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Review article

The medicinal value of tea drinking in the management of COVID-19

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A R T I C L E I N F O

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A B S T R A C T

Corona Virus Disease 2019 (COVID-19) is presently the largest international public health event, individuals infected by the virus not only have symptoms such as fever, dry cough, and lung infection at the time of onset, but also possibly have sequelae in the cardiovascular system, respiratory system, nervous system, mental health and other aspects. However, numerous studies have depicted that the active ingredients in tea show good antiviral effects and can treat various diseases by regulating multiple pathways, and the therapeutic effects are associated with the categories of chemical components in tea. In this review, the differences in the content of key active ingredients in different types of tea are summarized. In addition, we also highlighted their effects on COVID-19 and connected sequelae, further demonstrating the possibility of developing a formulation for the prevention and treatment of COVID-19 and its sequelae through tea extracts. We have a tendency to suggest forestalling and treating COVID-19 and its sequelae through scientific tea drinking.

1. Introduction

SARS-CoV-2 is spreading recklessly around the world. More than 500 million people have been diagnosed by May 2022 [1], and the global economy, medical care, education and other systems are facing huge tests. Although there are currently vaccines against SARS-CoV-2, the virus is still mutating and immune evasion occurs [2]. The clinical manifestations of patients with COVID-19 are mainly upper respiratory tract symptoms, including fever, cough, fatigue and other symptoms, severe patients even have symptoms such as dyspnea [3]. More than 80% of infected people will have sequelae of different symptoms, mainly including respiratory system, cardiovascular system, circulatory system and abnormal mental health [4], which seriously affect people's quality of life. At present, there is no specific drug that can prevent the spread of SARS-CoV-2 and effectively treat COVID-19 and its sequelae.

Tea, a functional drink, is the second largest beverage in the world. The active ingredients in tea include polyphenols, alkaloids, polysaccharides, triterpenoids and organic acids [5]. With anti-inflammatory and antiviral, anti-tumor, antibacterial and other effects, polyphenols are considered to be the main active components of tea [6]. And green tea polyphenol ornament preparation with EGCG as the major constituent, has been approved by the Food and Drug Administration (FDA) [7]. The alkaloids in tea show multiple functions

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such as activating the nerve center, protecting liver cells, and affecting the respiratory system, and are widely used in health care products and medicines [8]. Tea also contains a variety of amino acid components, of which L-theanine is a unique amino acid in tea (a non-protein amino acid). L-theanine has the functions of protecting cardiovascular, improving cognitive function, anti-inflammatory, anti-anxiety, and antioxidant [9,10].

Studies have shown that the antiviral activity of tea is crucial in the context of the COVID-19 pandemic. Polyphenols and tea tree oil in tea can interfere with membrane structural proteins, hinder the binding of SARS-CoV-2 to ACE2 receptors, and inhibit viral RNA replication. This effect has a certain broad spectrum and still has an effect on the mutated virus [11,12]. Even if the virus enters the body, various active ingredients in tea can still reduce the level of cytokine storm caused by SARS-CoV-2 through multiple mechanisms and improve the various sequelae of COVID-19 [13]. At the same time, the polysaccharides in tea can enhance the immune regulation of the body to play a key role in preventing secondary infection of the virus [14].

Since 2022, Maiti, S. et al. Found that theaflavins in tea can improve lung injury caused by SARS-CoV-2 [15]. Based on the antiviral activity of catechins and derivatives in tea, the Paiva, L. team and Eggers, M. team proposed the possibility of making a new beverage or preparation to prevent or treat COVID-19 [16,17]. A prospective cohort study proved that drinking tea, as an adjuvant therapy, can reduce the risk of exacerbation in patients with new coronary pneumonia [18]. Xu et al. also proposed the possibility that polyphenols in tea could prevent or treat new coronary pneumonia by regulating the gut-lung axis and enhancing immunity [19]. Although the correlation between the consumption of tea drinking and various diseases has been revealed, the degree of correlation between the type of tea drinking and COVID-19 and related sequelae is not clear [20].

The changes in the content of active ingredients in tea caused by different processing methods are necessary for exploring the role of tea in the prevention and treatment of new coronary pneumonia and sequelae. This article discusses the antiviral activity of the main active components of different teas and their mechanisms of action on the respiratory, cardiovascular and nervous systems through literature review and network pharmacology techniques. Meanwhile, we emphasize the possibility of scientific drinking tea to prevent and treat COVID-19 and its sequelae.

2. Types of tea and differences in active ingredients

The type of tea can be divided into six types such as black tea, green tea, oolong tea, white tea, yellow tea, dark tea according to the different fermentation processes, so the content of main components in different types of tea is different. Catechin compounds are one of the main types of components in tea [21]. With the extension of tea laying time, dehydration stress will cause the expression of genes related to the synthesis of catechins to be inhibited or simply catechins are oxidized to form various derivatives under the action of polyphenol oxidase (PPO) in tea [22,23]. However, the drying time of green tea is short, and high temperature fixation can reduce the activity of PPO, so the content of catechins in green tea is the highest [24,25]. The catechins mainly include 8 catechin monomers such as (−)-epigallocatechin (EGC), (−)-epicatechin (EC), (+)-gallocatechin (GC), (+)-catechin (C), (−)-epigallocatechin gallate (EGCG), (−)-epicatechin gallate (ECG), (+)-gallocatechin gallate (GCG), (−)catechin gallate (CG) [26]. During the production of black tea, the fermentation time becomes longer and higher temperature is not required [27], so that the catechins form the intermediate o-quinone under the action of polyphenol oxidase (POP) or peroxidase (POD), and then oxidatively polymerized to form theaflavins [28]. Theaflavins mainly include Theaflavin (TF1), theaflavin-3-*O*-gallate (TF2A), theaflavin-3′-*O*-gallate (TF2B) and theaflavin-3, 3′-di-*O*-gallate (TF3) [29]. In addition, catechins or catechin dimers can further form a multimeric compound called thearubigin through an oxidative cascade reaction [30,31]. With the deeper development of research, a new ingredient was discovered in black tea in 1980s, which was named tea theabrownin [32]. Theabrownin is a compound formed by the further oxidative polymerization of theaflavin and thearubigin (The brown macromolecular polymers of glycoproteins) [33,34]. Interestingly, the formation of theabrownin is more complex in Pu-erh, a lightly fermented tea, which involves the glycosylation of phenols and their oxidative polymerization products under the action of glycosyltransferase and the oxidation reaction of ascorbic acid under moist heat conditions [35]. As the source of bitterness in tea, alkaloids mainly use xanthoside as a substrate to synthesize theobromine, and theobromine is used as a precursor to further synthesize caffeine, which can be degraded into a very small amount of theophylline under the action of enzymes [36]. The highest caffeine in white tea may be related to the promotion of caffeine synthase-related gene (TCS) expression [37,38]. The flavonoids in tea include not only catechins, but also anthocyanins, flavonols and other compounds, which are important indicators for evaluating the quality of tea. During the process of high temperature fixation and fermentation, flavonoids, flavonols and their glycosides in tea are largely degraded [39], the content is highest in white tea that has not been treated at high temperature and fermented for a long time [7]. The flavonoids and flavonols in tea mainly conclude quercetin, kaempferol, myricetin and their glycosides [40,41]. There are many kinds of amino acids in tea, and content of them is closely related to the processing method. After the fixation process, the protein is hydrolyzed at high temperature to increase the amino acid content and the expression of free amino acid synthesis genes is active, which increases most amino acids but reduces the content of ethylamine, the precursor compound of L-theanine. Enzymatic hydrolysis is more effective than pyrolysis for protein decomposition during the withering process [42,43]. Therefore, white tea has the highest content of total amino acid, while green tea has the highest content of L-theanine. On the contrary, during the fermentation process of black tea, amino acids will combine with phenols and sugars in tea leaves to reduce the content of the amino acid [44].

