Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Phytomedicine Plus 3 (2023) 100402

Contents lists available at ScienceDirect

Phytomedicine Plus

journal homepage: www.sciencedirect.com/journal/phytomedicine-plus

Therapeutic potential of green tea catechin, (-)-epigallocatechin-3-*O*-gallate (EGCG) in SARS-CoV-2 infection: Major interactions with host/ virus proteases

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A R T I C L E I N F O

Keywords:
SARS-CoV-2
COVID-19
Epigallocatechin-3-O-gallate
Green tea
Host/viral proteases inhibitor

A B S T R A C T

Background: The current COVID-19 pandemic from the human pathogenic virus SARS-CoV-2 has resulted in a major health hazard globally. The morbidity and transmission modality of this disease are severe and uncontrollable. As no effective clinical drugs are available for treatment of COVID-19 infection till to date and only vaccination is used as prophylaxis and its efficacy is restricted due to emergent of new variants of SARS-CoV-2, there is an urgent need for effective drugs for its treatment.

Purpose: The aim of this review was to provide a detailed analysis of anti-SARS-CoV-2 efficacy of (-)-epigallocatechin-3-O-gallate (EGCG), a major catechin constituent of green tea (Camellia sinensis (L.) Kuntze) beverage to highlight the scope of EGCG in clinical medicine as both prophylaxis and treatment of present COVID-19 infection. In addition, the factors related to poor oral bioavailabilty of EGCG was also analysed for a suggestion for future research in this direction.

Study design: We collected the published articles related to anti-SARS-CoV-2 activity of EGCG against the original strain (Wuhan type) and its newly emerged variants of SARS-CoV-2 virus.

Methods: A systematic search on the published literature was conducted in various databases including Google Scholar, PubMed, Science Direct and Scopus to collect the relevant literature.

Results: The findings of this search demonstrate that EGCG shows potent antiviral activity against SARS-CoV-2 virus by preventing viral entry and replication in host cells in vitro models. The studies on the molecular mechanisms of EGCG in inhibition of SARS-CoV-2 infection in host cells reveal that EGCG blocks the entry of the virus particles by interaction with the receptor binding domain (RBD) of viral spike (S) protein to host cell surface receptor protease angiotensin-converting enzyme 2 (ACE2) as well as suppression of the expressions of host proteases, ACE2, TMPRSS2 and GRP78, required for viral entry, by Nrf2 activation in host cells. Moreover, EGCG inhibits the activities of SARS-CoV-2 main protease (Mpro), papain-like protease (PLpro), endoribonuclease Nsp15 in vitro models and of RNA-dependent RNA polymerase (RdRp) in molecular docking model for suppression of viral replication. In addition, EGCG significantly inhibits viral inflammatory cytokine production by stimulating Nrf2- dependent host immune response in virus-infected cells. EGCG significantly reduces the elevated levels of HMGB1, a biomarker of sepsis, lung fibrosis and thrombotic complications in viral infections. EGCG potentially inhibits the infection of original (Wuhan type) strain of SARS-CoV-2 and other newly emerged variants as well as the infections of SARS-CoV-2 virus spike-protein of WT and its mutants-mediated pseudotyped viruses . EGCG shows maximum inhibitory effect against SARS-CoV-2 infection when the host cells are pre-incubated with the drug prior to viral infection. A sorbitol/lecithin-based throat spray containing concentrated green tea extract rich in EGCG content significantly reduces SARS-CoV-2 infectivity in oral mucosa. Several factors including degradation in gastrointestinal environment, low absorption in small intestine and extensive metabolism of EGCG are responsible for its poor bioavailability in humans. Pharmacokinetic and metabolism studies of EGCG in humans reveal poor bioavailability of EGCG in human plasma and EGCG-4"-

Abbreviations: EGCG, (-)-epigallocatechin-3-O-gallate; HSPA5, heat shock protein family A (HSP70) member 5.

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https://doi.org/10.1016/j.phyplu.2022.100402
Received 12 December 2022; Accepted 24 December 2022
Available online 30 December 2022

sulfate is its major metabolite. The concentration of EGCG-4"-sulfate in human plasma is almost equivalent to that of free EGCG (Cmax 177.9 vs 233.5 nmol/L). These findings suggest that inhibition of sulfation of EGCG is a crucial factor for improvement of its bioavailability. In vitro study on the mechanism of EGCG sulfonation indicates that sulfotransferases, SULT1A1 and SULT1A3 are responsible for sulfonation in human liver and small intestine, respectively. Some attempts including structural modifications, and nanoformulations of EGCG and addition of nutrients with EGCG have been made to improve the bioavailability of EGCG.

Conclusions: The findings of this study suggest that EGCG has strong antiviral activity against SARS-CoV-2 infection independent of viral strains (Wuhan type (WT), other variants) by inhibition of viral entry and replication in host cells in vitro models. EGCG may be useful in reduction of this viral load in salivary glands of COVID-19 patients, if it is applied in mouth and throat wash formulations in optimal concentrations. EGCG could be a promising candidate in the development of effective vaccine for prevention of the infections of newly emergent strains of SARS-CoV-2 virus. EGCG might be useful also as a clinical medicine for treatment of COVID-19 patients if its bioavailability in human plasma is enhanced.

Abbreviations

ACE2	angiotensin-converting enzyme 2
ADAM17	a disintegrin and metalloprotease 17
BALF	bronchoalveolar lavage fluid
CC16	Clara cell secretory protein 16
COMT	catechol-*O*-methyl transferase
COVID-19	coronavirus disease 2019
CXCL17	C-X-C-motif chemokine ligand 17
DTDST	diastrophic dysplasia sulfate transporter
ER	endoplasmic reticulum
Foxp3$^+$ T cells	forkhead box P3-regulatory T cells for maintenance of immune homeostasis
G3BP1	ras-GTPase-activating (SH3 domain)-binding protein 1
GRP78	glucose-regulated protein 78
GST	glutathione S-transferase
HIF-1α	hypoxia-induced factor 1alpha
HMGB1	high mobility group box 1
HO-1	heme oxygenase 1
IFN-γ	interferon gamma
IL-6	interleukin-6
ISGs	IFN-stimulated genes
IPF	idiopathic pulmonary fibrosis
JAK	janus kinase
KL-6	Krebs von den Lungen 6
MDA5	melanoma differentiation-associated protein 5
MRP1	multidrug resistance-associated protein 1
NETs	neutrophil extracellular traps
NF-κB	nuclear factor kappa-light chain enhancer of activated B cells
NQO1	NAD(P)H: quinone oxidoreductase
Nrf2	nuclear factor erythroid 2 p45-related factor 2
PAI1	plasminogen activator inhibitor 1
TNF-α	tumor necrosis factor-alpha
RAGE	receptor for advanced glycation endproducts
RBD	receptor binding domain
RdRp	RNA-dependent RNA polymerase
RNA	ribonucleic acid
ROS	reactive oxygen species
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SELENOP	seleno P protein
Smad3	suppressor of mothers against decapentaplegic family member 3
SULT	sulfotransferase
TF	cellular tissue factor
tPA	tissue plasminogen activator
UGT	uridine 5′-diphospho-glucuronosyltransferase
vWF	von Willebrand factor

Introduction

The current COVID-19 pneumonia pandemic has posed a serious threat to our health care system and caused more than 6.49 million deaths among 603.625 million infected cases as on September 4, 2022 (https://coronavirus.jhu.edu/map.html) and will continue to threaten our health care systems in the coming years. The disease is caused by SARS-CoV-2 infection, a single-stranded positive sense RNA β-coronavirus, which is most likely of zoonotic origin that is transmitted from human to human via respiratory droplets of infected individuals and aerosols. Various risk factors, such as age, diabetes, cancers, obesity, cardiovascular diseases and allergic diseases, are associated with disease severity (Hu et al., 2021). Similarly to the patients of earlier coronavirus pandemic SARS-CoV and MERS-CoV, the COVID-19 patients showed the symptoms of viral pneumonia, including sore throat, fever, cough and chest discomfort and in severe cases dyspnea and bilateral lung fibrosis (Gralinski and Menachery, 2020). The SARS-CoV-2 virus enters into human cells mainly by binding its spike (S) glycoprotein to a human cell surface receptor protein, angiotensin-converting enzyme 2 (ACE2) by using host transmembrane serine protease 2 (TMPRSS2), cathepsin L and furin (Hoffmann et al., 2020; Jackson et al., 2022). Immunohistochemical studies revealed that ACE2 protein is abundantly expressed in the mouth salivary glands epithelial cells, nasal airway motile ciliated epithelial cells and in alveolar type II (AT2) pneumocytes in lung alveoli. As TMPRSS2 protein is also highly expressed in those cell types, it is likely that these cells represent the early entry site for SARS-CoV-2 and other respiratory viruses (Lee et al., 2020; Lloyd-Jones et al., 2021; Huang et al., 2021). Therefore, the use of anti-SARS-CoV-2 throat and nasal spray or mouth wash could be a promising therapeutic or prophylactic approach in inhibition of COVID-19 infection. Recent studies revealed that ER stress-related protein, glucose-regulated protein 78 (GRP78) acts as a host co-receptor for SARS-CoV-2 entry via forming a S/ACE2/GRP78 protein complex (Carlos et al., 2021). This group reported that GRP78 protein directly binds to RBD of SARS-CoV-2 spike (S) protein and ACE2 at the perinuclear region of ER in Vero E6-ACE2 cells. Knockdown of GRP78 in Vero E6-ACE2 cells, markedly reduced the ACE2 expression. Moreover, GRP78 depleting antibody hMAb159 significantly reduced the expression of ACE2 in human lung epithelial cells and blocked SARS-CoV-2 entry (Carlos et al., 2021).

SARS-CoV-2 entry factors, such as ACE2 and TMPRSS2 proteases are highly expressed in the epithelial cells of mouth salivary glands and oral mucosae, and accumulation of SARS-CoV-2 in these cells have been detected in SARS-CoV-2 infected individuals. In a study on SARS-CoV-2 entry points reported that viral RNA was detected in the gingival crevicular fluid (GCF) of 63.64% of COVID-19 positive patients (Gupta et al., 2021) . The virions in the oral cavity most-likely migrate into the gingival sulcus/periodontal pockets for their survival, replication, infection and spread to gingival capillaries. A higher prevalence of cytomegalovirus, Epstein-Barr virus and other viruses has been reported in the subgingival plaque-biofilm from periodontitis patients as compared to the patients with gingivitis or healthy periodontium individuals (Jankovic et al., 2011; Slots, 2007). Dental plaque is considered as a potential source of viral delivery to the vasculature during acute COVID-19 infection (Lloyd-Jones et al., 2021; Marouf et al., 2021).

Possibly, high levels of SARS-CoV-2 in saliva breakdown the primary immune barrier of the oral cavity and facilitate viral entry into blood capillaries, and permit the virus to reach superior vena cava and right side of heart, and subsequently the virus is pumped into pulmonary arteries and lungs. These findings suggest that oral cavity and secreted saliva are important sites for SARS-CoV-2 infection and saliva is a potential route of SARS-CoV-2 transmission. Salivary viral burden is correlated with COVID-19 symptoms including taste loss (Huang et al., 2021; Lloyd-Jones et al., 2021; Gupta et al., 2021). Therefore, maintenance of oral health by the use of low-cost, specific mouthwashes that can reduce salivary viral loads in COVID-19 positive patients, could be a potential strategy to prevent or mitigate the development of viral lung diseases including COVID-19 infection.

