Potential protective mechanisms of green tea polyphenol EGCG against COVID-19

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ABSTRACT

Background: The world is in the midst of the COVID-19 pandemic. In this comprehensive review, we discuss the potential protective effects of (−)-epigallocatechin-3-gallate (EGCG), a major constituent of green tea, against COVID-19.
Scope and approach: Information from literature of clinical symptoms and molecular pathology of COVID-19 as well as relevant publications in which EGCG shows potential protective activities against COVID-19 is integrated and evaluated.
Key findings and conclusions: EGCG, via activating Nrf2, can suppress ACE2 (a cellular receptor for SARS-CoV-2) and TMPRSS2, which mediate cell entry of the virus. Through inhibition of SARS-CoV-2 main protease, EGCG may inhibit viral reproduction. EGCG via its broad antioxidant activity may protect against SARS-CoV-2 evoked mitochondrial ROS (which promote SARS-CoV-2 replication) and against ROS burst inflicted by neutrophil extracellular traps. By suppressing ER-resident GRP78 activity and expression, EGCG can potentially inhibit SARS-CoV-2 life cycle. EGCG also shows protective effects against 1) cytokine storm-associated acute lung injury/acute respiratory distress syndrome, 2) thrombosis via suppressing tissue factors and activating platelets, 3) sepsis by inactivating redox-sensitive HMGB1, and 4) lung fibrosis through augmenting Nrf2 and suppressing NF-κB. These activities remain to be further substantiated in animals and humans. The possible concerted actions of EGCG suggest the importance of further studies on the prevention and treatment of COVID-19 in humans. These results also call for epidemiological studies on potential preventive effects of green tea drinking on COVID-19.

1. Introduction

Green tea, made from the leaves of the plant *Camelia sinensis*, is a popular drink worldwide. Historically, tea was used as a medicinal herb to treat a variety of diseases. In scientific studies during the past decades, green tea and its characteristic polyphenols, catechins, have been shown to have activities in the prevention of obesity, diabetes, cardiovascular diseases, cancer, and other diseases (Yang & Hong, 2013; Yang & Zhang, 2019). Tea catechins have also been shown to have anti-viral activities (Kaihatsu, Yamabe, & Ebara, 2018; Steinmann, Buer, Pietschmann, & Steinmann, 2013; Xu, Xu, & Zheng, 2017), as well as protective activities against diseases caused by oxidative stress and inflammation. Many of these activities may help alleviate the devastating pandemic of COVID-19, caused by the virus SARS-CoV-2. Just in the United States alone, there have been more than 26 million cases of COVID-19 and 0.44 million deaths by February 2021, currently with an all-time high daily death rate of over 3000 per day. There have been three recent articles suggesting the possible prevention and treatment of COVID-19 by tea (Chowdhury & Barooah, 2020; Menegazzi et al., 2020; Mhatre, Srivastava, Naik, & Patravale, 2020). The major active constituent is (−)-epigallocatechin-3-gallate (EGCG), the most abundant catechin in

Abbreviations

ACE2   angiotensin-converting enzyme 2
ALI   acute lung injury
ARDS   acute respiratory distress syndrome
DAMPs   damage-associated molecular patterns
EGCG   epigallocatechin-3-gallate
ER   endoplasmic reticulum
ERAD   ER-associated degradation
GPX   glutathione peroxidase
GST   glutathione S-transferase
HMGB1   high mobility group box 1
ICU   intensive care unit
LPS   lipopolysaccharides
M^{pro} main protease
NETs   neutrophil extracellular traps
NOX   NADPH oxidases
Nrf2   nuclear factor erythroid 2 p45-related factor 2
RAGE   receptor for advanced glycation end products
ROS   reactive oxygen species
SOD   superoxide dismutase

green tea. Green tea also contains other catechins, such as (−)-epi-gallocatechin, (−)-epicatechin-3-gallate and (−)-epicatechin. The structures of these catechins are shown in Fig. 1. This article is a comprehensive review of the mechanisms by which EGCG may inhibit SARS-CoV-2 infection and the different syndromes associated with COVID-19. The published results in the literature are critically evaluated – with the perspective of biological differences between rodents and humans, dose response relationships and possible side effects – to assess the possibility that EGCG or tea consumption can be useful for the prevention, alleviation and treatment of this pandemic disease.