In summary, different processing methods can cause changes in the content of active ingredients in tea leaves (Fig. 1, Fig. 2). The content of catechins is mainly high in unfermented green tea and yellow tea. Theaflavin, the product of oxidative polymerization of catechin, is higher in fermented black tea or white tea treated with long-term withering technology. Thearubigin and Theabrownin, oxidation products of theaflavins, are more abundant in dark tea fermented for longer time and oolong tea after repeated tossing. The content of several alkaloids is the highest in dark tea. White tea contains a higher total amount of amino acids than other teas, but the L-

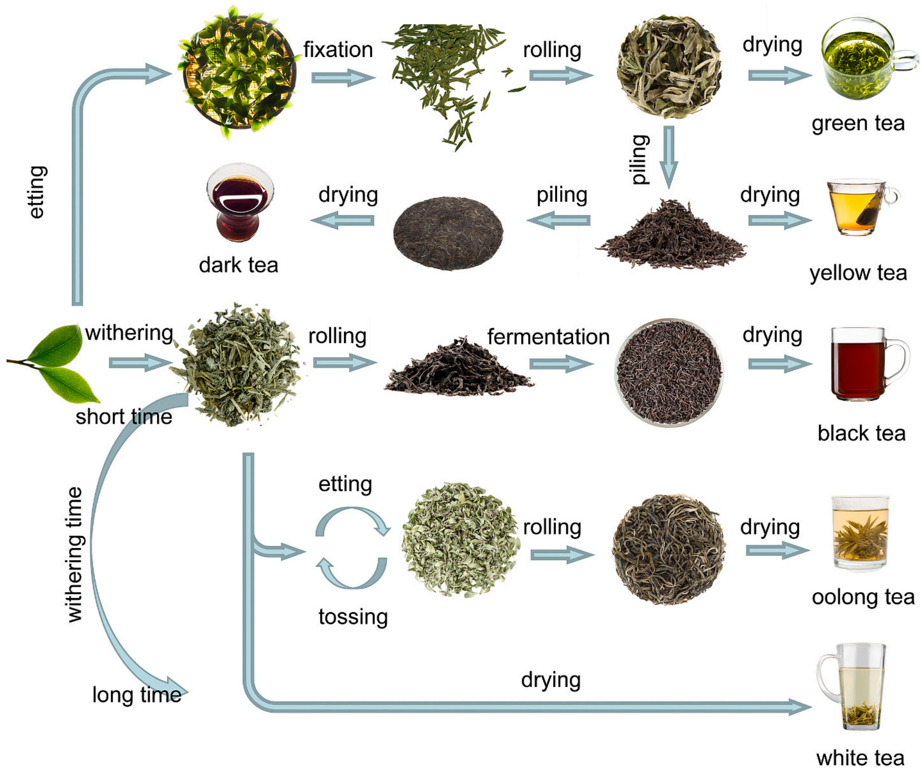

Fig. 1. Six different types of tea.

theanine, which is unique to tea leaves, is the highest in green tea. Therefore, the type of tea selected should vary from person to person, which is also in line with the overall concept of Chinese medicine theory and the concept of syndrome differentiation [45]. In the context of the wide spread of the world epidemic, scientific tea drinking under the guidance of the theoretical system of traditional Chinese medicine has become particularly important to prevent and reduce sequelae of COVID-19 (Table 1).

3. The effects of tea on COVID-19 and its sequelae

With the spread of COVID-19 around the world, its harm to people is not only reflected in the onset period, but also in the sequelae. The sequelae of COVID-19 are mainly reflected in the respiratory system, cardiovascular system, nervous system, and mental health [46-49]. It is worth exploring whether scientific tea drinking can effectively alleviate the sequelae of COVID-19.

3.1. The improvement effects of tea on respiratory sequelae

The main sequela of COVID-19 to the respiratory system is pulmonary fibrosis which accounts for about 40% of the sequelae with the respiratory system [50]. Currently, studies have reported that COVID-19 might cause abnormal immune mechanisms and promote pulmonary fibrosis through cytokine storms [51,52]. The treatment plans for pulmonary fibrosis caused by SARS-CoV-2 should firstly consider the effect of the compound on the replication and internalization of the virus, and secondly how to reduce the effects of cytokine storms on the body [53].

3.1.1. Antiviral effects of compounds in tea

EGCG can prevent Hepatitis C Virus (HCV) from binding to cells by adhering to the cell surface, playing a blocking role in the early stage of virus invasion into the body, and can moderately inhibit HCV-RNA replication by enhancing PolyI: *C*-induced interferon-λ1 production. But it seems to be related to the type of HCV [54-56]. Therefore, this also makes EGCG have a broad-spectrum antiviral effect. EGCG can block the binding of gp120 to T-CD4 at a certain concentration, making it unable to expose the coreceptor to block gp41 binding and reduce the activity of RNA reverse transcriptase. Fmix (A theaflavin derivative drug) can also directly mediate gp41, which blocks the binding of the Human Immunodeficiency Virus (HIV) envelope to the cell membrane [57-59]. In summary, it shows that the compounds in tea can hinder the process of virus invading the body at all stages, which makes it possible to explore the compounds in tea as potential drugs for preventing and treating COVID-19 and alleviating sequelae.

