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Tea as a natural gift for discovering antiviral candidates

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Abstract

Coronavirus disease (COVID-19) remains rampant worldwide and poses a serious threat to human health. Tea is a medicinal and edible homologous plant that exhibits potential anti-SARS-CoV-2 properties *via* the prevention of virus entry into host cells, inhibition of virus replication, and enhancement of the innate and cellular immune responses. In this review, the properties of six major types of tea were systematically summarized, including green tea, yellow tea, white tea, oolong tea, black tea, and dark tea. We focused on the primary components of tea exhibiting antiviral activities, which included (–)-epigallocatechin-3-gallate, (–)-gallocatechin gallate, tannic acid, oolonghomobisflavan A, theaflavins, and white-tip silver needle flavonoids. Among them, (–)-epigallocatechin-3-gallate is proposed to be an antiviral compound that interferes with the entire life cycle of SARS-CoV-2 by balancing inflammation and immunity. Thus, this compound can serve as a promising lead structure for the development of SARS-CoV-2 inhibitors.

Keywords: Catechins, (–)-Epigallocatechin-3-gallate, SARS-CoV-2, Tea

Graphical abstract: http://links.lww.com/AHM/A39.

Introduction

As of August 12, 2022, over 585 million cases of the coronavirus disease 2019 (COVID-19) have been confirmed, and more than 6.4 million deaths have been reported by the World Health Organization. COVID-19 caused by SARS-CoV-2 continues to spread globally[1]. Fortunately, therapeutics with traditional Chinese medicine (TCM) combined with Western medicine has been demonstrated as a successful practice for the treatment of COVID-19. TCM therapies such as "three TCM drugs and three herbal formulas" (Xuebijing injections, Lianhua Qingwen capsules, Jinhua Qinggan granules, Qingfei Paidu formula, Huashi Baidu formula, and Xuanfei Baidu formula) exhibited remarkable efficacy against COVID-19. TCM represents a powerful tool for use in both treatment and prevention[2], yet the underlying mechanism of TCM action is difficult to fully elucidate. The correct symbol is "due to characteristics of its multi-components, multi-targets, and multi-pathways". Therefore, it is imperative to screen bioactive substances and investigate the underlying mechanisms of TCM based on modern scientific theories and technologies. It will be helpful to elucidate the principle of TCM in regard to battling COVID-19 infection and facilitate the spread of the use of TCM throughout the world.

As a medicinal and edible homologous plant, tea makes a popular beverage that has been reported to inhibit SARS-CoV-2 activity[3–5]. As a natural plant, tea is rich in various substances such as polyphenols, pigments, micronutrients, amino acids, and vitamins. According to previous research, the primary compounds that prevent viral infections in tea, which are (–)-epigallocatechin-3-gallate (EGCG), (–)-gallocatechin gallate (GCG), tannic acid (TA), oolonghomobisflavan A (OFA), theaflavins (TFs), and white-tip silver needle flavonoids (WTSNF)[3].

In this review, the six major types of tea–green tea, yellow tea, white tea, oolong tea, black tea, and dark tea, are systematically summarized. To identify attractive drug targets against SARS-CoV-2, potential active compounds from tea were surveyed. This review will provide guidance for the discovery of novel anti-SARS-CoV-2 candidates.

The types of tea plants

As a beverage, tea was prepared from the leaves of *Camellia sinensis* in ancient China[6] and initially used as a survival food. The medicinal functions of tea have been gradually discovered and recognized as a result of its widespread consumption. During the Tang Dynasty, tea was honored as a cure for all diseases, thus providing a great summary of its medical benefits. Furthermore, tea has been demonstrated to possess numerous pharmacological effects such as anti-oxidation, anti-aging,

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anti-cancer, immune regulation, metabolism regulation, and physiological regulation, particularly in regard to antiviral and anti-inflammatory regulatory functions[7].

In China, tea plants can be classified according to a number of parameters such as quality, production area, cultivation environment, and processing method. As presented in Figure 1, tea can be divided into six major types according to the extent of fermentation, and these types include green tea (non-fermented), yellow tea (fermentation degree of 10%–20%), white tea (fermentation degree of 10%–20%), oolong tea (fermentation degree of 30%–60%), black tea (fermentation degree of 80%–90%), and dark tea (fermentation degree of 100%)[8]. The fermentation process is primarily determined due to the oxidative polymerization and condensation of catechins that are catalyzed by endogenous polyphenol oxidase and peroxidase.

Green tea

Green tea is the only type of tea that is not oxidized and named according to its yellow-green liquor and unfermented green leaves. It possesses a light aroma and tastes slightly bitter. This tea accounts for approximately 20% of the total tea production worldwide[9]. The famous green teas in China are Xihu Longjing Tea, *Lu Shan* Mist Tea, *Bi Luo Chun* Tea, and *Huang Shan Mao Feng* Tea. Fresh tea leaves are roasted or steamed to destroy the enzymes responsible for decomposing the pigments in leaves, thus maintaining maintain their green color during the rolling and drying process[8,10]. Green tea contains high levels of natural polyphenols.

