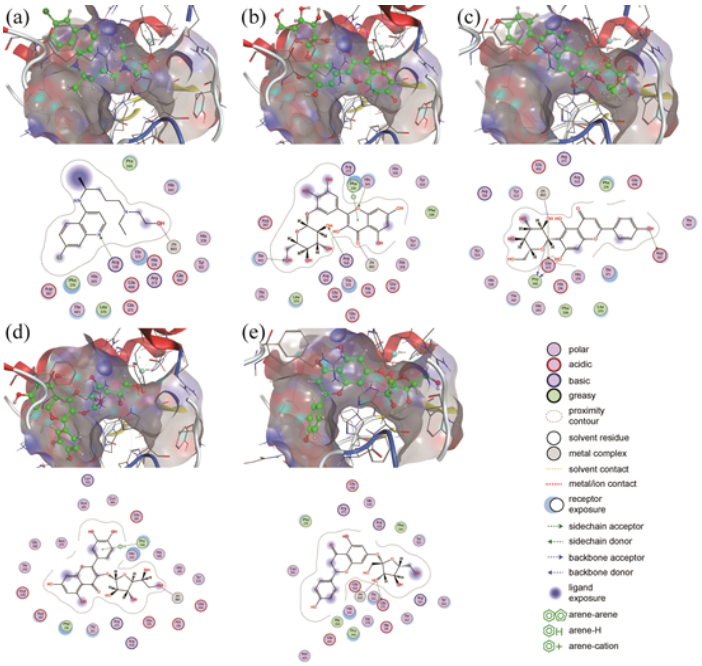


Figure 5 3D active pocket and 2D interaction of identified optimum conformation against ACE2 (1r4l) (A) Hydroxychloroquine (B) TMDB-00174 (C) Isovitexin (D) Q3G (E) TF



the cellular receptor ACE2 [32]. Hydroxychloroquine was thought to weaken the terminal glycosylation of the ACE2 [33]. TMDB-00229 (Figure 5B), isovitexin (Figure 5C), Q3G (Figure 5D), TF (Figure 5F) and the clinical drug hydroxychloroquine (Figure 5A) with ACE2 were exhibited in (Figure 5). According to the 3D interaction poses, five compounds could deeply enter the active pockets of ACE2. Among them, TF could completely embed in the active pockets of ACE2, while hydroxychloroquine failed to fold in the pocket. Furthermore, hydroxychloroquine's binding affinity with ACE2 was lower than 4 tea flavonoids based on the DS (Table 2-4).

According to 2D interactions, the ionic bonds were observed in 5 compounds that could coexist in the same residues of His374 and Glu402. Simultaneously, the hydrophobic interactions were identified between 5 compounds and the same residues of Thr371 and Tyr515 (Figure 5). TMDB-00174 with a lowest DS (DS = -10.03 kcal.mol^{-1}) was the optimum compound in all tea flavonoids (Table 3). Arg518 could form a hydrogen bond with TMDB-00174 and hydroxychloroquine (Figure 5A,5B). Additionally, TMDB-00174 and Q3G had a π-H interaction with Arg273 and Pro346, respectively (Figure 5B,5D). The residues of Thr445 and His345 formed two strong hydrogen bonds with TMDB-00174 (Figure 5B). Pro346 could form two strong hydrogen bonds with isovitexin (Figure 5C). TF formed a hydrogen bond with Glu375 (Figure 5E). It is suggested that TMDB-00174 may be a critical compound in that it could form various chemical bonds. Taken together, these tea flavonoids had common features binding to ACE2.

Tea flavonoids and the primary targets

Due to the various uncertainties, recurrent outbreaks of COVID-19 should be attracted attention all over the world. Remarkably, as a significant country with a population of more than 1.3 billion, China has effectively managed the epidemic outbreak in the short term. Except for the strict outbreak-contained measures, TCM played a critical role in preventing and treating COVID-19. Research on the clinical Chinese patent medicine demonstrated that flavonoids-derived Chinese herbs are considered as effective inhibitors for the target of SARS-CoV-2. Therefore, it is a reliable approach to screen inhibitors from herb-derived flavonoids. Flavonoids derived from Chinese herbs have antiviral effects and multiple organ protection [15], which could be regarded as candidate compounds for multiple organ failure caused by COVID-19. Tea contained abundant flavonoids has been proven to be effective for anti-virus and multiple organ protection. In this study, we conducted a molecular docking to screen potential anti-COVID-19 compounds from 468 tea flavonoids. DS-based compounds-targets network was constructed. We obtained 22 single-target compounds and 40 compounds with 3 targets. Significant interaction of two targets (ACE2 and RdRp) and candidate tea flavonoids (especially Q3G, isovitexin, TF, and more) were analyzed. Additionally, tea flavonoids could deeply embed to ACE2 compared to RdRp, which might be speculated that ACE2 was the primary target inhibited by tea flavonoids for protecting the cells against infection of SARS-CoV-2. Our results demonstrated the bioactive compounds and mechanisms of tea flavonoids in the prevention and treatment of COVID-19 from a bioinformatics perspective. They may also promote target drug design and basic research on anti-SARS-CoV-2.