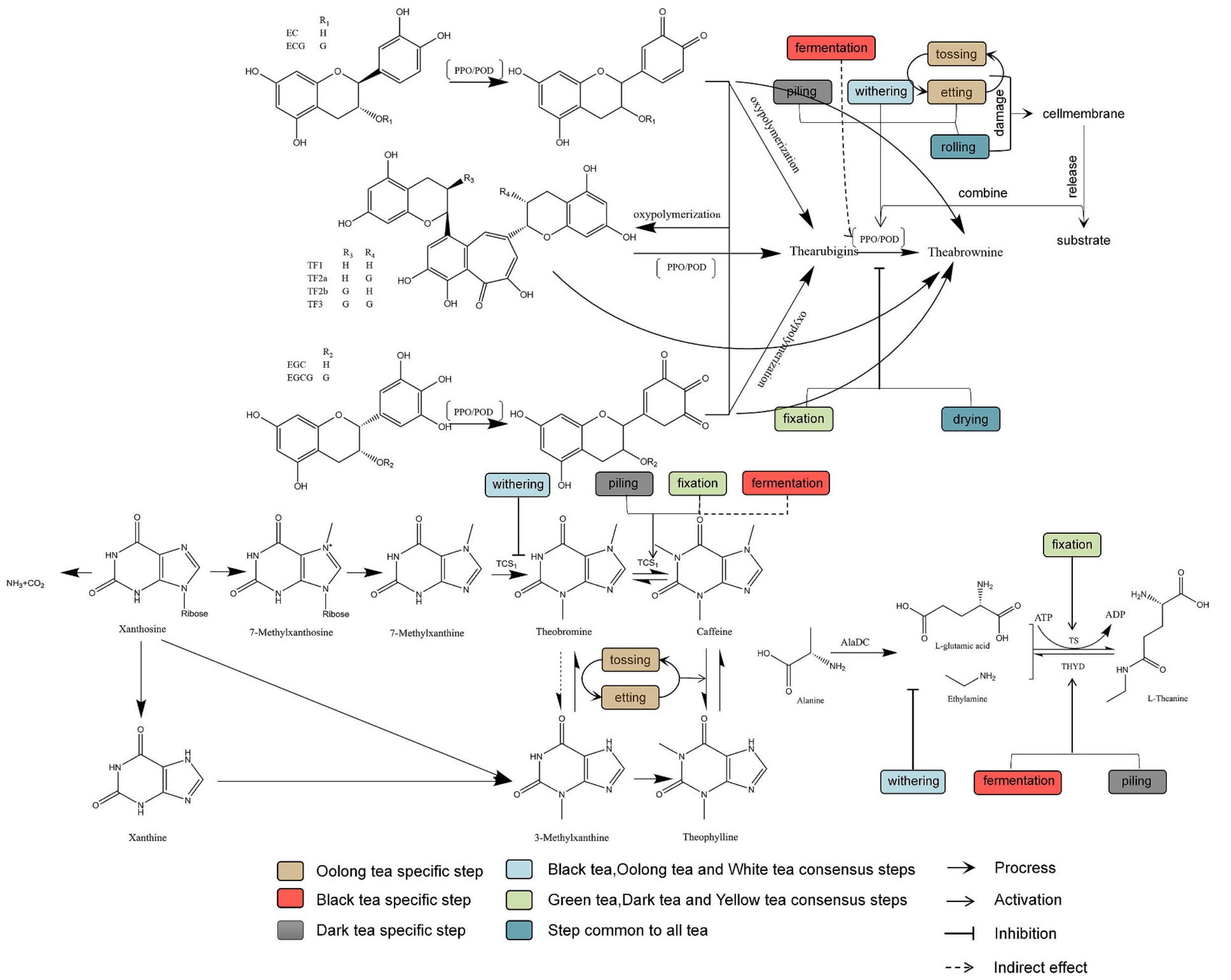

Fig. 2. Influence of tea making process on active ingredients.

Table 1
Major compounds in tea.

Types	Compound	PubChem CID	Representative of Tea Species
Catechin	(−)-Epicatechin	72,276	Green tea, Yellow tea
	(+)-Gallocatechin	65,084	Green tea, Yellow tea
	(+)-Catechin	9064	Green tea, Yellow tea
	(−)-Epigallocatechin	72,277	Green tea, Yellow tea
Ester catechins	(−)-Catechin gallate	6,419,835	Green tea, Yellow tea
	(−)-Epicatechin gallate	107,905	Green tea, Yellow tea
	(−)-Epigallocatechin gallate	65,064	Green tea, Yellow tea
	(+)-Gallocatechin gallate	5,276,890	Green tea, Yellow tea
Catechin derivatives	Theaflavin	135,403,798	Black tea, White tea
	Theaflavin-3-*O*-gallate	135,458,101	Black tea, White tea
	Theaflavin-3′-*O*-gallate	71,307,578	Black tea, White tea
	Theaflavin-3, 3′-di-*O*-gallate	136,055,243	Black tea, White tea
	Thearubigin	76,182,283	Black tea, Oolong tea
	Theabrownin	uncertain	Dark tea, Oolong tea
Alkaloids	Caffeine	2519	Dark tea, White tea
	Theobromine	5429	Dark tea, White tea
	Theophylline	2513	Dark tea, White tea
Amino acid	L-theanine	228,398	Green tea, White tea

Based on molecular docking technology, it has been proved that tea polyphenols, especially theaflavins (TF, TF2B), might inhibit the activities of NSP16 (coronavirus 2′-Omethyltransferase), Angiotensin-converting enzyme 2 (ACE2), RNA replicase (RdRp) and 3C-likeprotease (3CLpro) of SARS-CoV-2, and inhibit the replication and transcription of the virus, thereby preventing the spike protein from attaching to human cells [60-63]. In vitro verification confirmed that EGCG in tea could interfere with the binding of SARS-CoV-2 RBD to ACE2 of host cells, or by inhibiting the activity of 3CLpro, thereby blocking the initial invasion process of the virus [64–66]. GCG can also impede RNA replication by disrupting SARS-CoV-2 of the liquid–liquid phase separation of coronavirus nucleocapsid (N) protein [67], and experimental investigation indicates that tea extract can inhibit SARS-CoV-2 in saliva inactivation [68], while EGCG can improve lung injury by enhancing human autoimmunity and autophagy [69,70]. This indicates that the effect of the green tea extract on the surface receptor protein of SARS-CoV-2 is direct, non-specific. It has a remarkable effect on the whole stage of virus invasion, and EGCG has stronger antiviral activity in tea extract [71,72].