The major compounds in green tea are catechins, phenolic acids, flavonoids, and amino acids[11]. Among these, catechins in green tea exhibit higher anti-oxidant activity due to the minimal oxidation that occurs during the preparation process[12]. Catechins are the primary components in tea polyphenols. These compounds account for 70%–80% of catechins, including catechin (C), epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), and EGCG[13]. Among these, EGCG accounts for 50%–80% of the total catechin content[14]. The ingredients mentioned above contribute to the antiviral activity of green tea.

Yellow tea

Yellow tea is a slightly fermented tea with a fermentation degree of 10%–20% and is referred to as yellow tea based on the color of the leaves changing from green to yellow during fermentation. It yields a bright yellow tea liquid with a fresh and mellow taste. This tea can be divided into three types: yellow bud tea, yellow small tea, and yellow big tea. The renowned yellow teas are *Jun Shan* Silver Needle, *Huo Shan* Yellow Bud, Big Leaf Light Tea, and *Huo Shan Huang Da* Tea.

Yellow tea contains catechins, flavonoids, alkaloids, amino acids, and other ingredients[15]. The initial process is the same as that of green tea regarding to roasting or steaming, and it then requires a unique step known as "sealed yellowing" that can remove the grassy flavor of green tea while still retaining the healthcare values[16]. Prolonged yellowing has been reported to increase the contents of amino acids, soluble sugar, TFs, and non-esterified catechins while decreasing the contents of polyphenols, flavonols, thearubigins, caffeine, and esterified catechins[17]. In particular, the ester catechin content in yellow tea was significantly lower than that in green tea, and the content of non-esterified catechins and amino acids was higher than that in green tea. The total amount of tea polyphenols is similar to that of green tea and accounts for 20.44%–27.66% of the dry weight[18].

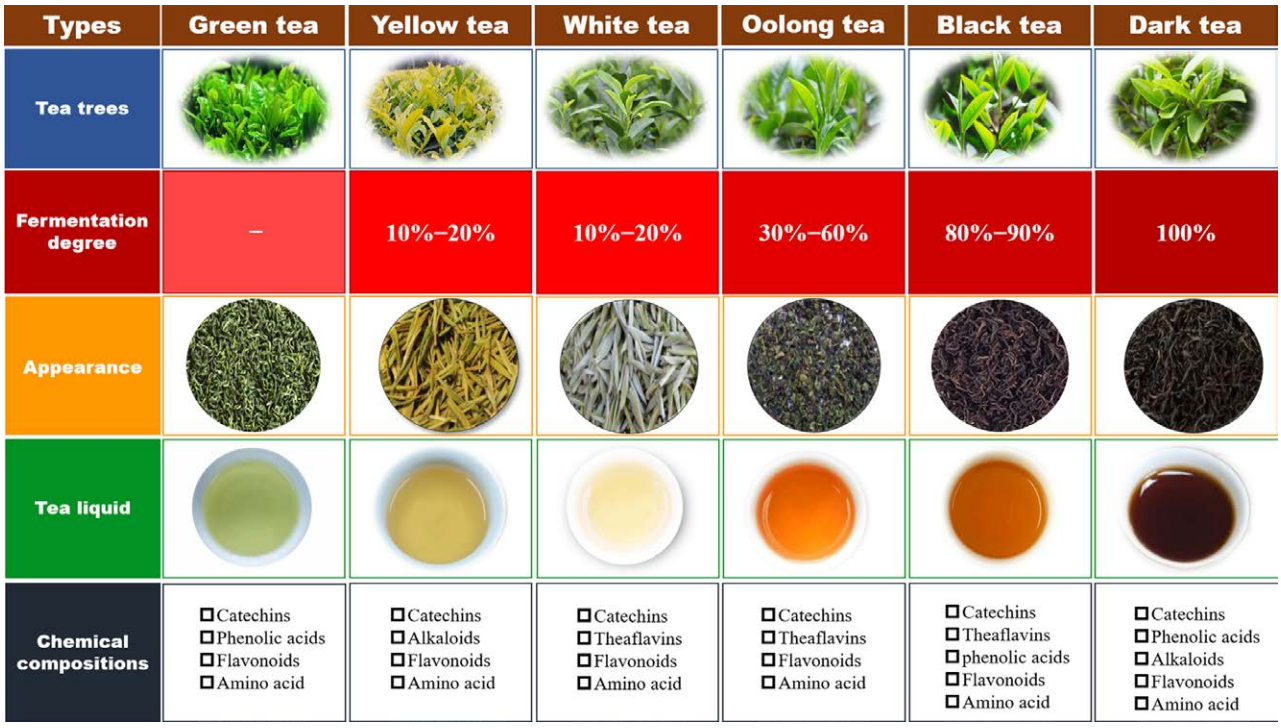

Figure 1. Six types of tea and their primary chemical compositions.

After fermentation, 85% of natural substances are retained, and these substances have been demonstrated to possess anti-cancer, anti-bacterial, free radical scavenging[19], gastrointestinal protection, and anti-oxidant activity[20].