2. EGCG, biological activities, and general anti-viral activities

EGCG, with a polyphenolic structure, is well recognized as a strong antioxidant through its activities in quenching reactive radicals and chelating metal ions to prevent the formation of reactive oxygen species (ROS). However, this redox-active molecule also undergoes auto-oxidation to produce superoxide radical and hydrogen peroxide. In cell lines, it can also be oxidized in the mitochondria to produce ROS (Tao, Forester, & Lambert, 2014; Tao, Park, & Lambert, 2015). At moderate levels of EGCG, the ROS produced can be beneficial via in-duction of nuclear factor erythroid 2 p45-related factor 2 (Nrf2) -mediated antioxidant and cytoprotective enzymes (Dong et al., 2016; Na et al., 2008; Sun et al., 2017; Yang et al., 2018), generally referred to as the indirect antioxidant activity of EGCG. These enzymes play far more important roles in cytoprotection than the free radical scavenging ac-tivity of EGCG. However, higher levels of ROS can cause oxidative stress, cellular damage and side effects, mainly hepatotoxicity (Yang & Zhang, 2019). In vivo, EGCG can also be oxidized to quinones, which can react with sulfhydryl groups of cellular proteins, leading to the loss of function.

EGCG, with eight phenolic groups, provides multiple electron ac-ceptors and donors for hydrogen bonding to a variety of molecules, especially to proteins. This is one of the reasons why EGCG has been shown to bind to many different proteins with high affinity and inhibit their activities. In studies in cell free systems, this is especially true as the inhibitory activity is stronger when lower concentrations of proteins are used in the assay. Without detailed characterization of the specificity or reversibility of the binding, these types of studies may result in the false identification of proteins as being "targets" for EGCG. The different activities and low bioavailability of EGCG makes extrapolation of results from in vitro studies to in vivo situations difficult.

With these chemical reactivities, EGCG has been shown to have many different biological effects, including anti-viral activities and these have been reviewed (Kaihatsu et al., 2018; Steinmann et al., 2013; Xu,
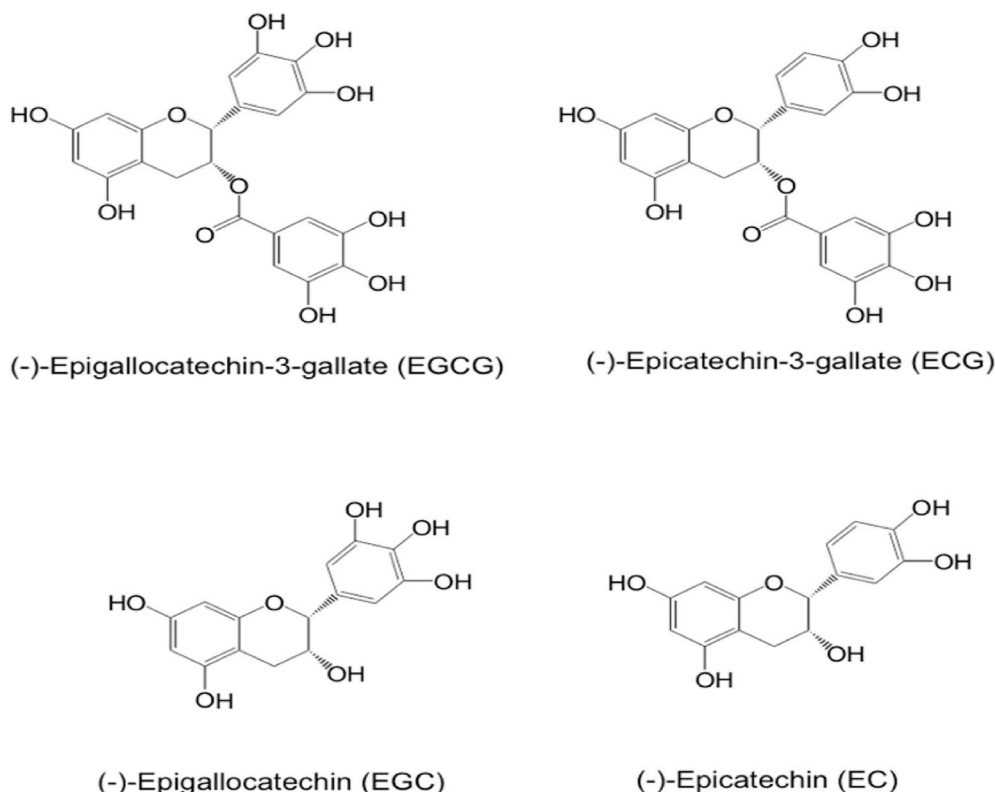