The specific binding with the receptors on the surface of human cells is the first step for the virus to invade the human body, and the continuous replication of the virus will aggravate the disease of the human body. The polyphenols in tea have good antiviral activity. Because this effect is by destroying the physicochemical properties of the viral membrane surface, preventing the virus from binding to receptor proteins, and inhibiting the enzymatic activity that controls viral nucleic acid replication [73]. Therefore, whether it is SARS-CoV-2 or a variant, or other viruses that may be produced in the future, tea can always show good antiviral activity [65]. One study found that this effect was not produced by just one compound, and that multiple components in tea work synergistically and in a concentration-dependent manner. The use of tea concentrate as an oral spray formulation may inactivate the virus in the mouth for preventive purposes [74].

All in all, the active ingredients in tea can inhibit the whole process of virus intrusion into the human body, and this effect is non-specific. At present, some studies have begun to use bioinformatics to screen the ingredients, and it is feasible to use the active ingredients in tea as a specific drug against COVID-19 in the future [75].

3.1.2. Effects of compounds in tea on pulmonary fibrosis induced by cytokine storm

Pulmonary fibrosis in patients with COVID-19 is mainly caused by cytokine storms invasion. The components in tea mainly delay the process of various stages of oxidative stress by directly inhibiting or synergistic antioxidants, and the process is dominated by the enzymatic antioxidant system [76,77]. EGCG can inhibit neutrophil migration to chemotactic stimuli and reduce neutrophil activity thereby reducing ROS and caspase 3 release, and can synergize with SU5416 (A VEGFR inhibitor) to inhibit the angiogenic pathway [78,79], EGCG can also reduce the aggregation of mutant proteins and promote protease degradation by activating the protease degradation pathway, or directly reduce the protease activity to inhibit the activation of matrix metalloproteinase-9 (MMP9) and matrix metalloproteinase-2 (MMP2), and its inhibitory effect is more obvious on leukocyte elastase [80-82], also attenuates the effects of matrix-degrading lysosomal hydrolases [83]. The extract of Black tea can reduce the expression of α-SMA by reducing the expression of TNF-β, up-regulating the expression of IFN-γ and inhibiting the TNF-β/Relaxin signaling pathway [84], or by activating the P13 K/Akt signaling pathway, up-regulating the expression of PTEN and inhibiting epithelial-mesenchymal transition (EMT) [85]. It can also induce the expression of Nrf2 by activating the Keap-Nrf2 signaling pathway and reduce the production of various pro-inflammatory factors such as TNF-α, IL-1β, and IL-17, increase the anti-inflammatory factor IL-10, inhibit the inflammatory response, and reduce collagen deposition [86,87]. Tsai M Jet al. Found that EGCG appeared to inhibit fibroblast growth by regulating cholesterol metabolism [88,89].

Pulmonary fibrosis, a common respiratory sequela in patients with COVID-19, is mainly due to damage to host cells after SARS-CoV-2 enters the lung, from which a large number of cytokines are released. Cells generate large amounts of collagen fibers and matrix components to repair damaged tissue. When this condition cannot be alleviated, phenomena such as continuous active fibroblasts and extracellular matrix deposition occur, which eventually lead to the formation of pulmonary fibrosis. The extracts in tea were able to reduce cytokines through several signaling pathways, such as TNF-β/Relaxin, P13 K/Akt and Keap-Nrf2, and alleviate EMT and extracellular matrix formation in a way that metalloproteinase inhibition, reduces the activity of fibroblasts.

In conclusion, the ingredients in tea are able to impede the invasion of SARS-CoV-2 and variants into the body, inhibit virus replication, and also reduce the cytokine storm produced after the virus damages the body's cells and thus alleviate the level of pulmonary fibrosis in patients.

3.2. The improvement effect of tea on the cardiovascular system

There are many cardiovascular system diseases caused by COVID-19, mainly including hypertension, arrhythmia, coronary atherosclerosis and other symptoms [90]. SARS-CoV-2 can directly affect the cardiovascular system through direct invasion of cardiomyocytes, the renin-angiotensin-aldosterone system (RAAS) [91]. Indirect damage to the cardiovascular system can also be mediated by cytokines [92], including the imbalance of coagulation factor levels, immune disorders, and drug side effects [93-95]. The results of social survey analysis have shown that appropriate daily tea drinking is inversely correlated with various cardiovascular system mortality [96,97]. Green tea is able to reduce the amount of vasoconstriction by inhibiting the expression of key contractile genes (RhoA, ROCK1, ROCK2 and CPI-17) and proteins (*p*-MYPT1, *p*-MLC20 and p-CPI-17) in the aorta of hypertensive mice [98]. L-theanine can regulate calcium-dependent and calcium sensitization pathways. It can regulate the contraction and relaxation of vascular smooth muscle to improve hypertension [99]. Interestingly, theabrownin and caffeine components in Pu-erh tea have similar effects [100]. EGCG can exert an inhibitory effect on ACE, and fermented tea leaves (black tea) seem to have the same inhibitory effect and reduce hypertension through other ingredients [101]. It has been demonstrated that tea polyphenols have no effect on normal blood pressure [102], which suggests that reasonable tea intake can relieve hypertension without causing adverse reactions. Tea intake is inversely associated with arrhythmias [103], although studies have shown that caffeine can trigger arrhythmias but it requires high doses [104]. Low-dose EGCG alleviates arrhythmias by modulating cardiac sodium channels, but when the concentration reaches a certain value (50 μM), it will have the same effect as caffeine [105,106]. EGCG can reduce the content of CK-MB and LDH in arrhythmia mice and improve arrhythmia [107]. Atrial fibrillation can also be ameliorated by inhibition of calmodulin [108]. Atherosclerosis is closely related to the level of lipid metabolism, and polyphenols in tea have an effective effect on the prevention and treatment of atherosclerosis [109]. Current studies have indicated that EGCG can increase the expression of lipid enzymolysis-related genes by inhibiting the expression of protein kinases, and inhibit the activity of synthases to maintain the stability of sclerotic plaques [110,111], and synergistically with heparin to reconstitute the insoluble fibrous polymer (atherogenic component) formed by apolipoprotein A-I (apo-1) to form soluble oligomers [112]. Inhibition of angiotensin 2 (Ang-2)-induced *C*-reactive protein (CRP) inhibits the secretion of inflammatory cytokines by T cells by interfering with mitochondrial apoptosis and AT-ROS-ERK1/2 signaling pathway to inhibit inflammation-related atherosclerosis [113,114]. It can also protect damaged vascular endothelial cells by regulating multiple signaling pathways such as Jagged-1/Notch signaling pathway, P13 K/AKt signaling pathway, and SIRT 1/AMPK signaling pathway [115,116]. The theaflavins in tea can also improve hemorheology in patients with atherosclerosis and promote the repair of damaged cells [117]. It may be related to the Nrf2/HO-1 signaling pathway and reduces factors secreted by vascular endothelial cells [118,119].