SARS-CoV-2 RNA genome having about 29,891 nucleotides and encoding 9860 amino acid residues, contains two flanking untranslated regions (5′-UTR in the left and 3′-UTR in the right direction) and 14 open reading frames (ORFs) or genes (Chan et al., 2020). These ORFs include replicase overlapping genes ORF1a and ORF1b at the 5′-terminus, and four structural proteins, spike (S), envelope (E), membrane (M) and nucleocapsid (N), and eight accessory proteins, 3a,3b, 6, 7a, 7b, 8b,9b and ORF14, that are interspersed between the structural proteins, and are located at the 3′-terminus (Chan et al., 2020; Wu et al., 2020). In infected host cells, such as in A549-ACE2, Vero E6 and Calu-3 cells, the viral replicase genes ORF1a and ORF1b are translated into the functional genes, polyproteins, pp1a and pp1ab, respectively, by the host cell translation machinery. These viral functional genes are processed by the autocatalytic cleavage by two viral proteases, encoded by papain-like protease (PLpro) that resides in non-structural protein 3, nsp3, and another protease, encoded by 3-chymotrypsin-like cysteine protease (3CLpro, also known as main protease (Mpro)) that resides in nsp5, into 16 nsps, nsp1–16. The PLpro releases three nsps, nsp1, nsp2 and nsp3, while Mpro releases the remaining nsps, nsp4 to nsp16 by the processing of eleven cleavage sites. Most of these nsps (2–16) are involved in the formation of viral replicase-transcriptase complex (RTC) for the synthesis of viral RNA. Among them, nsp2–11 are believed to provide the supportive functions, such as modulating host immune evasion, and providing cofactors for viral replication. The nsp12–16 are involved in RNA synthesis, RNA proofreading and RNA modifications (V'kovski et al., 2021). The viral RNA synthesis is a complex process involving the actions of several viral and host proteases and it occurs in double membrane vesicles (DMVs), located in the ER of the host cell. The key steps include: the nsp13 of replication-transcription complex (RTC) unwinds the viral ds-RNA genome as negative sense ss RNAs and these RNAs are used as templates by RdRp (nsp12) for synthesis of positive-sense full length progeny genomes and sub-genomic mRNAs. The subgenomic mRNAs are translated into structural and accessory proteins in convoluted membranes (CMs) and translocated to ER membranes. The positive-sense genomic RNA is capped by nucleocapsid (N) protein to generate nascent virion in the endoplasmic reticulum-Golgi-intermediate compartment (ERGIC), and is decorated with structural proteins S, E, and M to produce enveloped virion. The enveloped virion is then exported from the infected cell into adjacent cell by exocytosis (Hartenian et al., 2020; V'kovski et al., 2021; Klean et al., 2020). Since the viral proteases, PLpro and 3CLpro play key roles in viral survival and replication by the release of nsps and hence, the inhibition of the activity of these proteases is a potential therapeutic target in prevention of SARS-cov-2 infection. Moreover, the RNA-dependent RNA polymerase (RdRp) (nsp12) is a key player in viral RNA synthesis taking the supports from helicase (nsp13) and the nsp7-nsp8 complex, the inhibition of RdRp activity is a promising approach in prevention of COVID-19 infection (Gao et al., 2020). The multifunctional nucleocapsid (N) protein on oligomerization provides cap-binding activity of viral genomic RNAs in generation of new virions, modulates host cellular translation machinery to improve viral translation process, and blocks host immune response by inhibiting IFN synthesis via suppression of the activity of NF-κB (Surajit and Lal, 2010). Therefore, suppression of expression and activity of viral N protein in infected host cells is a potential antiviral drug target.

Current clinical approaches for possible treatments of COVID-19 pandemic include antivirals, immunomodulatory agents, immunoglobulins and antimalarials (Dixit et al., 2020). The development and authorization of vaccines against SARS-coV-2 infection certainly depict a milestone in fight against the present COVID-19 pneumonia pandemic. The vaccination alone is not sufficient to control this COVID-19 outbreak because of its inadequate neutralizing antibody against the infection of recent spread of SARS-CoV-2 variants. Moreover, the long-term efficacy and possible side effects of these vaccines are not yet fully investigated (Forni and Mantovani, 2021; Garcia-Beltran et al., 2021).

Therefore, there is an urgent need to discover and develop new drugs for prevention and supportive treatment of COVID-19 and similar viral infectious diseases that might occur. In addition to synthetic and biopharmaceutical substances, plant extracts and their bioactive constituents offer a wide range of antiviral effects and could be promising natural drugs against COVID-19 infection (Kim, 2021; Da Silva, 2021; Mehany et al., 2021).

The extracts from black tea and green tea rich in catechins rapidly (within a minute) inactivate SARS-CoV-2 in saliva in vitro (E. Ohgitani et al., 2021). Green tea, leaves of tea plant (*Camellia sinensis* (L.) Kuntze) (Theaceae) contain catechin derivative, (-)-epigallocatechin-3-*O*- gallate (EGCG) (Fig. 1) as major catechin. Phytochemical analysis of green tea extract revealed the presence of at least 75 chemical constituents including catechins, flavonoids (flavonol and flavones glycosides), proanthocyanins, phenolic acids, amino acids and alkaloids (Xin et al., 2018).

Both green tea and black tea are consumed as beverages in many countries because of their potent antioxidant polyphenols (catechins) contents and health-benefit effects in cancers, diabetes, obesity-related disorders. EGCG is the major catechin constituent of green tea extract, and it accounts for 50–80% of the catechins in a brewed cup of green tea and one cup (100 ml) of green tea contains 100–300 mg of EGCG (Park et al., 2021). Among the catechin constituents of green tea, epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC) are also found in high concentrations.

Mhatre et al. (2021) reported that EGCG exhibits potent antiviral effect against different RNA viruses including human immunodeficiency virus (HIV), hepatitis C virus (HCV), HBV, Zika virus, Chikungunya virus, West Nile virus (WNV), Dengue virus (DENV), influenza A (H1N1, H3N2) and B viruses, Rota virus, Ebola virus, porcine reproductive and

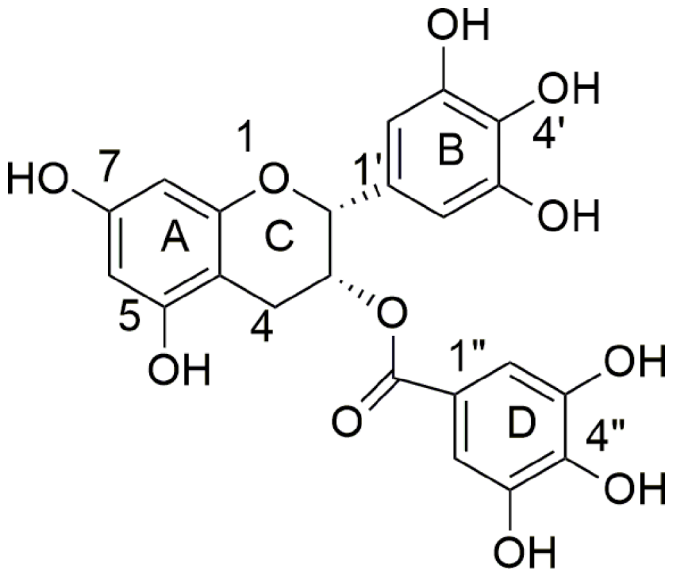

Fig. 1. Chemical structure of (-)-epigallocatechin gallate (EGCG).

respiratory syndrome virus (PRRSV), murine norovirus, feline calicivirus, and coronaviruses (HCoV-OC43, HCoV-229E, SARS-CoV and SARS-CoV-2) and highlighted the efficacy of EGCG in suppression of COVID-19 related symptomatic complications (Mhatre et al., 2021). During the period, 2000 to 2022, four published review articles highlighted the antiviral efficacy of EGCG against various types of coronaviruses and emphasizing the molecular targets of EGCG in suppression of SARS-CoV-2 infection and this infection-related various complications (Bimonte et al., 2021; Chourasia et al., 2021; Wang et al., 2021; D. Zhang et al., 2021). Another three review articles published in 2021, corroborated the antiviral efficacy of natural products against SARS-CoV-2 infection and pointed out the importance of EGCG in this context (Kaul et al., 2021; Llivisaca-Contreras et al., 2021; Khazeei Tabari et al., 2021). Among them, Llivisaca-Contreras et al., 2021 pointed out that various natural products including EGCG inhibit the entry of SARS-CoV-2 in human cells by maintaining a balance between rennin-angiotensin system (RAS) and ACE2 by reducing the expression of ACE2 in lung, mouth and kidney epithelial cells, which are highly used by virus for entry into host cells. A group of evidence demonstrates that an imbalance between RAS and ACE2 due to utilization of ACE2 by SARS-CoV-2 results in the development of COVID-19 related critical symptoms, such as endothelial dysfunction, inflammation, atherosclerosis, hypercoagulation, and adverse respiratory and cardiovascular effects (Wiese et al., 2020). None of these review articles elaborated how SARS-CoV-2 virus utilizes mouth and nasal epithelial cells for entry and accumulation in lung epithelial cells for severe infection and how EGCG during drinking of green tea as beverage neutralizes a significant part of viral load in salivary glands. Moreover, these review articles neither discussed about the major factors responsible for poor bioavailability of EGCG in human plasma and nor the metabolism of EGCG in liver, small intestine and colon as well as the attempts in improvement of EGCG bioavailability. The potential therapeutic efficacy of EGCG against SARS-CoV-2 infection as reported by the above mentioned review articles encourage us to write this review article to discuss the different aspects of EGCG related to its therapeutic efficacy as prophylaxis and treatment of SARS-CoV-2 infection and its related complications as well as the major targets of EGCG against the activity of host and viral proteases in suppression of viral infection and replication and how these potential efficacy of EGCG could be translated in clinical trials of COVID-19 patients.

For the preparation of this manuscript, we have collected the published literature from various sources on the experimental evidence supporting the antiviral efficacy of EGCG in prevention of SARS-CoV-2 infection and major targets against host and viral protease activities in suppression of viral entry, replication and spread of infection in host cells as well as experimental evidence on bioavailability and the factors responsible for poor bioavailability and the promising steps for optimization of its bioavailability.

Discussion

A group of majestic studies reported that EGCG promotes antioxidant Nrf2 signaling to reduce virus-induced oxidative stress in host cells and potentially inhibits the entry of SARS-CoV-2 in host cells and viral replication and infection in host cells. Moreover, EGCG decreases the severity of viral infection in host cells by suppression of cytokine storm, sepsis, thrombosis complications, lung fibrosis and RAGE-dependent HMGB1 expression. The major experimental results on antiviral efficacy of EGCG against SARS-CoV-2 infection are briefly discussed.