Fig. 1. Chemical structure of major green tea catechins.

Xu, & Zheng, 2017). EGCG has been shown to possess a broad spectrum of antiviral activities against RNA viruses such as hepatitis C virus, human immunodeficiency virus, Ebola virus and influenza virus, Zika virus, Dengue virus, West Nile viruses, Chikungunya virus, human porcine reproductive and respiratory virus; as well as DNA viruses such as herpes simplex virus, human papillomavirus, and hepatitis B virus. The structure-activity relationship of different catechins has been studied; EGCG has the highest activity, and the 3-galloyl and 5′-OH groups of EGCG appear crucial for the anti-viral activity (Kaihatsu et al., 2018).

EGCG mainly inhibits the early stages of viral infection, such as attachment, entry, and membrane fusion, by interfering with either viral membrane proteins or host cellular proteins or both. EGCG-fatty acid monoesters, which bind more effectively to viral and cellular membranes, have been shown to improve the anti-viral activity of EGCG against influenza and other viruses (Kaihatsu et al., 2018; Mhatre et al., 2020; Steinmann et al., 2013; Xu, Xu, & Zheng, 2017). Most of these studies were conducted in vitro under conditions that may be very different from those situations in humans, and these results should be interpreted with caution.

Many attempts have been made in developing EGCG into a therapeutic drug. Of note is that Veregen, a green tea polyphenol ornament preparation with EGCG as the major constituent, has been approved by the Food and Drug Administration (FDA) and European Medicine Agent (EMA) as a drug for topical treatment of external genital and anal warts caused by papillomavirus (Hara, 2011). The key reason of the success is topical application. How to deliver an effective dose of EGCG to the site of anti-viral action is a challenging issue in therapeutic application.

3. EGCG may reduce SARS-CoV-2 infection via activation of Nrf2

Nrf2, the cytoprotective transcription factor, regulates expression of a wide array of genes involved in antioxidation, detoxification, inflammation, immunity and antiviral responses (Mendonca & Soliman, 2020). Nrf2 knockdown in differentiated human nasal epithelial cells increases virus entry and replication, while Nrf2 activators, such as EGCG and sulforaphane, decrease viral entry and replication (Kesic, Simmons, Bauer, & Jaspers, 2011). Many other studies also showed that genetic and pharmacological manipulations to activate the Nrf2 pathway can inhibit viral replication and prevent virus-induced oxidative damage and inflammation (Lee, 2018).

SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as the receptor for cell entry and serine protease TMPRSS2 for spike protein priming (Hoffmann et al., 2020). These are the two crucial steps for cell entry of coronaviruses. Nrf2-activator PB125® downregulates the mRNA expression of both ACE2 and TMPRSS2 in human HepG2 cells (McCord, Hybertson, Cota-Gomez, Geraci, & Gao, 2020). Genetic deletion of Nrf2 or pharmacological inhibition of Nrf2 upregulates *ACE2* expression in renal proximal tubule cells; whereas its activator, oltipraz, downregulates *ACE2* expression (Zhao et al., 2018). Genes associated with Nrf2-dependent antioxidant response are highly suppressed in lung biopsies from COVID-19 patients, and Nrf2 inducers (4-octyl-itaconate and dimethyl fumarate) inhibit SARS-CoV-2 replication and inflammatory response (Cuadrado et al., 2020; Olagnier et al., 2020). These lines of evidence suggest that Nrf2 activation is a promising strategy to prevent the infection of SARS-CoV-2 and reduce the severity of COVID-19.

A large number of studies have shown that EGCG induces Nrf2-mediated antioxidant enzyme expression (Dong et al., 2016; Na et al., 2008; Na & Surh, 2008). In differentiated human nasal epithelial cells, pre-incubation with EGCG (1 μM) decreases influenza virus entry and replication, via activating Nrf2 (Kesic et al., 2011). The suppressive effects of EGCG cannot be observed in cells with knocked-down Nrf2 expression.

As discussed above, EGCG as an Nrf2 activator can inhibit the entry of SARS-CoV-2 into host cells (McCord et al., 2020), and prime host cells against SARS-CoV-2 infection (Kesic et al., 2011). In addition, through the activation of Nrf-2 regulated heme oxygenase 1, EGCG can mediate

antiviral responses by increasing the expression of type 1 interferons (Cuadrado et al., 2020; Espinoza, González, & Kalergis, 2017) and alleviating SARS-CoV-2-initiated inflammatory responses through crosstalk of Nrf2 and NF-κB in inflamed tissues, where innate immune cells are recruited (Cuadrado et al., 2020). It remains to be demonstrated whether EGCG can activate Nrf2 to such an extent in vivo to exert these possible actions.

4. EGCG may suppress SARS-CoV-2 replication via inhibiting main protease (M^{pro})

The replicase gene of SARS-CoV-2 encodes two overlapping polyproteins for viral replication and transcription. The pp1a and pp1ab polyproteins undergo extensive proteolytic processing, mainly mediated by a 33.8-kDa main protease (M^{pro}), to yield functional polypeptides. M^{pro}, also known as the 3C-like protease, plays a vital role in mediating the life cycle of SARS-CoV-2. There is no human homolog of M^{pro}. These features make it an attractive target for antiviral drug development. M^{pro} is a three-domain (domains I to III) cysteine protease and has a non-canonical Cys145-His41 dyad located in the cleft between domains I and II. Synthetic compounds with high activity in modifying Cys145 of M^{pro} exhibit strong inhibitory effect on the enzymatic activity of M^{pro} and anti-infection potency against SARS-CoV-2 (Dai et al., 2020). In a study evaluating potential medicinal herbs for M^{pro} inhibition, green tea extract is highly effective in inhibiting M^{pro} of SARS-COV-2 (Upadhyay et al., 2020). Green tea extract or EGCG shows a dose-dependent inhibitory activity against M^{pro} of SARS-CoV-2 in vitro, with an IC_{50} value of 2.8 μg/mL or 7.5 μM, respectively (Zhu & Xie, 2020). These concentrations will be compared with EGCG concentrations in humans in Section 12. Molecular docking shows that EGCG has higher binding affinity (−7.6 kcal/mol) than a well-recognized M^{pro} inhibitor N3 (−7.0 kcal/mol), and suggests that EGCG strongly interacts with His41 and Cys145, the catalytic moiety of M^{pro} of SARS-CoV-2 (Ghosh, Chakraborty, Biswas, & Chowdhuri, 2020). Another in-silico study also identified EGCG as a potential inhibitor of M^{pro} (Sharma & Deep, 2020). A recent study found that EGCG from 1 to 20 μg/mL inhibited M^{pro} activity and replication of HCoV-OC43 (a type of beta coronavirus, similar to SARS-CoV-2) in a dose-dependent manner, and even 1 μg/mL EGCG was able to significantly reduce levels of HCoV-OC43 proteins in the infected cells (Jang et al., 2021).