In conclusion, multiple components in tea leaves are able to play beneficial roles against cardiovascular diseases, among which polyphenolic compounds are the predominant ones. They protect cardiomyocytes and cardiovascular cells through P13 K/Akt, Nrf2/HO-1 and other signaling pathways related to oxidative stress, inflammatory factors, or by regulating lipid metabolic pathways, improving blood rheology [120]. However, it is related to tea intake, and an excessive intake can aggravate the degree of cardiovascular disease [104,121]. Therefore, scientific tea drinking methods and reasonable tea intake still need to be studied.

3.3. Effects of compounds in tea on improving nervous system

Researches have revealed that about 40% of patients with new coronary pneumonia have neurological abnormalities, mainly including cognitive impairment, hyposmia, postural tremors, and motor/sensory deficits [122]. These abnormalities are mainly due to the direct intrusion of SARS-CoV-2 into the central nervous system through the hematogenous and neural afferent pathways or enter neurons by binding to ACE receptor 2 of the nerve cell membrane, damage neuronal tissue and blood vessels, and increase the permeability of the blood-brain barrier [123,124]. Polyphenols in tea can protect nerve cells by regulating calcium homeostasis and gene expression of MAPK, protein kinase C, and antioxidant enzymes [125,126]. Cognitive dysfunction can also be improved by regulating corticosterone [127]. EGCG can be used as an adjunct drug to alleviate neuronal disorders in the hippocampus and improve the lesions of astrocytes and microkeratinocytes [128]. The effect of EGCG in improving learning and memory is related to dose and blood-brain barrier permeability, and L-theanine can produce the same effect as EGCG at low doses [129]. L-theanine can directly promote the proliferation and neuronal differentiation of neural precursor cells, and regulate cognitive function [130]. It can also indirectly protect the nervous system by affecting signaling pathways, regulating hormone levels, and reducing oxidative damage, improving cognitive dysfunction and abnormal mobility [131]. Some scholars believed that tea had a good effect on a variety of nervous system diseases [132].

Polyphenols and amino acids in tea are able to act as antioxidative stress agents through ERK signaling pathways and so on, thereby protecting neurons and promoting differentiation, effects that were even more pronounced after SARS-CoV-2 invasion resulted in altered permeability of the blood-brain barrier. The alkaloids in tea can also act as an excitatory center opposite to L-theanine. Therefore, choosing different tea seems to be a therapeutic method for improving neurological sequelae.

3.4. Effects of compounds in tea on mental health

Surveys have discovered that patients with new coronary pneumonia will generally have emotions such as anxiety and depression, and the resulting symptoms such as sleep disturbance, emotional distress, and memory loss [47,133]. It is mainly due to the longer hospitalization and isolation time, and the reduction of communication with people [134]. Another reason may be the overall global economic downturn brought about by the new crown pneumonia, which has reduced people's sense of job security and increased economic pressure [135]. A survey report showed that tea intake was negatively correlated with anxiety among students, which also had a significant effect on improving anxiety after surgery [136,137]. This may be that polyphenols in tea play an anxiolytic role by regulating the hyperactivity of HPA axis and controlling the content of DA and NE [138]. In addition to tea polyphenols, L-theanine can also fight anxiety by stimulating alpha-brain waves or regulating the production of γ-GABA [139]. It is interesting that although the symptoms of depression and anxiety are quite different, tea can still repair hippocampus damage and improve depression by regulating monoamine neurotransmitters [140].

Although reports have shown that various components in tea affect the symptoms and behavior of anxiety and depression, the impact of COVID-19 on people's mental health is comprehensive. Reasonable tea drinking is only suitable as an adjunct to psychotherapy to combat anxiety and depression after COVID-19 (Fig. 3).

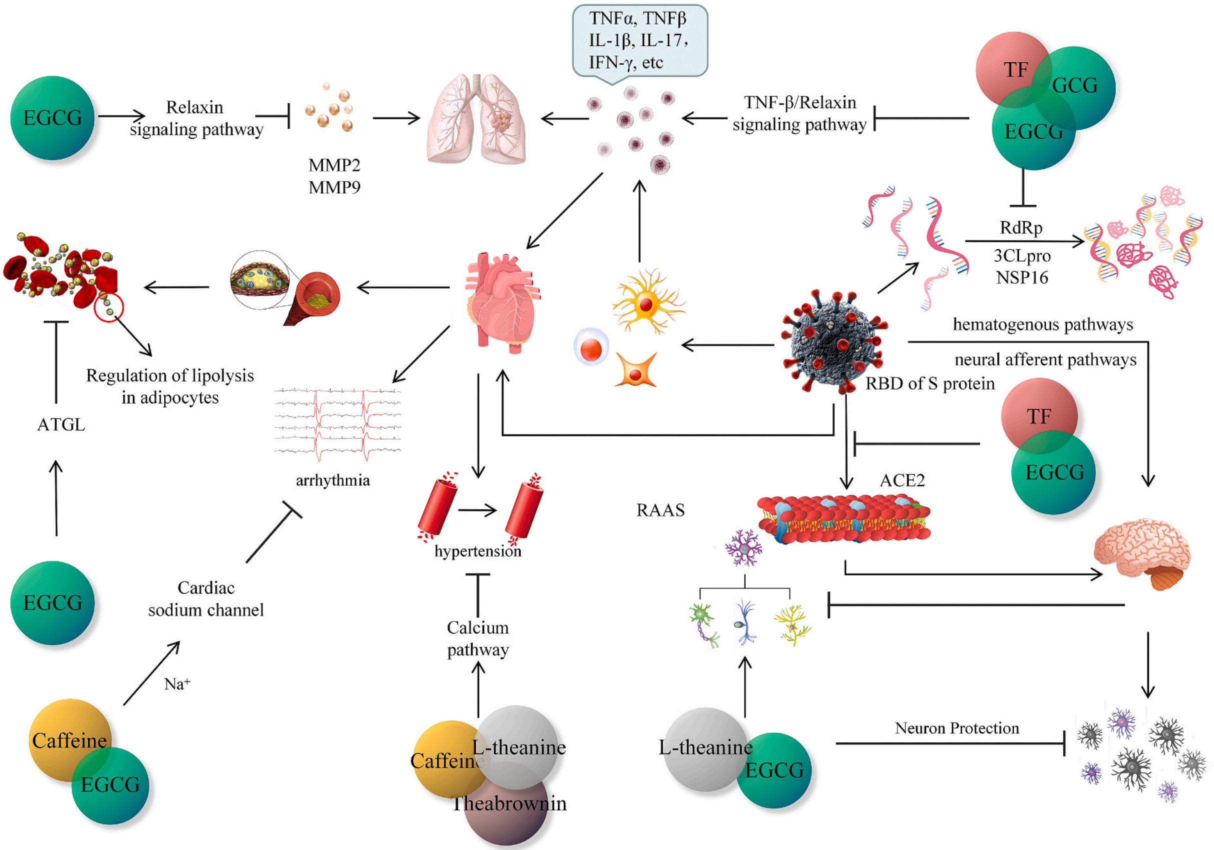

Fig. 3. Mechanism of tea in the treatment of COVID-19 and its sequelae based on literature review.