Role of EGCG in prophylaxis and treatment of SARS-CoV-2 infection

EGCG prevents SARS-CoV-2 infection and transmission

EGCG effectively inhibits the infections of SARS-CoV-2, SARS-CoV and MERS-CoV virus in Vero E6 cells with IC_{50} values of 1.73 μg/ml (or 3.14 μM), 0.83 μg/ml and 4.64 μg/ml, respectively. In SARS-CoV-2 spike (S) protein-mediated pseudo-typed lentiviral vectors (SSPL) infection assay, EGCG inhibits the entry of SSPL in HEK293T-ACE2 cells with an IC_{50} value of 2.47 μg/ml, suggesting that EGCG interferes in viral entry process. EGCG also inhibits the entry of SARS-CoV and MERS-CoV SSPL in HEK293T-ACE2 cells and Huh-7 cells, respectively, suggesting that the interaction of EGCG is non- specific concerning the viral surface protein structures (Henss et al., 2021). Another group reported that EGCG potently inhibits SARS-CoV-2 infection in Vero 76 cells with an EC_{50} value of 0.27 μg/ml (0.59 μM) and in Caco-2 cells with an EC_{90} value of 28 μg/ml (61 μM) (Hurst et al., 2021). Another study reported that EGCG significantly reduces the infection of live SARS-CoV-2 Wuhan type (WT) and the infection of pseudotyped lentiviruses bearing SARS-CoV-2 spikes (S) of WT and newly emerged variants, with single mutation in S (D614G, K417N, E484K and N501Y) and full set of mutations in S (UK-B.1.1. 7, SA-B-1.351 and CA-B.1.429) in HEK293T-hACE2 cells efficiently at 100 μM concentration. Moreover, this group in docking analysis, evaluated the binding affinity of EGCG on the S subunits (S1, S2 and RBD) to ACE2 receptor, and indicated that EGCG significantly blocked the binding of RBD to ACE2. It was supported by the western blot analysis. The recombinant RBD of SARS-CoV-2 S shows a binding affinity to ACE2 with an EC_{50} value of 4.08 ng/ml, while EGCG treatment significantly decreased the binding affinity of the viral S-RBD to ACE2 by 4.7 fold, with an EC_{50} of 19.19 ng/ml. In addition, EGCG also decreased the binding affinity of full length of viral S to ACE2 by 2.5 fold, (EC_{50} value of 107.6 ng/ml vs 43.48 ng/ml for the binding affinity of the viral recombinant full length S with ACE2). On the basis of these findings, this group suggested that EGCG possibly prevented the infection of SARS-CoV-2 virus by inhibiting the interaction of virion surface proteins to the host cells as well as inhibiting the binding of viral S RBD to host ACE2 receptor (Liu et al., 2021). Another group reported that EGCG inhibited the infectivity of diverse group of enveloped and nonenveloped human viruses by directly interacting with virion surface proteins, heparan sulfate for viruses, vesicular stomatitis virus (VSV), herpes simplex virus 1 (HSV-1), hepatitis C virus (HCV), and vaccinia virus (VACV), or with sialic acid for viruses like influenza A virus (IAV) and enterovirus 71, without affecting the fluidity or integrity of the virion envelopes. These findings suggest that EGCG competes with host extracellular glycans, heparan sulfate or sialic acid moieties for virion binding (Colpitts and Schang, 2014). In bilayer interferometry binding kinetic assay, EGCG shows a good binding interaction to SARS-CoV-2 spike RBD and ACE2 receptor, suggesting that EGCG interferes in the binding interaction of RBD to ACE2. EGCG shows a good binding interaction with SARS-CoV-2 RBD with a K_D value of 11.5 μM (D. Zhang et al., 2021). In an ELISA-based viral RBD-ACE2 interaction assay, EGCG at 50 and 100 μM concentrations, inhibited effectively the interaction of viral RBD to ACE2. Moreover, EGCG effectively inhibited the infectivity of pseudotyped lentiviruses bearing SARS-CoV-2 spike RBD of SARS-CoV-2 wild type, and four mutants (D614G, N501Y, N493K and Y453F) in HEK293-hACE2 cells at 100 μM concentration after 2 h of incubation. In molecular docking analysis, EGCG shows a good binding interaction to P2 site of the receptor-binding motif (RBM) of RBD of SARS-CoV-2 S wild type, and this site is not utilized by the mutants of wild type. The mutants, N439K corresponds to newly emergent strain B.1.141, Y453F to B.1.1.298, and N501Y to B.1.1.7 and B.1.351. These findings suggest that EGCG inhibits SARS-CoV-2 virus entry into host cells by inhibiting the binding of spike RBD to ACE2 receptor and is effective for suppression of viral infections of the newly emergent variants of SARS-CoV-2 (D. Zhang et al., 2021). The inhibitory effects of EGCG against the infectivity of spike (S) of SARS-CoV-2 (Wuhan type) and mutants-derived pseudotypedviruses have been tabulated in Table 1. One study reported that tea polyphenols, EGCG (1000 μM) from green tea, and dimeric EGCG, theasinensin A, TSA (Fig. 1) (40 μM) or TFDG (60 μM) from black tea almost inactivate SARS-CoV-2 and inhibit the interaction of viral S-RBD with ACE2 in

Table 1
Antibody neutralizing (prophylactic) activity of EGCG against the infections of spike protein of SARS-CoV-2 virus (original strain and mutants)-derived pseudotyped viruses.

Experiment (in vitro model)	Host cells used	Reference
EGCG inhibits the infectivity of pseudotyped-viruses bearing spike (S) of SARS-CoV-2 (Wuhan type strain) and its new mutants in S, with single mutation in S (D614G, K417N, E484K & N501Y), and full set of mutations in S (UK-B.1.1.7, SA-B.1.351 & CA-B.1.429)	HEK293T/ hACE2 cells	J. Liu et al., 2021
EGCG inhibits the infectivity of pseudotyped-viruses bearing S of 4 mutants of SARS-CoV-2 virus (D614G, N493K (B.1.141), Y453F (B.1.1.298), N501Y (B.1.1.7, B.1.351 & P1)	HEK293/ hACE2 cells	D. Zhang et al., 2021

Vero E6/TMPRSS2 cells and significantly reduce viral RNA replication (E. Ohgitani et al., 2021). All these findings suggest that EGCG inhibits the entry of the SARS-CoV-2 and other coronavirus (CoV) in host cells for inhibition of viral infection and transmission.

EGCG inhibits viral entry into the host cells

EGCG inhibits the entry of SARS-CoV-2 virus into host cells targeting the interactions with host and viral proteases responsible for binding interaction of viral spike (S) glycoprotein with host cell surface receptor ACE2 protein.

Accumulating evidence demonstrates that a herbal formulation, PB125® consisting of rosemary, ashwagandha and luteolin, on Nrf2 activation, downregulates the mRNA expression levels of both ACE2 and TMPRSS2 in human HepG2 cells (McCord et al., 2020). In differentiated human nasal epithelial cells, EGCG (1 μM) treatment on pre-incubation, significantly decreases the entry and replication of influenza A virus by activating Nrf2 signaling pathway (Kesic et al., 2011). Nrf2 activation stimulates the expression levels of antioxidant enzymes including HO-1 for suppression of virus-induced mitochondrial ROS production. Possibly, EGCG by Nrf2 activation, reduces the expression levels of ACE2 and TMPRSS2 in the epithelial cells of nasal and oral cavity and lungs for suppression of viral entry in these organs.

Glucose-regulated protein 78 (GRP78), also known as binding immunoglobulin protein (BiP) and heat shock 70 kDa protein family A member 5 (HSPA5), an ER stress sensor protein, has a key role for maintenance of cellular proteostasis. SARS-CoV-2 utilizes this host protease for enhancement of viral entry and life cycle in host cells. Two case control studies on COVID-19 patients reported that in severe SARS-CoV-2 infected patients, the serum GRP78 levels are increased by 7-fold as compared to healthy controls and serum GRP78 mRNA levels are four times higher in SARS-CoV-2 positive pneumonia patients as compared to SARS-CoV-2 negative pneumonia patients (Koseler et al., 2020; Palmeira et al., 2020). During viral protein synthesis stage, the virus S protein promotes about five-fold increase expression of GRP78 for proper folding, processing and assembly of viral structural and non-structural proteins (Chan et al., 2006). AR-12, an inhibitor of GRP78, significantly decreases the expression and ATPase activity of GRP78 as well as expression of SARS-CoV-2 spike protein in virus-infected HCT116 and Vero E6 cells. AR-12 increases the phosphorylation of eIF2α to stimulate the expression levels of beclin and ATG5, which in turn promotes autophagy process for degradation of GRP78 and viral S protein (Rayner et al., 2020). EGCG reduces the growth of cancer cells (breast, gastric and hepatocellular carcinomas) by inhibiting the ATPase activity of GRP78 via binding at the ATP-binding site and converting GRP78 from its active monomer to inactive dimer and oligomer and thereby blocking the formation of antiapoptotic GRP78-caspase 7 complex (Ermakova et al., 2006). Moreover, EGCG suppresses the replication of Ebola virus by decreasing GRP78 expression and activity (Reid et al., 2014). EGCG protects the mice from neurotoxicity by downregulating the expression of GRP78 in cisplatin-induced neurotoxicity in mice (Chen et al., 2015). In molecular docking analysis, EGCG shows a strong binding interaction at the ATPase domain of GRP78 with a docking score of −10.2 kcal/mol and in the interaction site of GRP78 with SARS-CoV-2 virus spike protein with a docking score of −10.5 kcal/mol via interactions to the residues Ser455, Ser452, Glu427, Ile450, Ala454 and Gln458 of spike protein for inhibition of viral entry into host cell (Allam et al., 2020). Therefore, EGCG inhibits viral entry into host cells by targeting host GRP78 protease.

As mentioned earlier, EGCG blocks the entry of SARS-CoV-2 into host cell by significantly decreasing the binding affinity of viral S protein-receptor binding domain (RBD) to ACE2 receptor (). Another group supported this opinion and reported that EGCG shows a strong binding affinity for SARS-CoV-2 spike RBD and mutant RBD (RBDm) from a UK variant (B.1.1.7) with a K_D value of 300 ± 200 nM. The docking analysis revealed that EGCG binds RBDm more efficiently than the RBD of original strain (Wuhan type) with an average BE of −22.1 kcal/mol for RBDm as compared to BE of −16.7 and −11.8 kcal/mol for RBD (WT) sites 1 and 2, respectively. Possibly, EGCG binds to the sites 1 and 2 of RBD at the RBD/ACE2 interface and forms a stable EGCG-site 1 complex by hydrogen bonds with Ser494 and Glu484 as well as by stacking interactions with Tyr449 and Phe490 residues (Tsvetkov et al., 2021). Accumulating evidence demonstrates that the RBD of SARS-CoV-2 spike (S) glycoprotein binds to host cellular heparan sulfate (HS) proteoglycans to increase the avidity for binding to cellular ACE2 via multivalent interactions. Exogenic heparin or tea catechin EGCG on binding to the same region of RBD of S protein, where HS binds, blocks the interaction of HS to ACE2 and prevents viral attachment and entry process (Liu et al., et al., 2021). Another study reported that EGCG inhibited the entry of SARS-CoV-2 pseudotyped virus particle in A549-ACE2B9 cells with an IC_{50} value of 24.0 μM. EGCG decreases the binding affinity of virus S protein to ACE2 by competing with exogenic heparin and cellular HS proteoglycans to prevent viral attachment and entry in host cells. EGCG also inhibited the infectivity of HCoV-OC43 and HCoV-229E in Huh-7 cells with IC_{50} values of 0.49 μM and 0.77 μM, respectively, via preventing viral entry process (LeBlanc and Colpitts, 2022). An *in silico* analysis on the binding interaction of EGCG with ACE2 reveals that EGCG binds to ACE2 with a binding score of −7.8 kcal/mol and identifies a hydrogen bond between R393 and ACE2, which is a key interacting residue of ACE2 in binding with spike RBD of SARS-CoV-2. It suggests that EGCG possibly inhibits viral entry by blocking the site of interaction between ACE2 and RBD (Ohisi et al., 2022).

