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REVIEW

An Overview on the Potential Roles of EGCG in the Treatment of COVID-19 Infection

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Abstract: Coronavirus disease-19 (COVID-19) pandemic is currently ongoing worldwide and causes a lot of deaths in many countries. Although different vaccines for the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection have been developed and are now available, there are no effective antiviral drugs to treat the disease, except for Remdesivir authorized by the US FDA to counteract the emergency. Thus, it can be useful to find alternative therapies based on the employment of natural compounds, with antiviral features, to circumvent SARS-CoV-2 infection. Pre-clinical studies highlighted the antiviral activities of epigallocatechin-3-gallate (EGCG), a catechin primarily found in green tea, against various viruses, including SARS-CoV-2. In this review, we summarize this experimental evidence and highlight the potential use of EGCG as an alternative therapeutic choice for the treatment of SARS-CoV-2 infection.

Keywords: COVID-19, EGCG, SARS-CoV-2, tea polyphenols, antiviral properties

Introduction

SARS-Cov-2 is a novel coronavirus causing the severe acute respiratory syndrome spreading around the world since the end of 2019.[1,2] It belongs to a family of single-stranded RNA viruses (+ssRNA), as the severe acute respiratory syndrome virus (SARS-CoV) and the Middle East respiratory syndrome virus (MERS-CoV). SARS-CoV-2 infection can cause mild to severe pneumonia and its mortality rate is higher in patients with comorbidities and older patients.[3,4] Although different vaccines for the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection have been developed and are now available,[5] there are no effective antiviral drugs to treat the disease, except for Remdesivir authorized by the United States Food and Drug Administration (US FDA) to counteract the emergency.[6] mRNA-based vaccines were developed by Moderna and Pfizer/BioNTech,[7,8] but there is still uncertainty about their efficacy (~95%), safety, and immunogenicity concerning SARS-CoV-2 spike glycoprotein (S protein). Similarly, viral vector vaccines were produced by Johnson and Johnson and by the University of Oxford/AstraZeneca, although the safety of AstraZeneca's vaccine is currently under revision.[9,10] Unfortunately, new strains of the virus have developed so far with new mutations and this could inhibit the effectiveness of vaccines, and delays the end of the pandemic.[11] Given the high infectivity of new mutations in the virus and the slowness of vaccine programming, herd immunity will be difficult to achieve in a short time. It is very likely that new coronavirus diseases may still emerge in the future. Thus, it can be necessary to develop alternative therapies based on the use of natural compounds, as

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epigallocatechin-3-gallate (EGCG), with antiviral features, to circumvent SARS-CoV-2 infection. EGCG, is the principal constituent and most important polyphenolic catechin found in green tea.[12–18] As largely reported, EGCG possesses many biological properties (ie antioxidant, antitumor, anti-inflammatory) due to a galloyl side chain contained in its chemical structure.[19] It has been shown that polyphenols and EGCG, through sticking with some molecules present in viruses, are able to regulate their functions. Specifically, EGCG by binding to the receptors present on the membrane of the host cells or directly to the viral surface inhibits the interaction between the host cells and the virus. As a result, EGCG represses the replication and the transcription of the virus, thus inactivating its activity.[20,21] As recently detailed described by Wang et al,[22] EGCG has inhibitory activities towards different viruses. Specifically, EGCG is able to suppress the replication, the transcription and the infection of DNA virus as Hepatitis B Virus (HBV),[23–27] Herpes Simplex Virus (HSV)[28–31] and Epstein-Barr Virus (EBV) through different molecular mechanisms.[32–35] Moreover, EGCG has similar effects on RNA virus as Human Immunodeficiency Virus (HIV),[37–42] Hepatitis C virus (HCV),[43–45] and Influenza A virus (IAV).[46–48] Additionally, in vitro studies demonstrated that EGCG is capable to inhibit the replication of some Enterovirus (CVB3, EV71) by regulating the oxidative stress of host cells.[49,50] Similar effects were also detected in Arboviruses, particularly in Chikungunya virus (CHIKV).[51–55] Finally, several pre-clinical studies confirmed the antiviral activity of EGCG also against Coronaviruses, especially against SARS-Cov-2.[56–73] Basically, EGCG can inhibit the cell entry of these viruses or their replication and transcription, through different molecular mechanisms which are not completely known. In this review, we summarize these experimental pieces of evidence and highlighted the potential use of EGCG as an alternative therapeutic choice for alleviating or treat SARS-Cov-2 infection.