Our study obtained several compounds of tea flavonoids according to DS of molecular docking. Although DS of the top 10 in Mpro was lower than the positive control lopinavir, a recent study indicated that green tea polyphenols (especially epigallocatechin gallate, epicatechin gallate and gallocatechin-3-gallate) were known to be used as potential inhibitors against Mpro. The top 10 tea flavonoids of Mpro in our study also included epigallocatechin gallate, which suggested epigallocatechin gallate would be a promising candidate drug. Some studies indicated that EGCG could counteract hyper-inflammation growing in COVID-19 because of its antiviral, anti-sepsis, anti-fibrotic effect and reduction in expression and signaling of many inflammatory mediators (like NF-κB) [18]. Remdesivir has been a strong drug candidate against COVID-19 through inhibiting RdRp [11,34]. DS of the top 7 tea flavonoids in RdRp was higher than remdesivir. Interaction between tea flavonoids and RdRp was very similar to remdesivir. Simultaneously, RdRp also is a major target of tea flavonoids.

ACE2, a target of hydroxychloroquine, is a homologue of ACE that catalyzes the conversion of Angiotensin II into Angiotesin 1-7, which induces vasodilation, anti-fibrotic, anti-proliferative and anti-inflammatory effects [35]. Chloroquine and Hydroxychloroquine have been confirmed in vitro. These drugs might inhibit SARS-CoV-2 by elevating the endosomal pH and alter ACE-2 terminal glycosylation thereby leading to the interruption of virus receptor binding [36]. However, the Food and Drug Administration of USA declared that accompanies the drug to state that co-administration of remdesivir and chloroquine phosphate or hydroxychloroquine sulfate may result in the reduced antiviral activity of remdesivir. Thus, it is essential to discover bioactive compounds against ACE2 for replacing hydroxychloroquine. In this study, we identified a major target ACE2 for anti-COVID-19 tea flavonoids. Meanwhile, our data suggested that DS of the top 10 tea flavonoids is higher than hydroxychloroquine. Interaction of tea flavonoids with ACE2 has more hydrogen bonds to form a stable ligand-target complex, compared with that of hydroxychloroquine. The single-cell RNA sequencing (scRNA-seq) data identified the organs at risk, like heart and kidney, based on ACE2 expression levels in some cell types of different organs [37]. A genome-wide association study identified a kidney failure-related 3p21.31 gene cluster as a genetic susceptibility locus in patients with COVID-19 with respiratory [38]. Moreover, the latest study demonstrated SARS-CoV-2 RNA and protein in anatomically distinct regions of the nasopharynx and brain [39]. Cumulative evidence indicates that a heart-brain-kidney network [40] may be associated with SARS-CoV-2 infection. Interestingly, the heart and kidney belong to little lunar (ShaoYin) meridian based on the meridian theory of TCM. Our lab's recent study revealed that flavonoid-rich yellow tea could activate little lunar meridian, a directional flow of body fluid, which provides a drug discovery strategy [41]. More importantly, the latest study indicated that spike glycoprotein alone can damage vascular endothelial cells by downregulating ACE2 and consequently inhibiting mitochondrial function [42]. Meanwhile, ACE2 is protective in the cardiovascular system.Therefore, flavonoids-rich foods with the cardiovascular protection such as yellow tea could be considered a compound of Chinese medicine preventing COVID-19 and tea flavonoids would be a promising drug candidate.

Conclusions

In this study, we investigated the potential therapeutic mechanisms of the tea flavonoids against COVID-19. The results highlight Q3G, isovitexin and TF would be considered as the potential drug candidate. Additionally, the RdRp and ACE2 were the main potential target for COVID-19 treatment in tea flavonoids. Given the limitations of virtual screening results, further experiments in vivo and in vitro are needed to verify the results of this study to provide an experimental basis for the research and development of the natural antiviral drug. Our study uncovered the potential bioactive compounds (especially Q3C, isovitexin, TF, and more) of tea flavonoids against COVID-19 by employing a pharmacology network and molecular docking-based virtual screening. In view of the efficiency of TCM therapy and the potential of these ingredients, we believe that tea especially tea flavonoids could be conducted randomized clinical trials or other detailed experiments for the prevention and adyunct treatment of COVID-19.

Competing interests

The authors have declared no conflicts.

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