EGCG inhibits SARS-CoV-2 main protease (Mpro) activity

EGCG potently inhibits the activity of SARS-CoV-2 Mpro (3CLpro) with an IC_{50} value of 0.874 μM as compared to ebselen with an IC_{50} value of 0.67 μM, in a FRET-based protease cleavage assay. The surface plasmon resonance (SPR) assay suggests that EGCG shows a good binding interaction with Mpro with a dissociation constant, K_D of 6.17 μM, but it is relatively weaker than quercetin having a K_D of 1.24 μM. In molecular docking analysis, EGCG shows a good binding affinity with viral Mpro with a calculated BE of −7.9 kcal/mol and forms hydrogen bonds with His41 and Cys145, the key residues of the active site of Mpro. In thermal shift assay, EGCG lowers the thermal stability of SARS-CoV-2 Mpro in a dose-dependent manner and depresses the melting temperature (Tm) of 53.80 °C in DMSO to 48.06 °C at 62.5 μM (Du et al., 2021). Another study reported that EGCG inhibits the activity of SARS-CoV-2 Mpro with an IC_{50} value of 4.24 μM, and weakly inhibits the activity of SARS-CoV with an IC_{50} value of 24.98 μM in a FRET-based protease cleavage assay. In molecular docking analysis, EGCG shows strong binding interactions with the substrate binding pocket of SARS-CoV-2 Mpro facing to the S2, S1' and S1 sites and forming hydrogen bonds with multiple residues including the catalytic residues Cys145 and His41 with a BE of −6.0 kcal/mol and −3.5 kcal/mol, respectively (Chiou

et al., 2022). Zhu and Xie reported that green tea extract and its main bioactive constituent EGCG inhibit the activity of SARS-CoV-2 Mpro with an IC_{50} value of 2.84 μg/ml and 7.51 μM , respectively (Zhu and Xie, 2020). EGCG also inhibits the 3CLpro activity of HCoV-OC43 and HCoV-229E with IC_{50} values of 14.6 μM and 11.7 μM, respectively (Jang et al., 2021).

EGCG inhibits SARS-CoV-2 papain-like protease (PLpro) activity

A group of studies on the activity of human severe acute respiratory syndrome coronavirus (SARS-hCoV) papain-like proteases (PLpros) strongly advocate that PL pros apart from their proteocatalytic activity in the processing of viral functional polyproteins pp1a and pp1ab to generate viral replicase complex for replication, efficiently remove interferon-stimulated gene 15 (ISG15) and Lys48-linked polyubiquitin from host cellular ubiquitin, and thereby dampening host innate immune responses, ensure viral efficient replication and spread of infection. Therefore, PLpros are essential for pathogenicity of the human SARS coronavirus (Harcourt et al., 2004; Mielech et al., 2014; Clasman et al., 2020). The ISG15, a 17 kDa ubiquitin (UB)-like protein of the host cells, conjugated to the ISGylation protein, is the central player of cellular antiviral responses against viral infection. It secretes the expression of type 1 interferons (IFNs) for suppression of viral infection (Perng and Lenschow, 2018; Ivashkiv and Donlin, 2014). The study on the mechanism of the deubiquitinase and deISGylase activity of SARS-CoV-2 PLpro indicates that SARS-CoV-2 PLpro preferencially cleaves ISG15, similar to PLpro in MERS-CoV, and has less ability in the cleavage of Lys48-linked UB substrate as compared to PLpro in SARS-CoV (Klemm et al., 2020; Freitas et al., 2020; Shin et al., 2020). A synthetic naphthalene analog, GRL0617, a potent inhibitor of SARS-CoV-2 PLpro, in vitro impairs the virus-induced cytopathic effect, maintains antiviral IFN signaling and reduces viral replication in infected cells (Shin et al., 2020). Therefore, inhibition of SARS-CoV-2 PLpro activity is a potential therapeutic strategy in treatment of COVID-19 infection.

Molecular docking analysis by a group reveals that EGCG shows a good binding interaction with SARS-CoV-2 PLpro through formation of hydrogen (H) bonds with backbone carbonyl oxygen of L162 and G163 residues of the viral protease as well as with the side chain residues D164 and R166, with a docking score of −8.601 kcal/mol and thereby inhibits the activity of viral PL protease. Possibly, EGCG binds to the S1-ubiquitin-binding site of PLpro, which might prevent the protease function in deubiquitinating and deISGylating activities. This property of EGCG counteracts the virus-induced acute respiratory distress syndrome (ARDS) via promoting antiviral responses (Chourasia et al., 2021). Another group also supported this property of EGCG. In their in vitro assay, EGCG inhibits the activity of SARS-CoV-2 PLpro deubiquitinase by about 13% at 100 μM concentration, whereas another green tea catechin ECG shows a relatively better inhibitory effect, about 20% at the same tested concentration (Pitsillou et al., 2021). In their blind docking analysis, EGCG shows strong binding affinity with SARS-CoV-2 PLpro with glide score energy of −56.4 kcal/mol and forms H bonds with Y273, E161, D164 and E167 residues of the virus protease within the naphthalene inhibitor binding pocket (Pitsillou et al., 2021). These findings suggest that EGCG exhibits its anti-inflammatory activity in coronaviral infection, at least in part, by suppression of deubiquitinating and deISGylating activity of viral PLpro in infected host cells.

EGCG inhibits the activity of SARS-CoV-2 endoribonuclease nsp15

The SARS-CoV-2 virus contains uridylate-specific endoribonuclease nsp15 and utilizes this non-structural protein in viral replication in addition to its proofreading function. Deletion of nsp15 significantly decreases viral replication. The viral nsp15 prevents the formation of host cellular cytoplasmic stress granules (SGs) to ensure effective viral protein synthesis and replication. A group of majestic studies indicate that RNA viruses generate double-stranded RNA (ds RNA) in order to replicate their genome. Virus-infected host cells consequently employ a variety of pattern recognition receptors (PRRs) to detect virus dsRNA and trigger innate antiviral responses, which play a pivotal role in fighting viral infections. The host dsRNA-activated protein kinase R (PKR) is the key element in innate antiviral defences. Activated PKR increases the levels of phosphorylated-alpha subunit of eukaryotic initiation factor (eIF2α), which in turn promotes the formation of SGs, specifically G3BP1/2. The SGs have been found to exert anti-viral functions by their involvement in entrapping viral mRNAs, viral protein synthesis shut off and recruitment of innate signaling intermediates. The SARS-CoV-2 viral nsp15 cleaves the 5′-polyuridines from viral negative sense RNAs to limit the accumulation of polyuridine-containing sequences in infected cells to escape from the host PRR-MDA5 (melanoma differentiation-associated protein 5, a RIG-1 like receptor of host dsRNA)-dependent antiviral responses. Other viruses including infectious Bronchitis Virus (IBV), porcine epidemic diarrhea virus (PEDV), porcine transmissible gastroenteritis virus (TGEV) and SARS-CoV utilize their nsp15 in replication via preventing SGs formation. Therefore, inhibition of viral nsp15 activity is a promising therapeutic target in suppression of viral infection and replication (Gao et al., 2021; Pillon et al., 2021; Hackbart et al., 2020; McCormick and Khaperskyy, 2017).

EGCG from green tea has been shown to inhibit efficiently the activity of SARS-CoV-2 nsp15 in vitro endoribonuclease assay with an IC_{50} value of 1.62 ± 0.36 μM, and inhibit the infection of a SARS-CoV-2 strain, isolated from COVID-19 patients, with an IC_{50} value of 0.20 μM (0.092 μg/ml) in plaque-reduction neutralization test. This inference was supported in molecular docking analysis. EGCG shows strong hydrophobic interactions with almost all the key residues (Lys290, Val292, Tyr343 and Leu346) at the active site of SARS-CoV-2 nsp15 nuclease and forms H bonds with His235, Gly248, His250, Lys290, Ser294 and Tyr341 at this site (Hong et al., 2021). These findings suggest that EGCG targets the viral nsp15 activity in inhibition of SARS-CoV-2 infection.

EGCG inhibits the activity of SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) in an in silico analysis

The enzyme RNA-dependent RNA polymerase (RdRp, also known as nsp12) of SARS-CoV-2 and other betacoronaviruses, is a key component of the replication machinery to make multiple copies of viral RNA genome (Elfiky, 2021). The RdRp of SARS-CoV exhibits about 97% sequence similarity with that of SARS-CoV-2. Human polymerases do not resemble in sequence and structural homology with the RdRp from human coronaviruses and hence, development of potential RdRp inhibitors could be a promising therapeutic strategy in treatment of COVID-19 infection (Jiang et al., 2021).

In a study of molecular docking analysis, tea catechin, EGCG exhibits high binding affinity with the active site of RdRp of SARS-CoV-2 virus with calculated binding energy (BE) of −7.3 kcal/mol, respectively, as compared to RdRp inhibitor remdesivir of −7.7 kcal/mol (Singh et al., 2021). However, further in vitro and in vivo studies are needed to validate the efficacy of this catechin against SARS-CoV-2 RdRp.

EGCG protects from lethal sepsis in severe COVID-19 infection

Sepsis refers to host's deleterious constant wide spread severe systemic inflammatory response against microbial infections and represents a leading cause of death. The pathogenesis of sepsis is complex and partly mediated by an elevated expression of damage-associated molecular pattern (DAMP) molecules, such as high mobility group box 1 (HMGB1) protein molecule. In severe COVID-19 patients, the complications like acute respiratory distress syndrome (ARDS), sepsis and septic shock are believed to be caused from an overactivation of immune system and the release of DAMP molecules as alarmin molecules from the damaged infected cells. HMGB1 is a key alarmin molecule and is a

central mediator of lethal (extreme) inflammation in severe COVID-19. For this reason, it is considered as a potential biomarker and therapeutic target in severe COVID-19 infection. Accumulating evidence demonstrates that serum HMGB1 level in severe COVID-19 patients is elevated to 189.40 ± 140.88 ng/ml as compared to 35.51 ± 41.92 ng/ml in non-severe COVID-19 patients and 7.16 ± 2.88 ng/ml in normal controls (Chen et al., 2020). The exogenous HMGB1 induces the expression of viral entry receptor ACE2 in alveolar epithelial cells via induction of advanced glycosylation endproduct-specific receptor (AGER, also known as receptor of advanced glycosylation endproducts, RAGE). Genetic deletion of AGER using AGER siRNA or inhibitor of AGER/RAGE blocks ACE2 expression via inhibition of HMGB1-RAGE-PKR signaling pathway. Treatment of AGER siRNA in Calu-3 cells significantly decreases ACE2 mRNA expression (Wang et al., 2014; Chen et al., 2020). A group of majestic studies strongly advocates that EGCG inhibits HMGB1 expression in inflammation and immune dysfunction in various severe infections. In vitro, EGCG (15 μM) in LPS-induced primary murine peritoneal macrophages or human peripheral blood mononuclear cells (PBMCs), completely abrogates LPS-induced HMGB1 release. In an animal model, EGCG treatment (4 mg (10 μM)/kg) to LPS-induced lethal endotoxemia in mice, at 24 h after onset of sepsis, followed by additional doses at 48 h and 72 h post-sepsis, significantly protects the mice against lethal sepsis by increasing the animal survival rate from 53% to 82%, suggesting the therapeutic potential of EGCG in the treatment of sepsis. The study of systemic accumulation of various inflammatory cytokines reveals that EGCG significantly reduces the levels of plasma HMGB1 possibly, at least partly by binding to plasma membrane lipid raft-related receptor, Fc epsilon receptor R1 (FcεR1) for inhibition of ERK1/2 phosphorylation and its surrogate marker IL-6 in mice (Wang et al., 2007; Li et al., 2007). Another study reported that EGCG decreases HMGB1 release in LPS-stimulated RAW 264.7 macrophage cells by stimulating LC3-II production and inducing the aggregation of HMGB1 via formation of lysosomal-associated membrane protein 2 (LAMP2)--mediated autophagasomes in cytoplasm and subsequent autophagic degradation. EGCG-mediated protection against lethal sepsis was partly impaired by co-administration of an autophagy inhibitor, chloroquine (N. Li et al., 2011). EGCG inhibits JAK/STAT1 activation for suppression of HMGB1 release from activated macrophages (Lu et al., 2014). LPS- or interferon- induced activation of macrophages/immune cells increases hyperacetylation (phosphorylation) of HMGB1 at the nuclear localization site, via activation of JAK/STAT1 signaling, and thereby promotes accumulation of HMGB1 in the cytoplasm. At present, tocilizumab, an IL-6 receptor blocker, widely used in the control of autoimmune diseases, has been found to exhibit promising results in suppression of sepsis in severe COVID-19 infection (Zhang et al., 2020).