White tea

White tea is a type of micro-fermented tea that originates from Fujian Province (China) and made from buds and new leaves with minimal processing steps such as withering and drying[21]. On the leaf surface, there is a covering of white fuzz that is referred to as light frost that can protect the growth of new leaves from insects. Additionally, the tea broth appears light in color and therefore it is referred to as white tea. *Bai Hao* Silver Needle and *Bai Mu Dan* Tea are the most famous white teas.

White tea has been deemed to be an excellent anti-inflammatory folk herb that exhibits better activities with the extension of storage time. Modern research has demonstrated that it is rich in polyphenols and flavonoids that contribute to its anti-oxidant and anti-inflammatory activities. After withering for a long period of time, the catechin content was markedly reduced due to chemical reactions that included oxidative polymerization and other reactions. However, the contents of TF, thearubigin, tea pigments, gallic acids, and acyl procyanidins increased significantly. In white tea, the total amount of amino acids is 1.13 to 2.25 fold higher than that of other teas [22], and the content of free amino acids is the highest and ranges from 5.97% to 8.89%[23]. A large number of animal and cell experiments have revealed that white tea exerts various beneficial activities such as anti-inflammatory, anti-oxidant, anti-tumor, bacterial and viral inhibition activities, and protection of the cardiovascular system and liver[24].

Oolong tea

Oolong tea is also referred to as *Wu Long* Tea in Chinese and considered as a semi-fermented tea originating from Fujian Province (China)[25] that possesses a strong aroma and light sweetness. Its leaves are green in the middle and red at the edge, and thus its leaves are typically referred to as red-edged green tea leaves. The manufacturing process consists of four steps that include withering, kneading, fermenting, and baking. It combines the processing methods of both green tea and black tea, thus resulting in a mixed taste. In China, *Da Hong Pao* Tea and *An Xi Tie Guan Yin* Tea possess a global reputation. With the extension of fermentation time, the sweet and green fruity flavors are enhanced, while the bitter flavor does not change. Furthermore, the content of catechins decreases, whereas that of TF increases significantly[26]. Oolong tea also contains a number of active components such as alkaloids, polyphenols, flavonoids, amino acids, proteins, polysaccharides, and vitamins that are beneficial to human health[27].

Black tea

Black tea is a fully fermented tea and the most popular tea worldwide[14]. *Qi Men* Black Tea, *Yun Nan Dian* Black Tea, and *Lapsang Souchong* Tea are famous in China. The liquid is clear and bright with a red-orange or bright red color, and a mellow, fresh and sweet taste.

Black tea contains not only catechins and TFs but also phenolic acids, flavonols, and amino acids[12]. Four processing steps include withering, rolling, fermentation, and drying. The activity of enzymes is increased with deepened fermentation that is used to degrade chlorophyll, drive the polymerization of catechins and polyphenols, and generate colored substances such as TFs and thearubigins. Thus, black tea possesses a bright orange-red color. Four major TFs have been identified, including TF, theaflavin-3-gallate (TF-3-G), theaflavin-3'-gallate (TF-3′-G), and theaflavin-3,3'-digallate (TF-3,3′-diG)[28]. Catechins can be oxidized and polymerized into higher-molecular-weight polyphenols by endogenous polyphenol oxidase and peroxidase[29] which have been reported to exhibit antiviral activities[30].

Dark tea

Dark tea is a unique type of fermented tea that is produced through solid-state fermentation by microorganisms[31] and possesses oily black or dark brown leaves due to its long accumulation time and fermentation. Famous dark teas in China are *An Hua* Dark Tea, *Pu'er* Tea, *Liu Pao* Dark Tea, and *Ya An* Tibetan Tea. The basic production process consists of four steps that include fixing, rolling, stacking, and drying. Stacking is believed to be a key step in the production of high-quality dark tea. This tea is abundant in various compounds, including catechin derivatives, flavonols, flavonoids, glycosides, phenolic acids, alkaloids, and terpenoids[32–34]. Meanwhile, it has received much attention due to its excellent health benefits such as prevention of hypertension and cardiovascular disease, relief of metabolic syndrome, and regulation of intestinal function and weight loss[35].

Structure of SARS-CoV-2 and the attractive drug targets

Coronaviruses are enveloped, single-stranded, positive-sense RNA viruses belonging to the *Orthocoronavirinae* subfamily of *Coronaviridae*. They can be divided into four major genera according to their genome sequences and serological reactions, including *Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus*[36–37]. SARS-CoV-2 belongs to the subfamily *Betacoronavirus* that possesses a unique structural feature on the virion surface referred to as a crown that contributes to the diversity of subunits. SARS-CoV-2 encodes 14 open reading frames (ORFs). Each of these ORFs (with except ORF10) was translated into 29 viral proteins. At the 3′ terminus of the viral genome, they encode four structural proteins that include the spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. At the 5′ terminus, two-thirds of the genome encodes two overlapping polyproteins (pp1a and pp1ab) that are digested by viral proteases into 16 non-structural proteins (Nsps) that play an essential role in viral replication and transcription[38]. Sixteen Nsps are necessary for the forming of the viral replication transcription complex (RTC) for viral RNA