4. Exploring the mechanism of tea treatment of COVID-19 and its sequelae based on network pharmacology

In order to further clarify the mechanism of action of tea on COVID-19 and its sequelae, the network pharmacology technology was used to screen the active ingredients in tea, to identify the common targets of compounds and diseases, and to determine the signaling pathway of tea in the treatment of new coronary pneumonia and sequelae through enrichment analysis in this paper.

The active ingredient targets of tea were calibrated with UniProt. By searching public databases, including Online Mendelian Inheritance in Man (OMIM, https://omim.org/), Therapeutic Target Database (http://db.Idrblab.net/ttd/), GeneCards Database (https://www.Genecards.org/) (Score in the top 1000) and DisGeNET (http://www.Disgenet.org/), remove duplicate targets, and get a database of possible targets [141]. Draw Venn diagrams using a free data analysis platform (http://www.graphbio1.com/). Integrating the common targets of tea and COVID-19 and sequelae, the results showed that 149 related targets from 12 compounds were matched with 4583 COVID-19 and complications related targets, and a total of 89 shared targets were identified (48 of them are related to respiratory diseases including COVID-19, pulmonary fibrosis, 51 are related to neurological diseases cognitive disorder including movement disorders, postural tremor, hyposmia, 64 are related to cardiovascular diseases including atherosclerosis, arhythmia, hypertension) (Fig. 4-A). The results of network showed that the therapeutic effects of tea on COVID-19 and complications were directly related to these 12 compounds and 89 genes. The data, compounds of tea, the co-action targets, related systems and diseases, were imported into Cytoscape 3.8.2 software to construct a "compounds-targets-systems-diseases" network diagram. Based on the screening results, the interactions between 89 overlapping genes and 12 compounds were listed in Tab. S2 (Fig. 4-B).

We imported the common targets of drugs and diseases into the STRING database. Removed the isolated protein, get the protein interaction network and data involving 89 target proteins, and import them into Cytoscape 3.8.2 software. The initial potential target protein interaction network was analyzed by MCC and the network topology parameters were analyzed by Network Analyze. Using the cytoHubba plug-in, the top 10 genes in the combine score were screened out: VEGFA, ITGB1, EGFR, ITGA3, MAPK14, ITGB3, VTN, MMP9, MMP2, HGF (Fig. 4-C).

Through DAVID setting, homo sapiens, shared targets were subjected to GO and KEGG pathway enrichment analysis, using PRISM software and a data analysis platform (http://www.graphbio1.com/#) to draw bar charts and advanced bubble charts. To further clarify the mechanism of tea's treatment of COVID-19 and sequelae, we used DAVID to perform GO enrichment analysis. The results of enrichment analysis showed that the regulation of COVID-19 and sequelae by tea involved BP such as signal transduction, proteolysis,