EGCG protects from thrombotic and thromboembolic complications in severe COVID-19 infection

A group of critical hospitalized patients with severe COVID-19 infection have been associated with thrombotic and thromboembolic complications, due to excessive inflammation, endothelial dysfunction and cell activation, platelet activation and hypercoagulability and have high risk of mortality. Several majestic studies revealed that low levels of platelet count, $< 100 \times 10^9$/l in compared to normal range of 130–350 $\times 10^9$/l, and platelet factor 4 (PF4) and high levels of blood coagulant factors, namely D-dimer, C-reactive protein (CRP), fibrinogen, cellular tissue factor (TF) (FVIIa complex), plasminogen activator inhibitor 1 (PAI-1), platelet surface protein P-selectin, von Willebrand factor (vWF), neutrophil extracellular traps (NETosis), tissue plasminogen activator (tPA), plasma complement factors including C5a, thromboxane B2, and inflammatory factors IL-6 and HMGB1 are responsible for thrombin formation in critically severe COVID-19 infections. On entry of SARS-CoV-2 in host lung and mouth epithelial cells by binding to ACE2, the expression and activity of ACE2 are reduced, resulting vasoconstriction and reduced blood flow in veins and arteries, and thereby increase vascular permeability of blood and high expression of TFs in subendothelial cells, leukocytes and platelets, which in turn trigger the activation of coagulation cascade for coagulation of blood. Endothelial dysfunction releases high levels of inflammatory cytokines including TNF-α and IL-6, vWF and platelet surface protein P selectin that promote thrombus formation. The reduced expression of ACE2 leads to increase the levels of Ang II, which stimulate the expression of PAI-1 in various cells including endothelial and muscle cells and adipocytes. Elevated expression levels of PAI-1 stimulate hypofibrinolysis and thereby increase the risk of thrombosis. The virus-induced TLRs signaling promote TF expression in monocytes, resulting in the activation of platelets and platelet aggregation. The SARS-CoV-2 infection in host epithelial cells promotes the expression levels and activation of neutrophils via excessive ROS production and Ca mobilization and neutrophils on activation initiate the process for the formation of neutrophil-derived extracellular traps (NETs) and this process is known as NETosis. The generated NETs are released in blood and the levels of NETs in circulation and tissues (mainly lungs, hearts,) are increased and leads to tissue injury and development of sepsis and apoptosis of the cells. The NETs and virus N protein-induced activated complement system mostly C5a promote the activation of coagulation factors, FVII to FIX, and activated factors FVIIa to FIXa complex initiate the coagulation cascade, for generation of thrombin from inactive prothrombin and fibrin from fibrinogen. A study on the mechanism of platelet aggregation reveals that in infected host cells, host cells release tissue factor (TF) mRNA in blood plasma for activation of extrinsic pathway of coagulation factors FX, via FVII and subsequent conversion of inactive prothrombin into active thrombin, which activates protease-activated receptor (PAR) 1 and 4 to increase host immune response and thereby increases the release of platelet surface protein P-selectin for platelet aggregation and clot formation (Puhn et al., 2022). The generated fibrin allows crosslinking of platelets and other cellular constituents and results in the formation of thrombus (clot). The elevated levels of tissue plasminogen activator (tPA) promote the conversion of plasminogen into plasmin and the generated plasmin breaks down fibrin at the site D to form D-dimer, the high levels of D-dimers reflect the degree of thrombosis and provide the prognostic value of pulmonary embolism and deep vein thrombosis (Veras et al., 2020; Busch et al., 2020; Gorog et al., 2022). Therefore, the inhibition of NETs release or activity or reduction of the levels of D-dimers represents a potential therapeutic strategy in treatment of COVID-19 infection. Severe COVID-19 patients with pulmonary embolism (PE) have significantly higher D-dimer levels (between 1000 and 4800 μg/l) as compared to the conventional cut-off level of 1000 μg/l in moderate-severe COVID-19 patients (Kwee et al., 2021). The extracellular vesicles TF activity strongly correlates with the occurrence of thromboembolic events in lungs and other organs as evident from microvascular obstruction by neutrophilic plugs as aggregates of neutrophils with NETs or NETs with platelets, generated from endothelial dysfunction or tissue damage from viral infection (Liao et al., 2020).

Tea catechin EGCG on treatment (30 mg/kg/d, *i.p.*, for 7 days) in mice prevents thrombosis of carotid arteries by inhibition of tissue factor activity. The study of molecular mechanism reveals that EGCG activates the endothelial cell surface membrane protein, 67 kDa laminin receptor (67LR) for inhibition of the phosphorylation of JNK1/2 and suppression of JNK-induced TF expression in aortic endothelial cells. Elevated levels of TF are detected in atherosclerotic plaques and thus suppression of TF expression in vascular cells is a potential strategy for treatment and prevention of arterial thrombosis (Holy et al., 2010). Another study reported that EGCG on oral administration of a single dose (10 or 50 mg/kg) in mice, prior to tail vein injection of platelet aggregation inducers, epinephrine plus collagen, protects the mice against death from pulmonary thrombosis by inhibition of platelet aggregation. The study of molecular mechanism reveals that EGCG inhibits thrombus formation in lung tissues by blocking collagen-mediated phospholipase (PL) Cgamma 2 and protein tyrosine phosphorylation and reducing cytosolic

calcium mobilization via maintenance of Ca^{2+} ATPase activity. EGCG completely blocks the activity of Ca^{2+} ATPase pump inhibitor thapsigargin in platelet aggregation, intracellular Ca^{2+} mobilization and protein tyrosine phosphorylation. In vitro, EGCG inhibited ADP-, collagen-, epinephrine- and calcium ionophore A23187-induced human platelet aggregation (Kang et al., 1999; Jin et al., 2008).

EGCG protects from lung fibrosis in COVID-19 infection

In the epithelial cells of lung tissues, the entry of SARS-CoV-2 by interaction of viral spike (S) glycoprotein with host cell receptor ACE2 reduces the expression of ACE2 and increases the accumulation of angiotensin II (Ang II) and the production of inflammatory cytokines including TNF-α and IL-6 receptor, and activation of macrophages to a proinflammatory stage via increasing the expression and activity of angiotensin I receptor (AT1R) and ADAM17 (a disintegrin and metalloprotease 17) (Gheblawi et al., 2020). Moreover, the virus nucleocapsid (N) protein interacts with host Smad3 by inhibiting its interaction with Smad4 in preventing cell apoptosis, and modulates the activity of Smad3 in the expression of transforming growth factor-beta (TGF-β) for tissue fibrosis via formation of Smad3-p300 complex. TGF-β1 plays a pivotal role in pulmonary fibrosis by increasing the secretion of extracellular matrix proteins (ECM) molecules and reducing the secretion of proteases like Bax and Bim. The TGF-β1 protein increases the expression of ECM molecules, PAI-1 and type 1 collagen in the vicinity of pneumocytes in lung tissue for development of lung fibrosis and thereby impairs the normal functioning of lungs and leads to failure of lung function and death of severe virus-infected patients (Zhao et al., 2008). Immunohistochemical studies of the lung tissues of died COVID-19 patients reveal the high levels of collagen 1 (mature) and III (immature), ACE2 gene, TGF-β1, α-SMA, MMP-9, CD44v6 and Akt in alveolar septal fibrosis. These results suggest that TGF-β1 signaling plays a key role in the development of pulmonary fibrosis in severe COVID-19 patients (de Paula et al., 2022). Two pneumoproteins, Krebs von den Lungen 6 (KL-6) and Clara cell secretoty protein 16 (CC16) are considered as biomarkers of COVID-19-related lung injury. KL-6, a high molecular weight glycoprotein, mainly found in type II alveolar epithelial cells (type II pneumocytes) , and bronchial grandular epithelial cells and plays a key role in lining the airway lumen and for maintenance of pulmonary innate immune system and is mainly secreted by damaged or regenerating type II pneumocytes and bronchial epithelial cells in cellular infection. In severe COVID-19 infection, SARS-CoV-2 infection/cytopathic effect against pneumocytes and epithelial cells causes cell injury and destroys the alveolar epithelium and basement membrane leading to the secretion of high levels of KL-6, which on leakage of air-blood barrier in alveoli, enters in blood causing an elevation of serum KL-6 levels (above 404 U/ml, about 1125 U/ml in severe COVID-19 infection as compared to 316 U/ml in non-severe group; another study shows 755 U/ml in COVID-19 patients with CT infiltrate and 305 U/ml in patients with no CT infiltrate). The elevated KL-6 levels in BALF and serum of severe COVID-19 patients are correlated to lung fibrosis and broad pulmonary lesion area and the high IL-6 levels in lung tissues (Xue et al., 2020; Naderi and Rahimzadeh, 2022). CC-16, a club cell secretory protein, is mainly secreted by the non-ciliated bronchial epithelial cells, for protection against inflammatory response via modulation of the activities of PLA2, IFN-γ and TNF-α. In COVID-19 patients, the serum levels of CC-16 are lower in compared to healthy controls. Possibly, the involvement of CC-16 in the repairing work of SARS-CoV-2 infected epithelial cells, causes its reduced levels. Another finding indicates that the serum KL-6 levels are higher in interstitial lung diseases (ILDs) as compared to severe COVID-19 patients, suggesting it as a promising biomarker in the early stages of lung injury in COVID-19 (Almuntashiri et al., 2021).

EGCG on treatment (20 mg/kg/d, *i.p.,* for 28 days) in bleomycin-induced rat model of lung fibrosis, significantly improves the lung function by reducing TGF-β1 expression and type 1 collagen accumulation, activity of NF-κB, and expression levels of TNF-α and IL-1β, and increasing the expression levels of Nrf2, GST and NQO1 in lung tissues. In vitro, EGCG in TGF-β1- stimulated WI-38 fibroblast cells, significantly decreases the expression levels of α-SMA, type 1 collagen, ROS and Smad3 mRNA (Sriram et al., 2009, 2015). In another animal model, EGCG in LPS-induced acute lung injury (ALI) in mice significantly protected the mice from ALI by reducing the elevated expressions of proinflammatory cytokines, TNF-α, IL-1β and IL-6 in lung, serum, and bronchoalveolar lavage fluid by suppression of TLR4-dependent NF-κB signaling activation (Wang et al., 2019). Accumulating evidence demonstrates that EGCG on binding to lung epithelial cell surface protein 67-kDa laminin receptor (67-LR), activates the protein for upregulation of the expression level of Toll-interacting protein (Tollip) for down-regulation of the TLR4 signaling cascade (Byun et al., 2010). In another study, EGCG on oral administration (600 mg/d, for 14 days) in patients with pulmonary fibrosis, significantly reduces the accumulation of type 1 collagens and the expression levels of Snail1 and phosphorylated Smad 3 in lung tissues and the levels of serum cartilage oligomeric matrix protein and periostin, the biomarkers of idiopathic pulmonary fibrosis (IPF) development and prognosis (Chapman et al., 2020). In vitro, EGCG in precision-cut lung slices from idiopathic pulmonary fibrosis patients (IPF-PCLS) culture, inhibits the production of collagen 1 type proteins by inhibiting the activity of lysyl oxidase like 2 (LOXL2) and TGF-β1 and increasing the expression of matrix metalloproteinase 1 (MMP1) activity. The MMP1, also known as fibroblast or interstitial collagenase has a unique ability for degradation of crosslinked and non-crosslinked collagens (Wei et al., 2021). These findings suggest that EGCG could be a promising drug for prevention of lung fibrosis in COVID-19 patients.