The Antiviral Activity of EGCG Against SARS-Cov-2: Findings from Preclinical Studies

COVID-19 is caused by SARS-CoV-2 infection.[56] The initial clinical manifestations of COVID-19 include respiratory symptoms, such as fever, fatigue and dry cough, are accompanied by atypical clinical manifestations such as sore throat, headache and diarrhea.[57] Around one week later, patients exhibited difficulty breathing and hypoxia, during which the secretion of intracellular pro-inflammatory factors Interleukin-6 (IL-6), Interleukin-17 (IL-17) and tumor necrosis factor α (TNF-α)) increased significantly, and the total number of circulating lymphocytes decreased. Then, the symptoms rapidly deteriorated into acute respiratory distress syndrome (ARDS), sepsis, blood coagulation dysfunction and irreversible metabolic acidosis. Eventually, some severe cases would lead to death. Structurally, SARS-CoV-2 contains four proteins including spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. During host cell entry, SARS-CoV-2 relies on its S proteins for binding to the host cell-surface receptor. The S protein binds to the host receptor through the receptor-binding domain (RBD) in the S1 subunit, followed by the fusion of the S2 subunit to the cell membrane. SARS-CoV-2 recognizes the cell membrane receptor angiotensin-converting enzyme 2 (ACE2) receptor to bind with the viral S protein, thus forming RBD–ACE2 complex, by which the virus is embedded into the host cell where it starts replication. Thus, if a substance can bind the S protein, or possesses a strong affinity to ACE2 receptor, which blocks the formation of RBD–ACE2 complex, it could suppress the viral entry into host cells. Regarding the antiviral effects of EGCG on SARS-CoV-2, different pre-clinical studies have been performed (Table 1). Basically, the inhibition effects of EGCG on SARS-CoV-2 replication occur through its actions on the ACE2 receptor, the main protease (Mpro, a 3C-like protease) and RNA-dependent RNA polymerase (RdRp) (Figure 1).

Mhatre et al[58] reviewed the antiviral activities of EGCG theaflavin-3,3′-digallate (TF3) against positive-sense single-stranded RNA viruses, including SARS-CoV-2. The authors suggested that both the tea polyphenols are capable to interact with the receptors present in the structure of SARS-CoV-2 virus, thus inhibiting its replication. Particularly, the theaflavins (TFs), can be employed as prophylactic agents due to their capacity to bind Spike receptor-binding domain (RBD), the principal binding domain of the S protein located on the S1 subunit of SARS-CoV-2 virus. EGCG can be used as a potential prophylactic due to its ability to dock to various active sites of SARS-CoV-2 virus. The authors highlighted the needing of additional studies on the specificity, safety, and efficacy of these polyphenols, to confirm their use not only as a dietary

Table 1 A Summary of Pre-Clinical Studies on the Antiviral Activity of EGCG Against SARS-Cov-2

Substance	Effect	Reference
EGCG, TF3, TFs	TF3 and EGCG by interacting with the receptors present in SARS-CoV-2 virus, thus inhibiting its replication. TFs bind to Spike RBD.	[58]
EGCG, GTE	EGCG and GTE are able to control the inflammation damage occurring in SARS-CoV-2 infection by acting on STAT, NF-κB, Nrf2 signaling pathways.	[59]
EGCG, TQ, VITAMIN D3	The combination of EGCG, TQ AND VITAMIN D3 activates Nrf2-dependent genes thus preventing the cells against SARS-CoV-2 infection.	[60]
EGCG, TF1, TF2a, TF2b, hesperidin, quercetagetin, and myricetin	EGCG, TF1, TF2a, TF2b, TF3 bind stably to the active site of RdRp.	[61]
SA, L-PGA, N-NPTA, ACPS, EGCG, KDH and SeM	ACPS and KDH are powerful species in the treatment of SARS-CoV-2 infection.	[62]
EGCG and TFs in HEK2937	EGCG and TF inhibited activity against the SARS-CoV-2 3CL-protease, in dose dependent manner e without citotoxity for treated cells.	[63]
EGCG, withaferin A, dolutegravir and artesunate	EGCG, withaferin A, dolutegravir and artesunate could be considered potential drugs for SARS-CoV-2 infection.	[64]
EGCG and TF3	EGCG and TF3 possess broad-spectrum antiviral activity in treatment of SARS-CoV-2 infection.	[65]
Flavan-3-ols and PAs	CAG, ECG, GCG, and EGCG inhibited the M^{pro} activity of SARS-CoV-2.	[66]
Trans-resveratrol, EGCG and BX795	Trans-resveratrol, EGCG and BX795 show multiple antiviral effects against SARS-CoV-2.	[67]
PGG, EGCG	PGG, EGCG inhibited the viral protease activity of SARS-CoV-2 3CLpro	[68]
EGCG, active ingredients of TCM	EGCG inhibits the 3CLpro activity of SARS-CoV-2.	[69]
EGCG	EGCG inhibits HCoV-OC43 and HCoV-229E replication.	[70]
EGCG, EGC	EGCG and EGC inhibited PLPro	[71]
EGCG	EGCG arrested the entry of SARS-CoV-2, MERS and SARS-CoV pseudotyped lentiviral vectors and restrained virus infections. An inhibition of the SARS-CoV-2 spike–receptor interaction was also detected.	[72]