synthesis in host cells[39]. Unlike other Nsps, Nsp5 (main protease, M^{pro}) and Nsp3 (papain-like protease, PL^{pro}), two highly conserved proteases, are produced by autolytic cleavage. They then cleave pp1a and pp1ab to produce other Nsps and form mature viral genomes[40]. Nsp12 (RNA-dependent RNA polymerase, RdRp) that is generated by M^{pro} cleavage is another important Nsp required for new virion assembly, and it has been demonstrated to be the target of remdesivir[41]. Therefore, M^{pro}, PL^{pro}, and RdRp are thought to be the primary targets for the development of SARS-CoV-2 inhibitors[42]. During the SARS-CoV-2 life cycle, viruses enter host cells through S protein binding to angiotensin-converting enzyme 2 (ACE2) receptors on the cell surface. This step relies on the action of transmembrane protease serine (TMPRSS2) that mediates the cleavage of the S protein and initiates the membrane fusion of viruses with the host[43]. Therefore, intervention in the binding of S protein to ACE2 receptor represents an ideal and promising approach. Thus, TMPRSS2 is a potential antiviral target.

An increasing number of studies have demonstrated that the release of virions into the body through exocytosis, which can trigger a cytokine storm, ultimately leading to systemic inflammation and damage to tissue and organ. Hence, an integrated treatment approach was proposed that targets not only the pathogen but also the key pathways of inflammation and immune response such as the NF-κB and JAK-STAT pathways.

Anti-SARS-CoV-2 compounds in tea

Multiple compounds possess antiviral activity in tea, including EGCG, GCG, TA, OFA, TFs, and WTSNF that can not only inhibit the invasion and replication of SARS-CoV-2 to some extent but can also regulate and restore the inflammatory response. They play a key role in the fight against SARS-CoV-2 infection. As presented in Table 1, EGCG can activate Nrf2 which inhibits the expression of ACE2 receptors to reduce the levels of ACE2 receptors. TA acts on TMPRSS2 to prevent SARS-CoV-2 from entering host cells. Moreover, EGCG, GCG, TA, OFA, and TFs have been demonstrated to interfere with the replication of SARS-CoV-2 *via* the differential targeting of M^{pro}, PL^{pro}, or RdRp. Additionally, EGCG, GCG, and WTSNF can regulate a variety of cellular inflammatory and immune factors, including interleukin (IL)-6, IL-1β, IL-17, IL-8, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), thus resulting in diminished and restored inflammation caused by SARS-CoV-2 invasion of host cells.

Catechins

Catechins is a class of phenolic active substances extracted from natural plants that account for approximately 70% of the total tea polyphenols[70], and it has been reported to exhibit beneficial effects *in vitro* and *in vivo* such as anti-oxidant and anti-bacterial activity, obesity control, and free radical scavenging. Catechins in tea include EC, GC, EGC, CG, ECG, GCG, and EGCG[71] which exhibit antiviral functions and protect against diseases caused by oxidative stress and inflammation. Compounds with antiviral activity in tea may contribute to curbing the devastation resulting from COVID-19 infection caused by SARS-CoV-2[72].

EGCG

EGCG is a major compound derived from green tea with a basic flavan-3-ol structure that has been reported to exert numerous pharmacological effects, including anti-tumor[73], anti-oxidation[74], degenerative disease protection[75], anti-bacterial[76], antiviral[77], hypoglycemic[78], anti-mutagenic[79], anti-inflammatory, and immunomodulatory properties[80–81]. EGCG is likely to represent a satisfactory candidate based on the demonstrated evidence of inhibition of SARS-CoV-2 entry and virus infection *in vitro*[3]. Furthermore, EGCG has been identified as a potential inhibitor of M^{pro} and PL^{pro}[48,82].

Inhibition of SARS-CoV-2 entry into host cells by EGCG

During infection, the S protein that is embedded in the SARS-CoV-2 surface lipid envelope recognizes ACE2 receptors and binds to them to allow for uncoating. In this step, the S protein is cleaved by certain proteases (TMPRSS2 and furin) to promote membrane fusion. Then, the viral genomes are injected into host cells to

Table 1

Major antiviral compounds in tea and their targets and functions

Compounds	Targets	Primary functions	References
EGCG	Nrf2	Reduction of ACE2 receptor expression in airway epithelial cells by activating Nrf2	[44–47]
	M^{pro}/PL^{pro}/RdRp	Interference with SARS-CoV-2 replication by inhibition of M^{pro}, PL^{pro}, and RdRp	[48–54]
	Nrf2/NF-κB pathway/JAK-STAT pathway	Reduction of the levels of IL-6, IL-1β, IL-17, IL-8, TNF-α, IFN-γ, and other pro-inflammatory factors	[55–63]
GCG	N protein	Interference with SARS-CoV-2 replication by disrupting the LLPS of N protein	[64]
	M^{pro}	Interference with SARS-CoV-2 replication by inhibition of M^{pro}	[49]
		Reduction of the levels of IL-1α, TNF-α, IL-4, and IL-1	[65]
TA	M^{pro}	Interference with SARS-CoV-2 replication by inhibiting M^{pro}	[66]
	TMPRSS2	Interference with SARS-CoV-2 invasion by inhibiting TMPRSS2	[66]
OFA	M^{pro}	Interference with SARS-CoV-2 replication by inhibition of M^{pro}	[6]
TFs	M^{pro}/PL^{pro}/RdRp	Interference with M^{pro}, PL^{pro}, and RdRp to block SARS-CoV-2 replication	[5,67–68]
WTSNF	NF-κB pathway	Reduction in the levels of IL-6, IL-1β, IL-17, IL-8, TNF-α, and IFN-γ	[69]