EGCG improves selenium deficiency in COVID-19 infection

Accumulating evidence indicates that the levels of selenium and the Se enriched seleno protein P (SELENOP) in plasma of COVID-19 patients decrease significantly and it inversely correlate with the risk of multi-organ dysfunction, severe pneumonia and death. The SELENOP is synthesized in liver and acts as Se transport system to different tissues for maintenance of homeostasis throughout our whole body. The viral infection or endotoxemia decreases the synthesis of selenocysteine (Sec), the basic units of SELENOP due to non-availability of multiple biofactors including selenoenzymes, selenophosphate synthetase 2, selenocysteine synthase, phosphoseryl tRNA kinase and selenocysteine lyase from high inflammation under oxidative stress. Human SELENOP contains ten Sec residues and is associated with endothelial cells in high concentrations, possibly through its heparin binding property for protection under oxidative stress (Bellinger et al., 2009; Sherlock et al., 2020). A clinical survey on plasma samples of COVID-19 patients reveals that Se and SELENOP levels are higher in the plasma of surviving COVID-19 patients than non-survivor patients (Se, 53.3 ± 16.2 vs. 40.8 ± 8.1 μg/l; SELENOP, 3.3 ± 1.3 vs. 2.1 ± 0.9 mg/l) (Moghaddam et al., 2020). Another study reported that the levels of plasma Se and SELENOP are lower in COVID-19 patients than in recovery COVID-19 patients (Se, 59.3 ± 16.1 μg/l vs. 75.4–88.2 μg/l; SELENOP, 4.5 mg/l vs. 6.8 mg/l) (Skesters et al., 2022).

EGCG shows potential anti-inflammatory and antioxidant activities. EGCG in selenium-deficient mice, promotes hepatic Nrf2 response to increase the expression levels of antioxidant enzymes, heme oxygenase 1 (HO-1), NAD(P)H:quinone oxidoreductase 1 (NQO1), thioredoxin R1 (TrxR1) mRNA and GST for restoration of Se levels by synthesis of selenoproteins, such as SELENOP (Dong et al., 2016). EGCG in $CoCl_2$-induced hypoxia in microglial BV2, protects the cells from injury and apoptosis by reducing ROS generation and IL-6 production via reduction of elevated HIF-1α expression and stimulation of Nrf2 activity and expression level of HO-1 (Kim et al., 2022). Accumulating evidence indicates that an increased expression of heme oxygenase 1 (HO-1) in host cells promotes IFN activation for suppression of virus-induced

inflammation and replication of many viruses including influenza A virus, enterovirus 71, Ebola and dengue virus, as well as reduces inflammation-induced coagulation and acute respiratory distress syndrome (ARDS) in COVID-19 patients (Singh et al., 2020).

EGCG prevents hyperglycemia-dependent glycolysis-induced SARS-CoV-2 replication and inflammation

Age-related hyperglycemia-induced mitochondrial dysfunction is considered as an enhancing factor of COVID-19 infection. In aged individuals with uncontrolled- hyperglycemia, SARS-CoV-2 infects monocytes to increase mitochondrial dysfunction for production of high levels of ROS, which in turn, induces the expression of HIF-1α in high concentrations. An elevated expression of HIF-1α promotes glycolysis to increase the expression of ACE2, and inflammatory factors, IL-1β, IL-6, TNF-α, IFN-α, -β, and -ϒ for increased SARS-CoV-2 replication and infection. Therefore, inhibition of the activity of ROS/HIF-1α/glycolysis axis is a promising therapeutic target for prevention of SARS-CoV-2 replication and infection (Codo et al., 2020).

In vitro, EGCG reduces the growth of breast cancer 4T1 cells by reducing the expression of HIF-1α and glucose transporter 1 (GLUT1), key players in regulating glycolysis, and the activities and mRNA levels of glycolytic enzymes hexokinase (HK), phosphofructokinase (PFK) and lactic dehydrogenase (LDH) and inducing autophagy by enhancing the expression of Beclin 1, Atg5 and LC3BI/II. In vivo, EGCG treatment (20 mg/kg/d, for 4 weeks) in xenografted mice, significantly reduces breast tumor weight and glucose (by 34%) and lactic acid levels and the expression of vascular endothelial growth factor (VEGF). EGCG induces the collapse of mitochondrial membrane potential to restore the mitochondrial normal functions. As glycolysis offers a selective advantage for rapid growth of cancer cells by generation of ATP more rapidly than oxidative phosphorylation, the inhibition of HIF-1α/glycolysis is a potential strategy in suppression of tumor growth (Wei et al., 2018).

EGCG reduces SARS-CoV-2 induced cytokine storm in infected lung epithelial cells

In COVID-19 patients, SARS-CoV-2 triggers a robust interferon (IFN) response by increasing the expression levels of several IFN-stimulating genes (ISGs), such as IL-1β, CXCL17, CXCL8, CCL2 and SOCS3 in infected respiratory tract epithelial cells for recruitment of activated neutrophils, other monocytes and immune cells, and leads to a persistence of inflammatory status to promote viral replication via induction of JAK/STAT signaling pathways. Therefore, suppression of JAK/STAT pathway is a potential therapeutic target in treatment of cytokine storm in severe COVID-19 patients (Zhou et al., 2020).

EGCG in hepatocellular carcinoma HCC cells, suppresses cell proliferation and induces cell apoptosis by decreasing the expression of IL-6 and IL-6 dependent STAT3 phosphorylation (Wang et al., 2013). In vivo, EGCG in IL-1 receptor antagonist knockout (IL-1RaKO) mice, a model of autoimmune arthritis, suppresses collagen accumulation and arthritic pain and inflammation in the synovium of arthritic joint by reduction of the activation of m-TOR and m-TOR-induced HIF-1α expression and STAT3 activation and Th17 cells population and expression of cytokines including IL-1β, IL-6 and IL-23 and increased the population of $Foxp3^{+}$ Treg cells in the spleens of mice (Yang et al., 2014). These findings suggest that EGCG could be useful in suppression of STAT activation and STAT-induced cytokine storm in severe COVID-19 patients.

Poor bioavailability of EGCG and attempts for its optimization

The tea catechin EGCG has been shown to possess many health benefit effects and could be a potential chemotherapeutic agent. However, the poor bioavailability and extensive metabolism of EGCG make it difficult to translate its beneficial effects in humans as medicines and functional foods (Mereles and Hunstein, 2011). The oral bioavailability of EGCG is estimated to be about 0.1% and 0.3% of ingested EGCG in rats and humans, respectively (Chen et al., 1997; Nakagawa and Miyazawa, 1997).

Pharmacokinetics of EGCG in humans

Pharmacokinetic parameters are useful in selecting the dose and dose frequency for achieving optimal EGCG levels in human plasma. Several studies on the pharmacokinetics of EGCG in humans are reported. A clinical pharmacokinetic study on EGCG in humans reported that ingestion of a single oral dose of EGCG or polyphenon E (contains decaffeinated green tea catechin extract and each capsule contains 200 mg EGCG, 37 mg EGC, 31 mg EC and other constituents) by human healthy subjects ($n = 5$ for each dose) after overnight fasting, the average maximum concentration (C_{max}) of unchanged EGCG in plasma were 0.16, 0.24, 0.37 and 0.96 μM, or 72.7, 125.3, 165.7 and 377.6 ng/ml after 200, 400, 600, and 800 mg doses of EGCG, respectively, or average C_{max} of plasma unchanged EGCG (free form) were 0.16, 0.27, 0.36 and 0.82 μM after polyphenon E ingestion at doses that contained 200, 400, 600 and 800 mg of EGCG, respectively. Moreover, the mean area under plasma concentration-time curve (AUC) of unchanged EGCG after 24 h of drug administration were 22.5 vs 21.9, 35.4 vs 52.2, 101.9 vs 79.7 and 167.1 vs 161.4 μg.min/ml for the doses, 200, 400, 600 and 800 mg of EGCG or polyphenon E, respectively. In polyphenon E administration, EGCG was mainly detected in plasma, while EGC and EC were mainly found in conjugated forms. Following EGCG administration, EGCG was detected in plasma mainly in free form and plasma EGCG levels did not change significantly after treatment of plasma samples with deconjugating enzymes, β-glucuronidase/sulfatase. Neither EGCG nor its glucuronic acid/sulfate conjugates were detectable in urine after EGCG or polyphenon E administration. Although both AUC and C_{max} of EGCG after the 800 mg dose, were found to be highest than the lower tested doses, some subjects experienced mild headache and fatigue, possibly due to catechin. These findings also indicate that consumption of two cups of green tea (containing 195 to 220 mg of EGCG) the maximum plasma EGCG concentration of about 0.16 μM is achieved (Chow et al., 2001; Chow and Hakim, 2011). One pharmacokinetic study reported that plasma EGCG level reaches only 0.6 μM in average after receiving an oral dose of 150 mg EGCG twice daily by healthy human subjects for 5 days (Scholl et al., 2018). Another pharmacokinetic and phase II metabolism study of EGCG in humans reported that after oral intake of a single dose of 350 ml of catechin-rich green tea beverage containing 615 mg of catechins (135 mg of EGCG, 127 mg of EGC, and other catechins) by healthy volunteers ($n = 10$), the following pharmacokinetic parameters of EGCG and its two metabolites, EGCG-4″-sulfate and EGCG-4″- glucuronide in plasma were observed after 6 h of green tea ingestion: C_{max} 233.5 ± 77.6, 177.9 ± 61.5, 75.3 ± 21.5 nmol/L, T_{max} 1.4 ± 0.32, 2.5 ± 0.60, 1.3 ± 0.26 h, $AUC_{0\rightarrow 6\ h}$ 664.1 ± 77.8, 715 ± 127.1, 198.9 ± 23.8 nmol/L, and $T_{1/2}$ 2.1 ± 0.46, 3.9 ± 1.5, 1.5 ± 0.64 h, for EGCG, EGCG-4″-sulfate and EGCG-4″-glucuronide, respectively. These findings suggested that EGCG-4″-sulfate is the key metabolite of EGCG and this metabolite has longer $T_{1/2}$ (3.9 h) than that of EGCG (2.1 h), indicating it is removed slowly from the body. In addition, this metabolite is about 3.6 fold more predominant than EGCG-4″-glucuronide. Moreover, in vitro kinetic study of sulfation of EGCG in liver and small intestinal cytosols revealed that the sulfation is 2-fold and 60–300 fold higher than that of methylation and glucuronidation, respectively. Recombinant human sulfotransferases, SULT1A1 and SULT1A3 are responsible for sulfation in the liver and intestine, respectively. These findings suggest that SULT1A1- and SULT1A3-mediated sulfation is the key factor, responsible for poor bioavailabilty of EGCG (Hayashi et al., 2022). A group of studies demonstrate that EGCG is mostly absorbed in the small intestine in humans and then passes to large intestine, where it breaks down into phenolic acids by colonic microbiota. Moreover, a significant amount of absorbed EGCG is biotransformed in liver and small intestine mostly by

phase-II metabolizing enzymes, such as sulfotransferase (SULT), UDP-glucuronosyltransferase (UGT) and catechol-*O*-methyltransferase (COMT) leading to sulfated, glucuronidated and methylated conjugate metabolites. In vitro study, EGCG-4″-glucuronide is the major metabolite formed by human microsomes (Hong et al., 2003; Lambert et al., 2007).