Abbreviations: EGCG, epigallocatechin-3-gallate; TF3, theaflavin-3,3′-digallate; TFs, theaflavins; RBD, receptor-binding domain; STAT, signal transducer and activator of transcription; NF-κb, nuclear factor kappa-light-chain-enhancer of activated B cells; Nrf2, nuclear factor erythroid-derived 2-related factor 2; TQ, thymoquinone; RdRp, RNA-dependent RNA polymerase; SA, succinic acid; L-PGA, L-pyroglutamic acid; N-NPTA, N-phenyl-thioacetamide; ACPS, 2-amino-5-chloropyridine hydrogen succinate; KDH, 2-oxoglutarate dehydrogenase E1 component, putative; SeM, selenomethionine; PAs, proanthocyanidins; M^{pro}, main protease; CAG, catechin-3-O-gallate; ECG, (–)-epicatechin-3-O-gallate; PA2, procyanidin A2; PB2, procyanidin B2; PGG, 1,2,3,4,6-pentagalloylglucose; 3CLpro, chymotrypsin-like protease; TCM, traditional medicine; HCoV-OC43, beta coronavirus; HCoV-229E, alpha coronavirus; PLPro, papain-like protease protein.

supplement, but also as therapeutic agents for COVID-19 infections. Menegazzi et al,[59] speculated that EGCG and others catechins (ie, GTE) supplementation could be effective in controlling the inflammation damages occurring in SARS-CoV-2 infection, through complex molecular mechanisms involving different interacting transcriptor factors (ie signal transducer and activator of transcription, STAT; nuclear factor kappa-light-chain-enhancer of activated B cells, NF-κB; NF-E2–related factor 2; Nuclear Factor Erythroid-Derived 2-Related Factor 2, Nrf2). Similarly, Mendonca et al,[60] suggested that the combination