EGCG: (–)-epigallocatechin-3-gallate; GCG: (–)-gallocatechin gallate; LLPS: Liquid–liquid phase separation; OFA: Oolonghomobisflavan A; TA: Tannic acid; TFs: theaflavins; WTSNF: white-tip silver needle flavonoids.

translate polyproteins that are cleaved by the primary proteases (M^{pro} and PL^{pro}) to produce mature Nsps. This is a key step in the replication of SARS-CoV-2. These Nsps are assembled to form the RTC for the transcription and synthesis of new genomic RNAs. All viral proteins are translated and assembled into mature virus particles by the host translation machinery. Finally, mature viral particles are released by exocytosis and trigger a cascade of immune responses. Cytokine storm is a lethal immune response.

As presented in Figure 2, EGCG can interfere with SARS-CoV-2 entry into host cells by activating Nrf2 which can then downregulate ACE2 and TMPRSS2 expression[44]. Nrf2 is reported to be an important cytoprotective transcription factor that regulates the expression of various genes, including aging, anti-oxidation, detoxification, inflammation, neurodegeneration, immunity, and antiviral response genes[45–47].

Several studies have revealed that EGCG can interfere with the invasion of SARS-CoV-2. EGCG can inhibit the multiplication of SARS-CoV-2 in pseudotyped models that have been employed to reveal the inhibitory activity of EGCG[3]. Ohishi et al. revealed that EGCG could effectively interfere with the interaction between the SARS-CoV-2 S protein RBD and ACE2[83].

Interference with the replication of SARS-CoV-2 by EGCG

Regarding the replication of SARS-CoV-2, studies have demonstrated that EGCG inhibits M^{pro} and PL^{pro}[30,48,84]. The IC_{50} value of EGCG for M^{pro} was reported at 73 μmol/L, and molecular docking was used to reveal the possible binding mechanism[49–53]. Research has also revealed that EGCG plays a superior role in the inhibition of PL^{pro} by molecular docking[48,54]. Furthermore, EGCG decreases the levels of viral RNA and proteins in infected cells to inhibit viral replication *in vitro*, and this is related to the inhibition of M^{pro} and PL^{pro}[85–87].

Balance the inflammation and immunity by EGCG

In the serum of patients with severe or critical COVID-19[55], cytokines such as IL-6, IL-1β, IL-17, IL-8, TNF-α, and IFN-γ are excessively elevated[56–57], ultimately leading to cytokine storm. EGCG can alleviate and restore inflammation by regulating inflammatory pathways such as the NF-κB and JAK-STAT pathways to regulate the synthesis and secretion of several cytokines and chemokines[58–59]. Nrf2 also regulates inflammation by repressing pro-inflammatory factors and managing stress and inflammatory responses. Studies have demonstrated that Nrf2 can counteract the NF-κB pathway that drives