Factors influencing EGCG bioavailability

Gastrointestinal tract inactivation of EGCG. During drinking of green tea as beverage, a significant amount of EGCG interacts with salivary proteins, alpha amylase, S100 and cystatins for their precipitation. This effect of EGCG prevents the activity of α-amylase in the formation of fermentable carbohydrates that are involved in caries formation. Moreover, a significant amount of EGCG is consumed in inactivation of α-amylase in enterocytes of small intestine (Hara et al., 2012). Accumulating evidence demonstrates that after drinking of two to three cups of green tea, the level of EGCG in saliva is 4.8–22 μg/ml, much higher in magnitude than in plasma (Yang et al., 1999). Moreover, EGCG is unstable at higher pH of intestinal fluid (pH, above 4) due to chemical degradation into dimmers and epimerization into gallocatechin gallate (GCG) (Xu et al., 2019). In human gastrointestinal tract, the intraluminal pH rapidly changes in different regions, from highly acidic in stomach to pH 6 in the duodenum and then gradually increases in small intestine to about pH 7.4 in ileum; then drops to 5.7 in caecum and again increases to pH 6.7 in the rectum (Fallingborg, 1999).

Low absorption of EGCG in the human small intestine. EGCG being polar hydrophilic in nature, inhibits intestinal luminal emulsification and micellar solubilisation and reduces its uptake in brush border lipid membrane of the enterocytes by ATP-dependent multidrug resistance-associated protein (MRP) efflux pumps, MRP1 and MRP2 in a passive diffusion process. MRP1 located on the basolateral membrane of the enterocytes, pumps the absorbed EGCG from the interior of the cells into bloodstream or intestinal space. MRP2 expressed in the apical surface of the enterocytes, pumps a part of EGCG before or after being methylated by intestinal COMT, from enterocytes into intestinal lumen. The portion of EGCG left in the enterocytes, is absorbed into portal circulation and enters in the liver. In human jejunum, the expression of MRP2 is about 10 fold higher than that of MRP1, resulting in the predominant efflux of MRP2 on EGCG, and leads to poor availability of EGCG in bloodstream (Hong et al., 2003). Another study reported that the expression level of diastrophic dysplasia sulfate transporter (DTDST) protein is increased in the ileum of rats after repeated oral administration of EGCG or green tea extract and transports EGCG from ileum into bloodstream and it works under alkaline, neutral and acidic pH conditions. Possibly this protein present in human ileum, plays an active role in the transport of EGCG to improve its bioavailability on repeated oral ingestion of EGCG or drinking of green tea (Ishii et al., 2019).

Extensive metabolism of EGCG in the liver and small intestine. Several studies reported that phase II metabolizing enzymes, sulfotransferases (SULTs), UDP-glucuronosyltransferases (UGTs) and catechol-O-methyltransferase (COMT) present in human liver and small intestine cytosols convert a significant part of absorbed EGCG into sulfated, glucuronidated and methylated metabolites. In vitro study indicates that the sulfotransferase SULT1A1 present in both liver and small intestine cytosols and SULT1A3 mainly in small intestine, catalyzes EGCG for the formation of its sulfate conjugates. Among UGTs, EGCG is catalyzed predominantly by UGT-1A1, −1A8 and −1A9, and among them, UGT1A8 has been shown to have highest catalytic activity on EGCG and these UGTs form both EGCG-3″-glucuronide and EGCG-4″-glucuronide. The enzyme COMT present in both liver and intestine mainly catalyzes the formation of 4″-MeEGCG (Lambert et al., 2007; Hayashi et al., 2022). An in vivo study indicates that in human, EGCG-4″-sulfate is the major metabolite and is about 3.6 fold more predominant than EGCG-4″-glucuronide (Hayashi et al., 2022).

An in vitro study on the metabolism of EGCG by gut microbiota reported that the fermentation of human fecal mass, collected from healthy volunteers, with EGCG for 24 h, 14 phenolic metabolites of EGCG were identified, namely epigallocatechin (EGC), gallic acid, pyrogallol, 4-phenylbutyric acid, 3-(3′,4′-dihydroxyphenyl) propionic acid, 3-(4′-hydroxyphenyl) propionic acid, 1-(3′,4′-dihydroxyphenyl)−3-(2″,4″,6″-trihydroxyphenyl) propan-2-ol, 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone, 5-(3′,4′,5′-trihydroxyphenyl) valeric acid, 3-phenylpropionic acid, 2-(3′,4′-dihydroxyphenyl) acetic acid, 2-(4′-hydroxyphenyl) acetic acid, phenylacetic acid and 4-hydroxybenzoic acid, and these were formed through consecutive ester hydrolysis, C-ring opening, A-ring fission, dehydroxylation, and aliphatic chain shortening. Most of these metabolites are circulated in the body. Notably, this catabolism of EGCG promotes the growth of some bacteria of genus *Bacteroides, B. uniformis* and *B. vulgaris*, which have potential health-benefit effects in production of anti-inflammatory cytokines and in protection from coronary artery disease, respectively (Liu et al., 2020).

Serum albumin levels for EGCG transport in blood. Accumulating evidence demonstrates that human serum albumin (HSA) transports EGCG in the body by covalent bonding interaction with EGCG having a binding constant K_D of about 14 μM, and thereby it prevents the polymerization and decomposition of EGCG. For this reason, low HSA levels may decrease the plasma EGCG levels (Ishii et al., 2011; Maiti et al., 2006; Sun et al., 2019).

Use of hard water in oral intake of EGCG. The presence of Ca^{2+} , Mg^{2+}, and other metals including iron in hard water decreases the absorption of EGCG in small intestine. Possibly, these metal ions are able to form EGCG-metal chelate complexes, resulting in the reduction of the transport of EGCG across the enterocytes (Ryan et al., 2007; Kim et al., 2008).

Optimization of EGCG bioavailability

Storage of EGCG capsules at low temperature and low relative humidity. Chemical degradation of EGCG is enhanced in high relative humidity and high temperature (above room temperature of 25 °C) (N. Li et al., 2011). Therefore, storage of EGCG capsules in dry and cool condition prevents from chemical degradation of EGCG.

Oral intake of EGCG in empty stomach. Several studies on bioavailability of EGCG strongly advocate that oral intake of EGCG with breakfast or full meal decreases the absorption in small intestine due to delay of gastric emptying and secretion of pancreatic bicarbonate solution into duodenum for neutralization of the acidity of chyme coming from stomach for absorption in the small intestine. Moreover, the presence of proteins in ingested food may reduce the acidity of the chyme. The protecting EGCG from the alkaline pH in the small intestine is needed for improvement of EGCG bioavailability. A comparative pharmacokinetic study on EGCG reported that ingestion of a single dose of 500 mg EGCG in capsule by human healthy subjects in empty stomach (overnight fasting) showed maximum EGCG concentration (C_{max}) in plasma of 824.3 ng/ml, as compared to its plasma C_{max} of 231.8 or 218 ng/ml on intake of EGCG with breakfast or in strawberry sorbet, respectively. Moreover, the $AUC_{0\rightarrow 8\ h}$ was 2.7 or 3.9 times higher than that of $AUC_{0\rightarrow 8\ h}$ when EGCG capsules were taken with a light breakfast or with EGCG embedded in the strawberry sorbet, respectively (Naumovski et al., 2015).

Oral intake of EGCG with specific nutrients. An oral intake of EGCG in a formulation with ascorbic acid and sucrose improves the bioavailability of EGCG, in which ascorbic acid reduces the oxidation of EGCG to increase its stability and sucrose increases the absorption of EGCG by

enhancing the viscosity of the fluid (Peters et al., 2010). Similarly, oral administration of EGCG as green tea extract simultaneously with fish oil, rich in antioxidant omega-3-fatty acids in mice, significantly increases the concentration of EGCG in plasma of mice (Shirai and Suzuki, 2008). Another study reported that intragastric coadministration of piperine, an alkaloid from black pepper, with EGCG in mice, increases the bioavailability of EGCG in mice plasma by enhancing both C_{max} (0.66 vs 0.32 μM/L) and AUC values by 1.3 fold as compared to mice treated with EGCG alone. Piperine has been shown to inhibit the glucuronidation of EGCG in mouse small intestine by about 40%, and inhibits gastric emptying and gastrointestinal transit of EGCG in colon and thereby increases the absorption of EGCG in small intestine (Lambert et al., 2004).

Structural modifications of EGCG. A series of monoester derivatives of EGCG were synthesized by lipase-catalyzed transesterification method for addition of long acyl chains (C16–18), and these derivatives have been shown to increase the stability of EGCG by 10 fold in tissue culture and exhibit potential antiviral activity against influenza A virus (H1N1), about 44-fold higher as compared to native EGCG, as well as exhibit potent antibacterial and antifungal activities (Mori et al., 2008; Matsumoto et al., 2012). Other groups also reported the synthesis of EGCG derivatives and evaluated their potential antitumor activities (Vyas et al., 2007; Tanaka et al., 2007).

EGCG-loaded nano-carriers based drug delivery system. Several studies have shown that encapsulation of EGCG with lipids, proteins, carbohydrates used as carriers in different nanoformulations, such as in nanoparticles, nanoemulsions, nanoliposomes or using other wall materials significantly improves the bioavailability of EGCG by enhancing its solubility, preventing its degradation in the intestinal environment and increasing its permeability in small intestine, resulting in increased concentrations in human bloodstream (Ye and Augustin, 2019; Dai et al., 2020). For instance, encapsulation of EGCG in chitosan nanoparticles significantly enhances the intestinal absorption of EGCG as compared to free EGCG in vitro study, possibly by increasing the stabilization of EGCG in intestinal fluid (Dube et al., 2010). A nanoliposome formulation of EGCG consisting of phospholipid, cholesterol, Tween 80 and EGCG in a mass ratio of 16: 2.4: 4 : 1, improves the stability of EGCG in intestinal fluid and sustained release property (Zou et al., 2014). Encapsulation of EGCG and its stearate derivative in double emulsions containing whey protein isolate, bacterial cellulose and salt, increases the absorption of EGCG by 1.93 fold higher than that of EGCG alone in rats (Evageliou et al., 2019). EGCG-loaded albumin nanoparticles have been reported to increase the concentration of EGCG in rat plasma by 1.5 fold (136 vs 53.1 μg/ml) and longer half-life of EGCG as compared to free EGCG after administration of a single dose of 10 mg/kg bw in rats. It was found to be safe upto a dose of 2000 mg/kg in rats (Ramesh et al., 2019).

Safe-dose of EGCG in long-term therapy

EGCG in high doses causes adverse effects including hepatotoxic, hypoglycaemic and anxiolytic effects. A daily dose of 800 mg caffeine-free EGCG for 4 weeks administration was reported to be safe and well-tolerated in healthy human individuals (Chow et al., 2003).