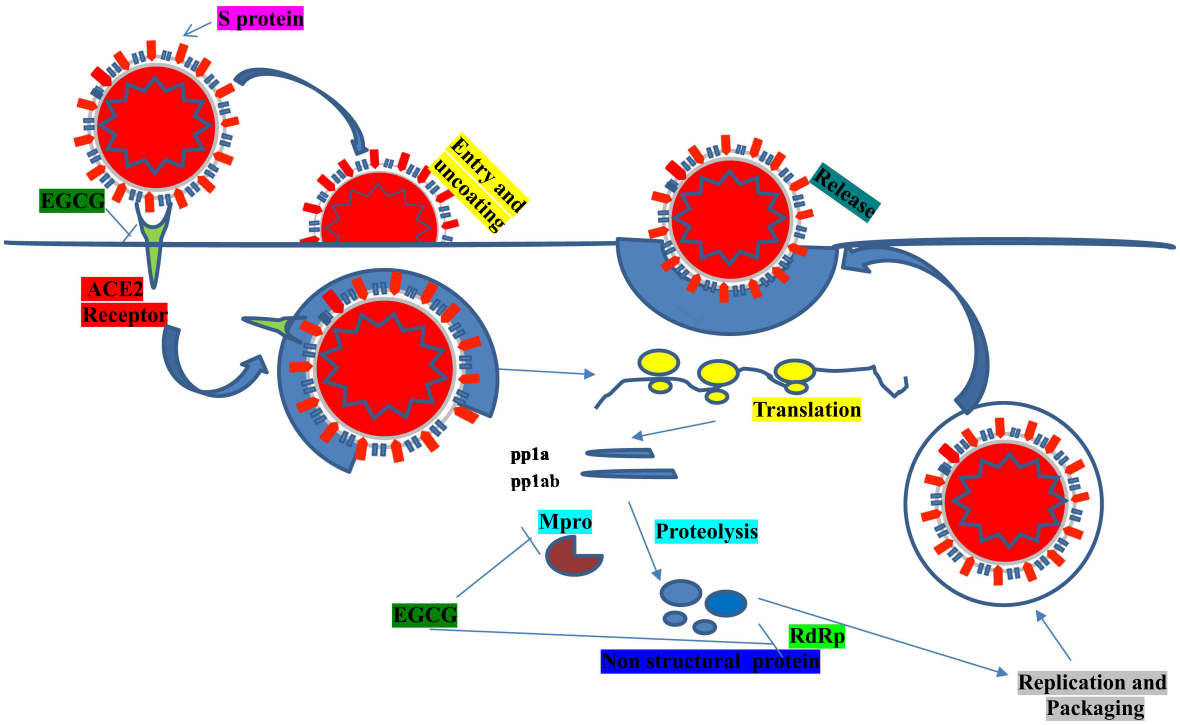

Figure 1 The inhibitory effects of EGCG on SARS-CoV-2 life cycle. The figure represents the inhibitory effects of EGCG on SARS-CoV-2 cycle. Basically, the inhibition effects of EGCG on SARS-CoV-2 replication occurs through its actions on the ACE2 receptor, the main protease (Mpro, a 3C-like protease) and RNA-dependent RNA polymerase (RdRp).

Abbreviations: EGCG, epigallocatechin-3-gallate; pp1a, nuclear protein phosphatase 1 α; pp1ab, 2′-O-methyltransferase; Mpro, main protease; ACE2, angiotensin-converting enzyme 2; S-protein, spike protein; RdRp, RNA-dependent RNA polymerase.

of EGCG, thymoquinone (TQ), and vitamin D3 can activate Nrf2-dependent genes and preserve the cells against SARS-CoV-2 infection. Singh et al,[61] studied the binding of polyphenols (ie, EGCG, TF1, TF2a, TF2b, hesperidin, quercetagetin, and myricetin) with SARS-CoV-2 RdRp and thus tested their potential to treat COVID-19. The authors demonstrated that EGCG, TF1, TF2a, TF2b, TF3, can bind (in highly stable manner) to the active site of RdRp. These four natural polyphenols can act as potential inhibitors for the SARS-CoV-2 RdRp, although additional studies will be necessary to validate their efficacy against SARS-CoV-2 infection. An in-silico analysis conducted by Sagaama et al,[62] revealed that the succinic acid (SA), L-pyroglutamic acid (L-PGA), N-phenyl-thioacetamide (N-NPTA), 2-amino-5-chloropyridine hydrogen succinate (ACPS), epigallocatechine Gallate (EGCG) or, 2-oxoglutarate dehydrogenase E1 component putative (KDH) and, selenomethionine (SeM) compounds could represented potential antiviral candidates for treatment of COVID-19 based on B3LYP/6-311++G** calculations and molecular docking. Data emerged from this study suggest that the compounds ACPS and KDH are powerful species in the treatment of SARS-CoV-2 infections. A different study conducted by Jang et al,[63] demonstrated that EGCG and theaflavins, inhibited activity against the SARS-CoV-2 3CL-protease, in HEK293T cells, in a dose-dependent manner and without signs of cytotoxicity for both compounds at any dose used. Sharma et al,[64] performed an in-silico drug repurposing followed by molecular dynamics (MD) simulation and MM-GBSA calculation for targeting SARS-CoV-2 main protease (M^{pro}). M^{pro} was screened for already known FDA approved drugs and some natural compounds, including EGCG. Specifically, the authors proposed that EGCG, withaferin A, dolutegravir and artesunate could be considered potential drugs for COVID-19. A molecular docking studies was also conducted by Mhatre et al,[65] to study the exact interaction of EGCG and TF3 with the putative binding sites of SARS-CoV-2. The in-silico results emerged from this study should promote the evaluation of the broad-spectrum antiviral activity of the tea polyphenols in the treatment of COVID-19. Similarly, Zhu et al[66] performed in vitro studies by using of the M^{pro} of SARS-Cov-2 for docking simulation to screen flavan-3-ols and proanthocyanidins (Pas), to identify potential candidates for counteracting SARS-Cov-2 infection. Data emerged from docking simulation and in vitro assay, indicated that (–)-catechin