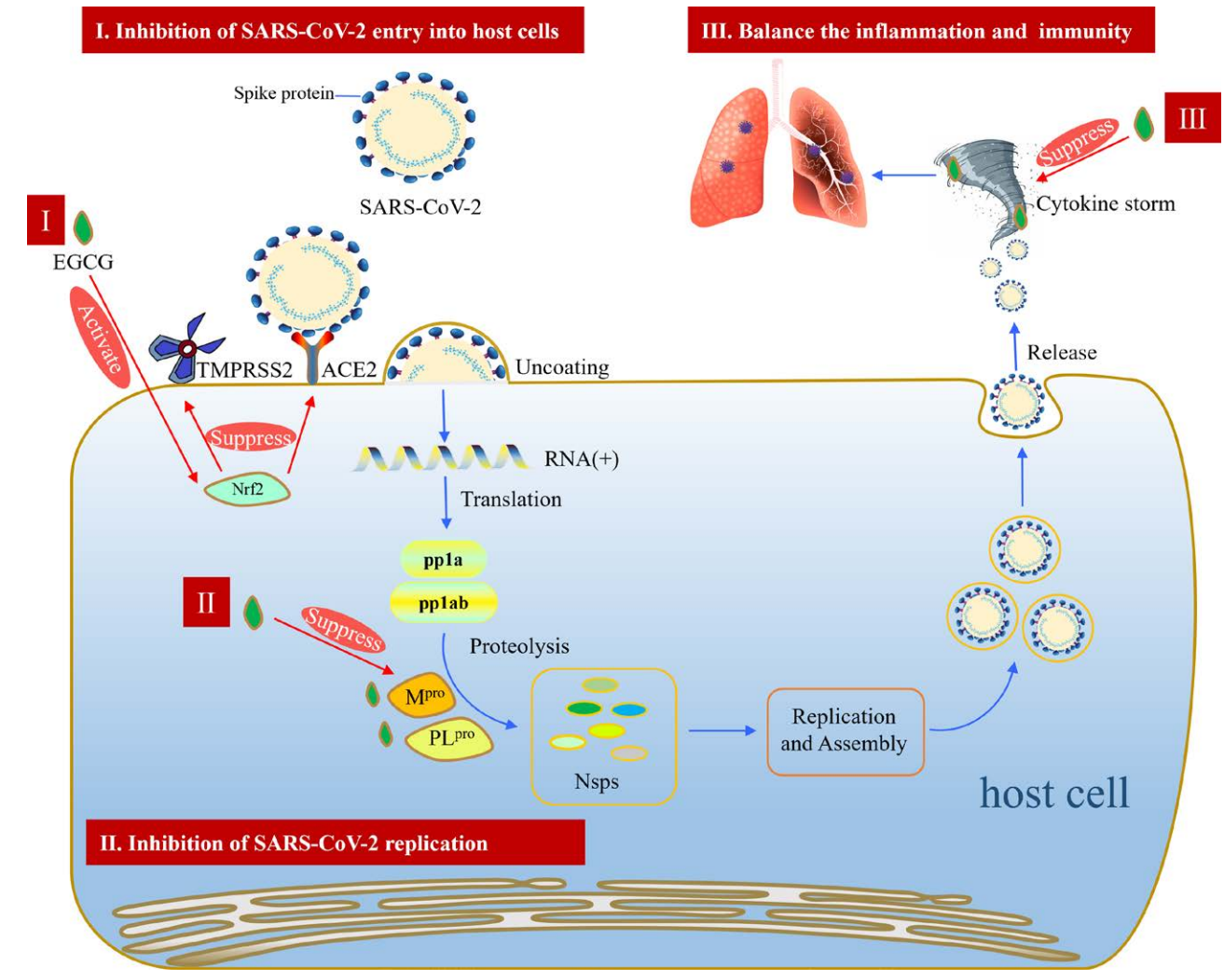

Figure 2. Potential inhibition of the SARS-CoV-2 life cycle and cytokine storm by EGCG treatment.

inflammatory responses in much experimental models[60]. Nrf2 is considered to be an upstream regulator of cytokine production[61–62], and it not only regulates cellular defenses against oxidative stress but also induces anti-inflammatory effects by its activation[61,63]. Previous studies have demonstrated that EGCG can activate Nrf2. Therefore, EGCG is a promising candidate for the reversal of excessive inflammation.

Molecular docking of EGCG with the primary targets of SARS-CoV-2

According to previous studies, EGCG is a potential inhibitor of SARS-CoV-2. In this review, we used EGCG as an example to dock with M^{pro} (PDB ID:6LU7), PL^{pro} (PDB ID:7JCM), and the S protein RBD-ACE2 (PDB ID:7T9L) to predict the possible mechanisms. As presented in Table 2, the docking score with M^{pro} was -60.04 kcal/mol. As indicated in Figure 3A, the EGCG-M^{pro} complex exhibited van der Waals interactions, hydrogen bonding, and other hydrophobic effects. EGCG formed two hydrogen bonds with the key amino acid residue Glu 166 and formed non-covalent interactions such as pi-sulfur or pi-alkyl interactions with Cys 145 and His 41 that are important catalytic dyads in the active pocket of M^{pro} domains I and II. The docking score with PL^{pro} was –54.12 kcal/mol. As presented in Figure 3B, EGCG combined with the active pocket (Cys 111, His 272 and Asp 286) and formed hydrogen bonds with Gly 266 and Tyr 268. The docking score for EGCG for the S protein RBD-ACE2 was -55.15 kcal/mol. As presented in Figure 3C, EGCG combined with the core region (Cys 378–Cys 432) and formed multiple hydrogen bonds with Tyr 385, Gly 395, Glu 398, and Glu 402. It exhibited considerable binding affinity to block the interaction in the invasion and replication of SARS-CoV-2[51].

GCG

GCG is a type of catechin and is considered to be another active compound in tea that acts against SARS-CoV-2, and this compound can inhibit the replication of SARS-CoV-2 as a potential inhibitor of M^{pro}. *In silico* docking and molecular dynamics simulation studies revealed that GCG exhibited good binding and strong interactions with the key amino acid residues of M^{pro} *via* hydrophobic or hydrogen bonding interactions[49,53].

Additionally, GCG inhibits the replication of SARS-CoV-2 by disturbing liquid–liquid phase separation (LLPS)[88]. LLPS is thought to be critical for N protein transcription and translation during viral assembly[64]. The N protein is a highly conserved RNA-binding factor that serves as a powerful target for the development of effective antibodies for neutralization[89]. Other studies have observed that GCG can effectively inhibit the expression of inflammatory factors such as IL-1α, TNF-α, IL-4, and IL-1, and it is expected to provide a strong defense against COVID-19[65].

Table 2

The docking scores of EGCG with the potential targets

	CDOCKER INTERACTION ENERGY (kcal/mol)		
Compound	M^{pro} (PDB:6LU7)	PL^{pro} (PDB: 7JCM)	S protein (PDB: 7T9L)
`EGCG	–60.04	–54.12	–55.15

EGCG: (–)-epigallocatechin-3-gallate.