The major interactions of EGCG with host and viral proteases in modulation of their activities in prevention and treatment of SARS-CoV-2 infection and replication in host cells are summarized (Table 2).

Conclusions

The current coronavirus disease 2019 (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a worldwide emergency, as its rapid spread and high mortality rate has caused more than six million of death in the last two and half years. Despite the significant progress made in the understanding of SARS-Cov-

Table 2
Major therapeutic interactions of EGCG with host and viral proteases in modulation of their expression and activities for prevention of SARS-CoV-2 infection and replication in host cells.

Targets of EGCG against host/viral proteases	Functions of EGCG	References
Host Nrf2 response in epithelial cells	It reduces the expression of ACE2 and TMPRSS2 for suppression of viral entry in epithelial cells	Kesic et al., 2011
Viral spike (S) protein RBD	On binding to S-RBD, prevents the interaction of S-RBD with ACE2 in viral entry process	Liu et al., 2021; Tsvetkov et al., al., 2021; D. Zhang et al., 2021; LeBlanc and Colpitts, 2022
Host ER-stress regulatory GRP78	It inhibits the expression and ATPase activity of GRP78. On binding to SBD of GRP78, prevents the binding interaction with viral S protein and thereby reduces the interaction with ACE2 in viral entry	Reid et al., 2014; Allam et al., 2020
Viral 3CLpro (Mpro)	It inhibits the activity of 3CLpro in both in vitro assay and in molecular docking analysis	Du et al.,2021; Chiou et al., 2022
Host infected cellular HMGB1	EGCG inhibits the secretion of HMGB1 by suppression of endotoxemia/microbial infection-induced JAK/STAT1 activation and reduces the expression levels of HMGB1 by autophagic degradation	Wang et al., 2007; Li et al., 2007; N. Li et al., 2011; Lu et al., 2014
Host laminin receptor (67LR) in epithelial cells	EGCG activates 67LR for suppression of JNK1/2 phosphorylation and JNK-induced arterial thrombosis. EGCG also activates 67LR for upregulation of Tollip protein expression for downregulation of TLR4 signaling cascade	Holy et al., 2010 Byun et al., 2010
Host cellular protein tyrosine phosphatase and cytosolic Ca^{2+}ATPase	EGCG reduces virus ROS-dependent phosphorylation of PTP-1B for suppression of NF-κB activation and lymphocyte activation and decreases cytosolic Ca mobilization by maintenance of Ca^{2+}ATPase activity for inhibition of platelet aggregation	Kang et al., 1999 ; Jin et al., 2008
LOXL2 and Smad3 in host lung epithelial cells	EGCG inhibits LOXL2-dependent Smad3 phosphorylation for suppression of TGF-β1 expression and TGF-β1-induced lung fibrosis	Sriram et al., 2009, 2015; Chapman et al., 2020; Wei et al., 2021
Nrf2 in hepatocytes	EGCG promotes Nrf2 activation for synthesis of seleno proteins in hepatocytes	Dong et al., 2016
Cellular glycolysis-related enzymes HK, PFK, LDH, HIF-1α and GLUT1	EGCG reduces the expression and activities of HIF-1α, GLUT1, HK, PFK and LDH for suppression of HIF-1α-dependent glycolysis	Wei et al., 2018
Viral Nsp15 endoribonuclease	EGCG inhibits the activity in both in vitro assay and molecular docking analysis	Hong et al., 2021
Viral papain-like protease (PLpro)	EGCG inhibits its deubiquitinase and deISGylating activity in	Chourasia et al.,2021 ; Pitsillou et al., 2021

(*continued on next page*)

Table 2 (*continued*)

Targets of EGCG against host/viral proteases	Functions of EGCG	References
	both vitro assay and molecular docking analysis	
Viral RNA-dependent RNA polymerase (RdRp)	EGCG inhibits its activity in molecular docking analysis	Singh et al., 2021

2 pathology and clinical management of COVID-19 by the use of repurposed drugs and vaccines, the virus illness is still a health concern as outbreak continues to resurge due to emergence of mutant variants of SARS-CoV-2 virus, that resist the vaccines. Therefore, there is an urgent need for therapeutics that can block viral transmission and progression from infection to severe symptomatic illness.

Natural products could be a valuable source of drugs for the management of COVID-19 infection, because these compounds can act on multitargets and through different mechanisms including inhibition of viral entry and replication pathways, modulation of immune response and regulation of pathophysiological stress response.

The World Health Organization (WHO) has adopted a global strategy for the use of traditional medicine in modern biomedicine for a better care of health in patients suffering from COVID-19 infection by scientifically proving its quality, safety and efficacy and in achieving a goal of ensuring its access to all people.

In this review article, we have critically discussed the research findings from more than thirty research papers reported during the period, 2000–2022, on the anti-SARS-CoV-2 potential of EGCG, a major catechin constituent of popular green tea beverage, which has been consumed through the world for thousands of years as a safe drink (Park et al., 2021). All the studies confirmed the antiviral efficacy of EGCG in SARS-CoV-2 infection in different in vitro models or chemical docking models, none of these studies tested the antiviral efficacy of EGCG clinically in COVID-19 patients. In fact, the study of anti-SARS-CoV-2 activity of EGCG or green tea catechins extract in vivo models are more relevant for assessment of the efficacy of EGCG for treatment of COVID-19 patients. We have also discussed the findings on the bioavailability of EGCG from the reported pharmacokinetic and metabolism studies of EGCG or green tea catechins extract in humans. Furthermore, we have discussed the major factors influencing the poor bioavailability of EGCG (maximum concentration of EGCG in human plasma of about 0.16 μM after ingestion of a single oral dose of 200 mg of EGCG by human subjects and 0.32% of ingested EGCG) in humans. We have highlighted the steps for optimization of bioavailability of EGCG in humans. The main findings from the reported evidence in their studies are:

(a) EGCG inhibits the infection of SARS-CoV-2 original strain (Wuhan type) and other newly emergent variants by inhibition of viral entry in host cells and replication in infected host cells.
(b) EGCG inhibits the interaction of viral spike RBD with ACE2 receptor and reduces the expression of ACE2 in host cells for inhibition of viral entry.
(c) EGCG inhibits the expression levels of cellular stress responsive protein GRP78 and glycolytic enzymes and HIF-1α for inhibition of viral infection and replication.
(d) EGCG reduces viral replication by inhibition of the activities of viral main protease (3CLpro), papain-like protease (PLpro), RNA-dependent RNA polymerase (RdRp) and endoribonuclease Nsp15.
(e) EGCG inhibits virus-induced HMGB1 secretion into cytoplasm of infected host cells.
(f) EGCG prevents virus-induced cytokine storm in lung epithelial cells, lung fibrosis and thrombotic complications, possibly targeting PLpro activity.
(g) EGCG promotes Nrf2 signaling in host cells for suppression of ACE2 expression and stability of RAS.
(h) Most of the orally ingested EGCG decomposes in the environment of gastrointestinal tract fluid and only a small amount is absorbed in the small intestine.
(i) Uptake of EGCG in small intestine takes place by the activity of two efflux protein pumps, MRP1 and MRP2. The expression of MRP2 in human jejunum is about 10 fold higher than that of MRP1, resulting in predominant activity of MRP2 in the intestine leading to poor bioavailability of EGCG into bloodstream.
(j) In repeated dosing of EGCG or repeated green tea beverage drinking, bioavailability of EGCG in human plasma increases possibly by upregulation of EGCG transporter protein DTDST in human ileum.
(k) A major part of absorbed EGCG is metabolized by the phase II metabolizing enzymes, SULTs, UGTs and COMT in liver and small intestine, and by gut (colon) microbiota.
(l) EGCG-4″-sulfate is the major metabolite and its concentration in human plasma (C_{max}: 177.9 nM/L, $AUC_{0\rightarrow 6\ h}$ 715.2 nM.h/L) is almost equivalent to free EGCG (C_{max} :233.5 nM/L, $AUC_{0\rightarrow 6\ h}$: 664.1 nM/L) after ingestion of a single dose of green tea beverage containing 135 mg of EGCG.
(m) Gut microbiota convert EGCG into its 13 phenolic metabolites.
(n) Bioavailabilty of EGCG in human plasma may be optimised by oral intake of EGCG in empty stomach or with a mixture of ascorbic acid and sucrose or with piperine.
(o) Bioavailability of EGCG may be enhanced by its structural modification or its nanoformulations.
(p) The published EGCG-loaded nanoformulations studies reported the bioavailability of EGCG in rat models or in vitro models. The toxicities and pharmacokinetics of EGCG-loaded nanomaterials in humans are not yet evaluated.

From these findings, it is evident that poor bioavailability of EGCG in human plasma, due to low absorption in small intestine and extensive metabolism in liver, small intestine and colon, is one of key factors for use of EGCG as a therapeutic agent in the clinical trials in COVID-19 patients. As EGCG-4″ sulfate was identified in human plasma, the enzymes SULT1A1 and SULT1A3 are responsible for its formation in liver and intestine, suppression of the activity of these enzymes, may be a promising strategy for improvement of EGCG bioavailability. In pseudovirus infection assay, EGCG potentially inhibits the infections of spike of original SARS-CoV-2 virus strain and other mutants-derived pseudoviruses, suggesting its use in the formulation of vaccines against COVID-19 infection. A sorbitol/lecithin based throat spray containing green tea extract, rich in EGCG (having a concentration of EGCG in the range between 344 and 407 μg/ml saliva) significantly reduces the viral loads and infection in the saliva and GCF of COVID-19 patients (Kicker et al., 2022). It indicates that EGCG could be useful in the formulation of mouthwash for COVID-19 patients. Treatment of greenselect phytosome (GSP), a lecithin-based green tea catechin extract (300 mg, equivalent to 44.9 mg of EGCG/d) to breast cancer patients for 4 weeks, shows the levels of EGCG in plasma from 17 to 121 ng/ml (Lazzeroni et al., 2022). In another study, oral administration of EGCG and ascorbic acid loaded PEGylated PLGA nanoparticles in transgenic APP_{swe}/PS1dE9 mice, an Alzheimer's disease model in mice, increased the bioavailability of EGCG by about 5 fold at 5–25 h after administration of drug, in both plasma and brain and increased the therapeutic efficacy of EGCG in reduction of amyloid β (Aβ) plaque burden in mice brain, by increasing the stability of EGCG in gastrointestinal environment and intestinal absorption (Cano et al., 2019). These findings suggest that nanoformulation is the promising strategy for improvement of bioavailability of EGCG. However, in the preparation of these nanoparticles/nanoliposomes, the added organic solvents are not completely removed, which may lead to potential toxicity in humans. Moreover, the polymers used in the formulation of nanoparticles are also toxic to

humans in long-term therapy (Amoabediny et al., 2018).

Therefore, future study on the enhancement of bioavailability, dose levels, administration frequency and potential adverse effects including toxicity in long-term treatment of EGCG is needed to utilize the beneficial effects of EGCG as clinical medicine for prophylaxis and treatment against SARS-CoV-2 infection in COVID-19 patients.

Funding

This work was not supported by any specific funding agencies in the public, commercial or profit sectors.

CRediT authorship contribution statement

Biswanath Dinda: Conceptualization, Data curation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **Subhajit Dinda:** Data curation, Software, Writing – original draft, Writing – review & editing. **Manikarna Dinda:** Resources, Software, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

Author M.D. is thankful to the Department of Biochemistry and Molecular Genetics, University of Virginia, Charlottesville, USA for the award of a PDF in the research group of Prof. J.S. Smith.

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