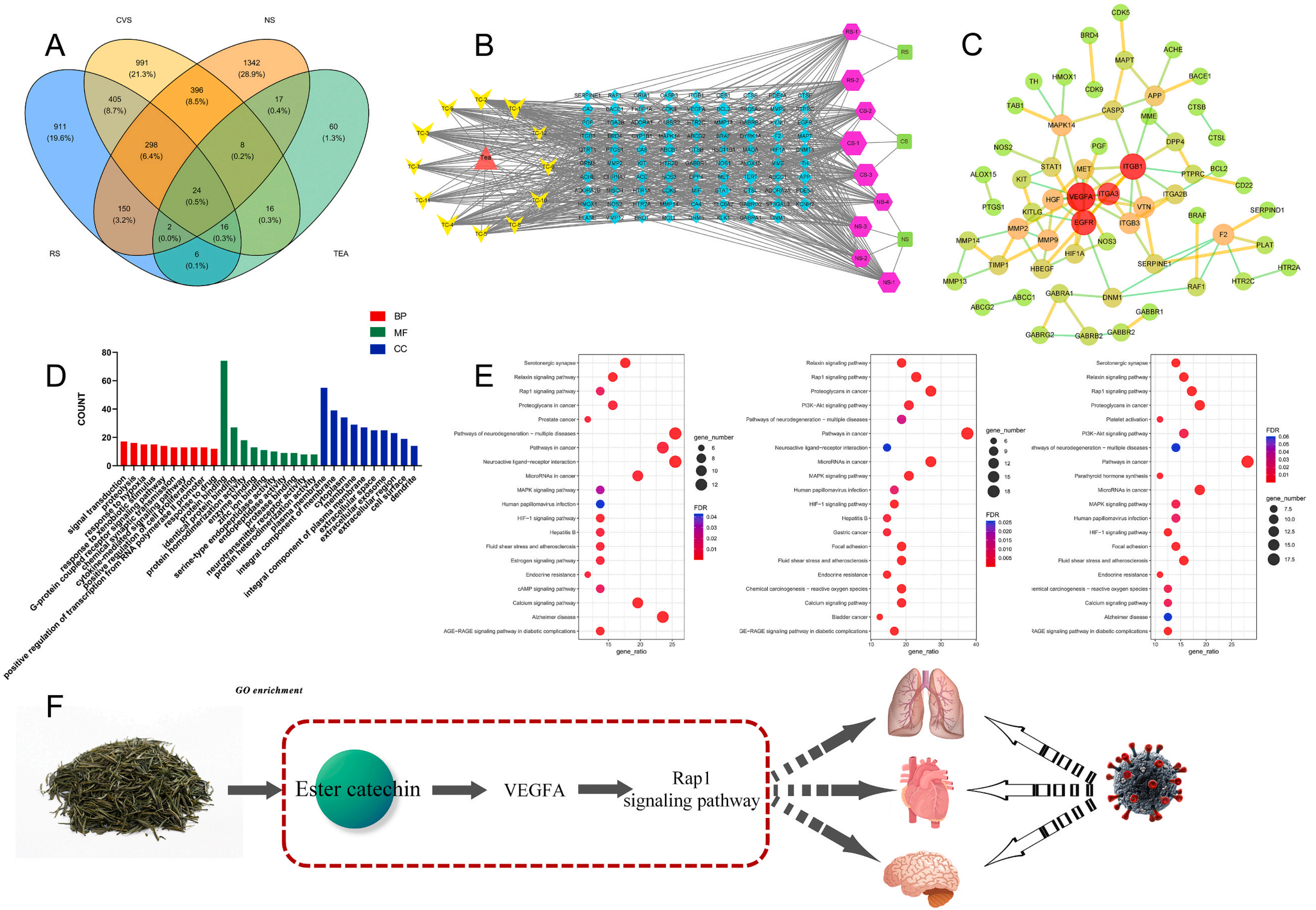

Fig. 4. Network pharmacology of tea to treat COVID-19 and sequelae. A: Tea and cardiovascular system, respiratory system, neurological sequelae targets Venn Diagram B: Tea disease target network C: PPI protein network diagram D: GO enrichment analysis E: KEGG enrichment analysis diagram (From left to right: cardiovascular system, nervous system, respiratory system, respectively) F: Key targets and pathway flow screened out by network pharmacology.

response to hypoxia, involved MF such as protein binding, identity protein binding, protein homodimerization activity, and involved CC such as plasma membrane, integral component of membrane and cytoplasm. The results of GO enrichment analysis clarified that the active components in tea mainly affect various diseases through anti-oxidation, control the expression of disease-related genes, and regulate the hydrolysis and synthesis of proteases. It can also play an antiviral role by binding to cell membrane receptors or blocking receptor formation. It is the same as the mechanism by which the components in tea have antiviral effects and effects on various diseases by regulating signaling pathways (Fig. 4-D). The result of KEGG analysis showed that pathways of tea in the treatment of COVID-19 and sequelae were significantly enriched, mainly including Rap1 signaling pathway, Calcium signaling pathway, MAPK signaling pathway, PI3K/Akt signaling pathway and Relaxin signaling pathway. The first 20 pathways were selected and displayed in the form of a bubble chart (Fig. 4-E,F).

5. Discussion

COVID-19 is a major disease faced by the world, and the spread of the new coronavirus affects the development of society in many aspects. At present, the plan of treatment for COVID-19 patients is mainly antiviral, antibacterial, anticoagulant, and immune drugs. And critically ill patients are also given extracorporeal respiratory support and circulatory support [142]. After the disease, most patients have sequelae in the respiratory and cardiovascular system, and these sequelae pose a greater threat to those who originally had underlying diseases [51]. It has been reported that the mortality rate of patients with underlying diseases is much higher than that of patients without underlying diseases, the prognosis time is prolonged, and the effect of drugs is weakened [143]. The role of chemical constituents in tea has been widely studied, including antioxidant, antibacterial, blood lipid regulation, blood pressure lowering, hypoglycemic and other effects, but the effect of tea on COVID-19 and its sequelae is still unclear [144,145]. Although tea shows a wide range of effects, excessive intake of tea polyphenols can cause vomiting, diarrhea and other adverse reactions, so the scientific way of having tea deserves to be proposed [146].

The classification of tea leaves is based on the differences in the production process, and is divided into 6 types based on the oxidation speed and degree of flavanols, including green tea, yellow tea, dark tea, black tea, oolong tea, and white tea. The medicinal properties of the six types of tea are different. Green tea has the coldest medicinal properties, dark tea the warmest, while yellow tea and oolong tea are relatively mild [147]. Therefore, residents in summer or areas with perennial hot temperatures are suitable for having green tea, on the contrary, fermented teas are more suitable for drinking in winter or areas with perennial low temperature [148]. In addition, the timing of having tea is also considered. The caffeine in the tea leaves with the empty stomach has a stimulating effect on the gastric mucosa. If you drink tea immediately after a meal, the tannin in the tea leaves will be combined with protein, which is not easy to excrete and increases the burden on the stomach. The alkaloids and amino acids in tea can refresh the mind, and the tea polyphenols can promote lipid metabolism [149-151]. The theory of traditional Chinese medicine believes that patients with COVID-19 belong to the syndrome of stagnant and jamming dampness-heat, and both yellow tea and oolong tea have good improvement effects. For mild new coronary pneumonia patients with Qi deficiency, Yin deficiency, Qi and Yin deficiency syndrome, yellow tea is universal, and green tea has a better effect of nourishing Yin. For severely ill patients, the dampness-heat of lung causes more cardiovascular sequelae such as atherosclerosis and coronary heart disease, but due to the severe degree of the disease, it will also lead to deficiency of spleen-yang and kidney-yang, so it is suitable to have white tea or yellow tea with slightly cold properties to reconcile [51, 148].

By reviewing and summarizing literatures, we discussed the active ingredients and mechanism of tea in the treatment of new coronary pneumonia. It provided a new view on the treatment of COVID-19 and its sequelae with tea, and provided a basis for the clinical treatment of COVID-19 with tea. Scientific tea consumption is able to reduce the activity of SARS-CoV-2 receptor and inhibit the release of inflammatory factors caused by the virus, thus reducing the damage to the body from cytokine storm. It can also adjunctively reduce the level of pulmonary fibrosis by regulating multiple signaling pathways after SARS-CoV-2 infection. In addition to relieving respiratory complications, research suggested that tea contain a variety of active ingredients, including catechins, alkaloids, and amino acids. Among them, catechins and alkaloids can reduce blood pressure, regulate heart rate and improve atherosclerosis by regulating vasoconstriction and relaxation, regulating ion channels and accelerating lipid metabolism, without damaging normal cells. Nearly half of patients with new coronary pneumonia will have neurological sequelae, which are mainly reflected in cognition, smell, movement, etc. The L-theanine in tea can promote neuron differentiation and promote proliferation. At the same time, polyphenols in tea can repair damaged neurons, protect damaged nerve cells, and also improve depression or anxiety caused by new coronary pneumonia.

In addition, the secondary infection of new coronary pneumonia is also one of the difficult problems, T-cells and B-cells can respond quickly and provide protection when the body is re-infected with SARS-CoV-2, although it is unclear how long this effect will last [152]. A study showed that EGCG in tea improves the apoptotic resistance of B-cells and T-cells stimulated by cytokines, prompting apoptosis of damaged cells without affecting healthy cells [153,154]. Another study showed that EGCG can promote the proliferation of T-cells and B-cells in leukemia mice to enhance the body's immune function [155]. These results make it possible for tea to prevent secondary infection of SARS-CoV-2, especially SARS-CoV-2 variants.