Tannins

Tannin is a category of water-soluble polyphenolic compounds that are primarily divided into two types that include hydrolyzable tannins and condensed tannins[90]. Tannins exhibit various biological activities, including anti-oxidant[91], anti-tumor[92], antiviral[93], and anti-bacterial[94] activities. TA is a water-soluble polyphenol that is a member of the hydrolyzable tannins and is primarily present in teas and fruits[95]. In recent studies, TA has been demonstrated to inhibit both TMPRSS2 and M^{pro} to prevent SARS-CoV-2 invasion and replication[66,96]. TA also disrupts the interaction between the S protein RBD and ACE2 receptors[97]. Overall, TA may represent a useful strategy for preventing SARS-CoV-2 infections. TA is a natural product extracted from plants that possess a good safety profile, is suitable for clinical trials, and exhibits good medicinal properties.

OFA

OFA is a typical compound in oolong tea and is a dimer formed by EGCG[98]. *In silico* docking and molecular dynamics simulation studies revealed that OFA was screened from a series of structurally similar compounds in tea due to its excellent binding interaction with M^{pro}. The virus suppressive effect was not significantly different between OFA and other reported drugs (atazanavir, darunavir, and lopinavir) against COVID-19[14]. OFA is a potentially active molecule that acts as an inhibitor of M^{pro}.

Tea pigments

Tea pigments are water-soluble phenolic pigment products derived from the oxidative polymerization of tea polyphenols. During fermentation, a variety of tea pigments are generated, including TFs, thearubigins, and theabrownins. The higher the degree of fermentation, the greater the production of pigment compounds[99–100]. Studies have confirmed that tea pigments exert various pharmacological effects. TFs exhibit anti-oxidant, anti-inflammatory, antiviral, anti-cancer, and neuroprotective properties. Thearubigin possesses anti-inflammatory, bacteriostatic, and anti-oxidant properties. Theabrownin exhibits lipid-lowering, weight loss, hypoglycemic, and anti-tumor activities[101–103].

TFs are the products of the oxidative polymerization of catechins and the major components of tea pigments[104], which are composed of four isomers that include TF, theaflavin-3-gallate (TF2a), theaflavin-3'-gallate (TF2b), and theaflavin-3,3'-digallate (TF3)[71,105]. TFs have exhibited good antiviral activity against SARS-CoV-2 as reported by previous pharmacological studies[30,106].