-3-O-gallate (CAG), (–)-epicatechin-3-O-gallate (ECG), (–)-gallocatechin-3-O-gallate GCG), EGCG, procyanidin A2 (PA2) and B2 (PB2) are able to inhibit the M^{pro} activity of SARS-Cov-2, thus can be used to interfere with SARS-Cov-2 infection. Wang et al,[67] conducted in-depth and comprehensive bioinformatics analysis for the screening of therapeutic drugs and their related pathways in COVID-19 disease. Results indicated that trans-resveratrol, EGCG and BX795 possess multiple anti-viral effects. It is of note that coronaviruses encode for polyproteins that are cleaved by 3CL protease for maturation. Thus, 3CL protease could be considered the main target of antivirals against coronaviruses. Based on this concept, Chiou et al,[68] conducted an in vitro study on the inhibitory effects of 1,2,3,4,6-pentagalloylglucose (PGG) and EGCG against the SARS-CoV-2- 3-chymotrypsin-like protease (3CLpro) protease. Data revealed that PGG and EGCG inhibited of viral protease activity of SARS-CoV-2 3CLpro, thus suggesting their potential application in the treatment of SARS-CoV-2 infection. Later on, in a fascinating study Du et al,[69] screened and identified, by using multiple strategies (ie molecular docking, surface plasmon resonance, fluorescence resonance energy transfer (FRET)-based inhibition assay) different active ingredients of Traditional Chinese Medicine (TCM) with inhibitory effects against SARS-CoV -2 3CLpro, including EGCG. Results demonstrate that EGCG showed a higher affinity with SARS-CoV-2 3CLpro thus suggesting its potential in the treatment of COVID-19 disease. A fascinating in vitro study performed by Jang et al,[70] demonstrated that EGCG can inhibit coronavirus replication. Specifically, the authors used low pathogenic human coronavirus HCoV-OC43 (beta coronavirus) and HCoV-229E (alpha coronavirus), as a coronavirus model system to dissect the effect of EGCG on coronavirus processing. Results demonstrated that EGCG treatment decreases viral RNA and viral protein production in the media suggesting that EGCG inhibits coronavirus replication. By using the molecular docking approach, Chourasia et al[71] demonstrated that the catechins (mainly EGCG and ECG) inhibited papain-like protease protein (PLPro). Specifically, catechin bind to the S1 ubiquitin-binding site of PLPro, which restrain its protease function and abolish SARS-CoV-2 inhibitory function on ubiquitin proteasome system and interferon stimulated gene system. Considering EGGC's antiviral and anti-inflammatory properties, the authors concluded that these natural compounds could be considered as a putative therapeutic agent for SARS-CoV-2 infection. Finally, a recent research conducted by Henss et al,[72] examined the antiviral activity of EGCG against SARS-CoV-2. EGCG arrested the entry of SARS-CoV-2, MERS and SARS-CoV pseudo typed lentiviral vectors and restrained virus infections in vitro. Moreover, an inhibition of the SARS-CoV-2 spike–receptor interaction was also detected. Altogether these finding highlighted the potential use of EGCG as an alternative therapeutic choice for the treatment of SARS-CoV-2 infection.

Conclusions and Future Perspectives

Here, we summarized recent findings on the potential role of EGCG in the treatment of SARS-CoV-2 infection. Accumulated pieces of evidence reported that EGCG has antiviral properties against different viruses, including SARS-Cov-2.[22] Specifically, it has been proved that EGCG inhibits the enzymatic activity of the coronavirus 3CL protease, thus interfering with its replication. Moreover, EGCG can regulate specific target as the viral S protein and RdRp. EGCG is also capable of inhibiting the replication of coronaviruses in cell cultures. Results from molecular docking analyses demonstrated that EGCG prevents SARS-CoV-2 entry into the target cell through inhibition of RBD in viral membrane identifying with ACE2. Finally, EGCG can interfere with the viral start replication by suppressing Mpro activity, although all these effects should be confirmed in vivo. A set of experiments evaluated the in vivo distribution of EGCG in human bodies[74–79] and data showed that the values of EGCG concentration in the colon and intestine were higher than most of the concentrations necessary to promote 3CL protease required to effectively 3CL protease inhibition. More pre-clinical studies, clinical trials and epidemiological analysis will be extremely needed to validate EGCG anti-COVID-19 applications. EGCG and its stable lipophilic derivatives could also be potential prophylactic as well as therapeutic agents looking at their properties to dock at various active sites of SARS-CoV -2. Results from these studies will shed light on the role of the EGCG and the underlying molecular mechanisms for the treatment of SARS-CoV-2 infection. However, based on the current results published in the literature, it is not possible to say at all that EGCG can be considered as an election therapeutic drug for Covid-19. Due to the absence of specificity, EGCG could bind to other proteins present in the human body, thus provoking side-effects. EGGC

may not be used in the treatment of COVID-19, but as a nutraceutical or dietary supplement, especially in the earlier stages of clinical manifestations of COVID-19. After extensive studies on EGGC and other similar polyphenols regarding their specificity, activity, bioavailability and safety, there can be considerations on their use in the treatment of viral infections including COVID-19.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval for the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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