In the review, tea targets, chemical components and related action pathways were analyzed by network pharmacology technology, and the treatment and improvement effects of tea on new coronary pneumonia and complications were verified. From the analysis results, it was determined that catechins are the key compound type, among which (−)-catechin gallate and (−)-epigallocatechin gallate are upstream active components, which is consistent with the previous review. TERT is the core target of tea for the treatment of COVID-19 and its complications. It is associated with six sequelae of arrhythmia, atherosclerosis, hypertension, pulmonary fibrosis, cognitive impairment, and motor deficits. It is also a target gene of 10 active ingredients including (−)-catechin gallate and

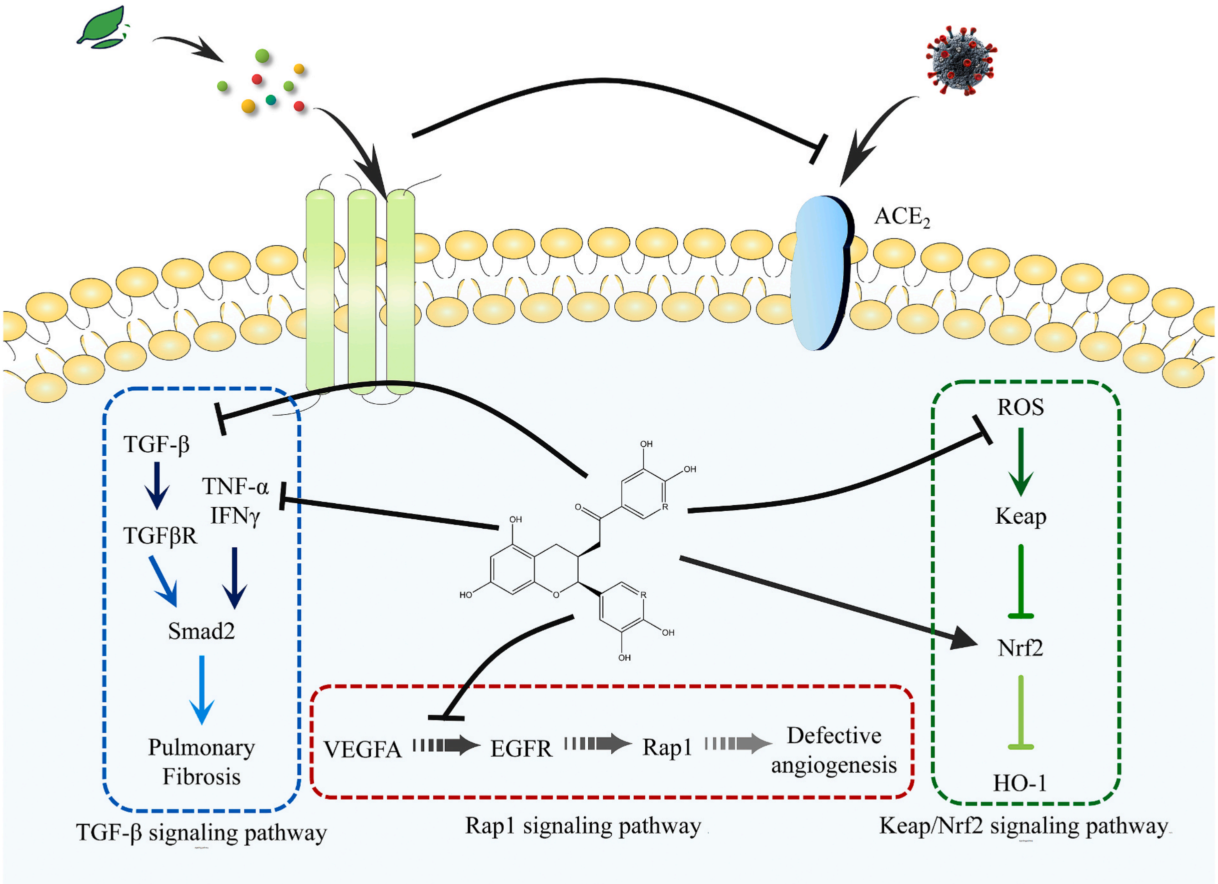

Fig. 5. Mechanism of tea anti SARS-CoV-2 and treatment of sequelae of COVID-19.

(−)-epigallocatechin gallate. As a key pathway, Rap1 signaling pathway is related to respiratory system, cardiovascular system, and nervous system sequelae. Some experiments have confirmed that drugs can activate the Rap1 signaling pathway to restrict blood vessel formation and improve the symptoms of pulmonary fibrosis by regulating genes related to the Rap1 signaling pathway [156,157]. The Rap1 signaling pathway can regulate the differentiation of bone marrow mesenchymal stem cells and play a role in the treatment of cardiovascular diseases [158]. Moreover, the Rap1 signaling pathway can activate the extracellular signal-regulated kinase 5 of neurons in the central nervous system to achieve the effect of treating neurological diseases [159].

COVID-19 is still a difficult problem faced by the world at present, and targeted treatment options need to be studied. This paper provides a data basis for the mechanism of action of tea in the treatment of COVID-19 and its sequelae, and offers new ideas for the development of new treatments for COVID-19 and its sequelae by literature review and network pharmacology technology.

6. Conclusion

EGCG is the main active ingredient in tea, and the other ingredients are able to synergistically prevent and treat COVID-19 and its sequelae. The content of active ingredients varies among different teas, and prevention or alleviation of COVID-19 and sequelae by a scientific way of tea drinking is necessary. Ingredients in tea are able to hinder SARS-CoV-2 from invading the body and inhibit RNA replication of the virus. After viral invasion, the active ingredients in tea will alleviate COVID-19 and its sequelae by reducing cytokine levels through TGF-β/Relaxin, P13 K/Akt, Keap-Nrf2 and other signaling pathways, and they also respond to reinfection with SARS-CoV-2 and variants by modulating the immune system. Based on the review and network pharmacology, different teas are able to prevent and treat COVID-19 and its sequelae through multiple pathways. In the future, the active ingredients in tea may have the potential to be used as drugs for the prevention and treatment of COVID-19 and its sequelae through more in-depth clinical studies (Fig. 5).

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Data availability statement

No data was used for the research described in the article.

Declaration of interest's statement

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e12968.

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