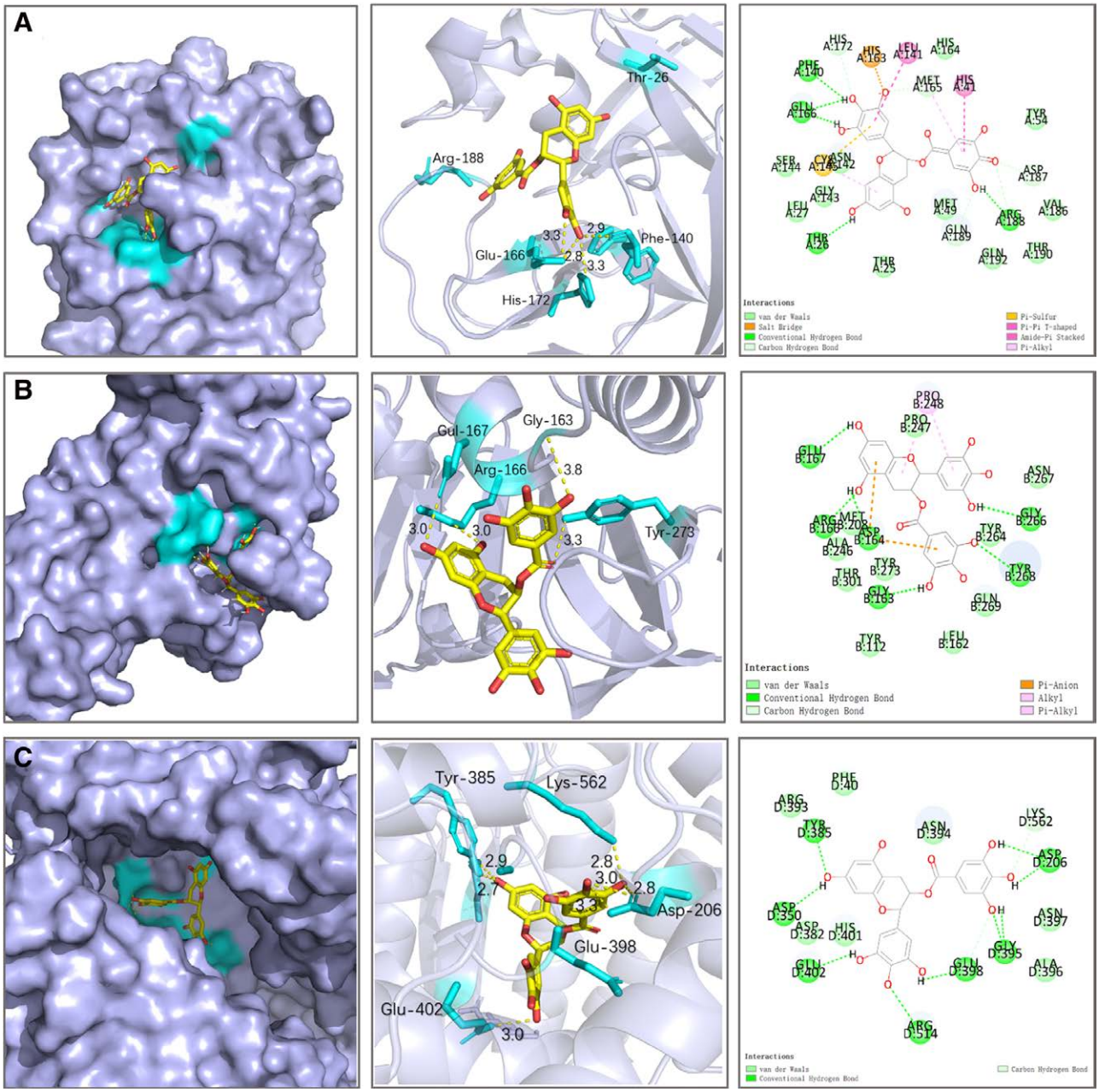

Figure 3. Molecular docking of EGCG with M^{pro} (PDB: 6LU7) (A), PL^{pro} (PDB: 7JCM) (B), and S protein (PDB: 7T9L) (C).

Recent studies have determined that TFs can significantly inactivate SARS-CoV-2 *in vitro*. For example, theasinensin A (TSA) and theafflavin 3,3'-di-O-gallate (TFDG) can significantly reduce the infectiousness of viruses, RNA replication of viruses in cells, and secondary virus production at a certain concentration. TSA and TFDG can prevent the interaction between the S protein RBD and ACE2 receptors[67]. Bioinformatics and molecular docking studies by Maiti and Banerjee demonstrated that the TF gallate exhibits greater binding affinity to the SARS-CoV-2 S protein than does hydroxychloroquine (HCQ), thus indicating its superior inhibitory activity compared to that of HCQ[107]. Theaflavin-3'-O-gallate (TFMG) is an enriched compound in black tea that has been demonstrated to block the active portion of SARS-CoV-2 RdRp with better docking than that of remdesivir[68]. Additionally, a virtual screening and molecular dynamics simulation study revealed that TF3 and TF2a exhibit the highest binding affinities towards RdRp, M^{pro}, and PL^{pro} targets on SARS-CoV-2[5]. Jang *et al.* designed experiments to demonstrate that TF inhibits the activity of SARS-CoV-2 M^{pro} *in vitro* in a dose-dependent manner[108]. Based on the studies illustrated above, we conclude that TFs and their derivatives can diminish the activity of SARS-CoV-2, thus displaying a potential and promising role in the fight against the COVID-19 outbreak.

Flavonoids

Flavonoid is a class of natural polyphenols that are distributed widely in nature with extensive pharmacological activities, and it primarily exhibits anti-cardiovascular disease, anti-oxidant, anti-cancer, anti-bacterial, anti-inflammatory, and other related activities[109]. WTSNF is a flavonoid that is unique to white tea and has been

demonstrated to possess anti-oxidant and anti-inflammatory properties that can ameliorate organ damage, modulate the levels of relevant immune factors, inhibit the expression of NF-κB, and reduce the levels of inflammatory factors such as IL-6, IL-1β, IL-17, IL-8, TNF-α and IFN-γ[69]. Li et al. performed experiments using WTSNF that contained baicalin, kaempferol, kaempferide, quercetin, isorhamnetin, lespenephryl, and rutin. They concluded that WTSNF may play a beneficial role in alleviating lung inflammation and oxidative stress damage caused by SARS-CoV-2.

Conclusions

In general, tea as a natural gift, exerts antiviral and anti-inflammatory effects based on the characteristics of multi-compounds, multi-targets, and multi-pathways. As bioactive compounds in tea, EGCG, GCG, TA, OFA, TFs, and WTSNF have been demonstrated to inhibit the invasion and replication of SARS-CoV-2 to some extent and balance inflammatory factors. Furthermore, EGCG is highly promising for use in combating COVID-19 due to its powerful anti-inflammatory activity. However, systematic studies should be performed to produce sufficient evidence of its efficacy *in vivo* and *in vitro*. It requires a long amount of time and effort for the tested compounds from tea to be developed as anti-SARS-CoV-2 drugs. Notably, the discovery of the characteristics of the reported active compounds in tea is conducive to the design and development of antiviral drugs. Natural molecules from Chinese medicine are considered to be promising approach for developing new drugs.

Conflict of interest statement

Weili Wang is a cofounder of Bioentropy Therapeutics Inc., and declares no conflict of interest. Other authors declare no conflict of interest.

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Author contributions

Yuefei Wang, Weili Wang, and Min Zhang participated in this review and revised the manuscript. Changjian Wang and Zhiying Yang wrote the manuscript. Xin Chai contributed to data analysis. All authors have read and agreed to the published version of the manuscript.

Ethical approval of studies and informed consent

Not applicable.

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