EGCG auto-oxidation leads to the formation of EGCG quinone, which can react with protein cysteinyl thiol to form quinone proteins (Ishii et al., 2008; Zhang et al., 2017). Via quinone protein formation, EGCG can irreversibly inhibit glyceraldehyde-3-phosphate dehydrogenase (Ishii et al., 2008). It is possible that EGCG can inhibit M^{pro} of SARS-CoV-2 by covalent bonding to Cys145 and this possibility remains to be investigated.

In addition to M^{pro}, EGCG interferes with SARS-CoV-2 spike-receptor interaction and blocks the entry of SARS-CoV-2 pseudotyped lentiviral vectors with an IC_{50} value of 2.5 μg/mL (Henss et al., 2021). Studies in silico suggest that EGCG may also inhibit papain-like protease protein via binding to its S1 ubiquitin-binding site and impede COVID-19 (Chourasia, Koppula, Battu, Ouseph, & Singh, 2021). Based on these studies, ChourasIia et al. suggested that EGCG may serve as a broad spectrum therapeutic in asymptomatic and symptomatic COVID-19 patients (Chourasia et al., 2021).

5. Oxidative stress prevention and mitochondria protection by EGCG

In general, respiratory viruses augment ROS production in host cells (Khomich, Kochetkov, Bartosch, & Ivanov, 2018). SARS-CoV-2 increases oxidative stress of host cells by at least the three following mechanisms.

a. *Suppressing antioxidant enzymes and activate pro-oxidant enzymes.* Respiratory syncytial virus infection decreases antioxidant and

detoxifying enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPX) and glutathione S-transferase (GST), and suppresses Nrf2 expression in murine lungs. The infection also significantly decreases these enzymes in the airways of children with severe bronchiolitis. Severity of clinical illness in infected infants correlates with the decrease of these enzymes (Hosakote et al., 2011). Similarly, decreased expression of SOD3 in the lungs of elderly COVID-19 patients correlates with disease severity (Laforge et al., 2020). Blood SELENOP which is secreted from the liver for selenium delivery is dramatically lowered in severe COVID-19 patients (Moghaddam et al., 2020), probably due to pronounced hypoxia and/or marked IL-6 elevation that suppress hepatic *SELENOP* (Becker et al., 2014; Martitz et al., 2015). Thus, severe COVID-19 patients have an impaired biosynthesis of selenoproteins, most of which have antioxidant functions via selenocysteins in their active sites (Zhang, Saad, Taylor, & Rayman, 2020). Respiratory viruses are known to induce ROS-generating enzymes such as NADPH oxidases (NOX) (Fink, Duval, Martel, Soucy-Faulkner, & Grandvaux, 2008; Kaul, Biagioli, Singh, & Turner, 2000; Khomich et al., 2018; To et al., 2017). Inhibition of NOX2 activity ameliorates influenza A virus-induced lung inflammation (Vlahos et al., 2011), while NOX2 activation is associated with severe disease and thrombotic events in COVID-19 patients (Violi et al., 2020).

b. *Inducing neutrophil extracellular traps (NETs) and ROS burst.* Neutrophils are recruited early to sites of infection to destroy viruses intracellularly by "cellular atomic bomb" composed of potent oxidants and free radicals (superoxide anion, hydrogen peroxide, hypochlorous acid, peroxynitrite and hydroxyl radicals) (Kalyanaraman, 2020). Moreover, neutrophils can ensnare viruses to kill them extracellularly via formation of NETs, which are web-like structures of DNA and proteins expelled from neutrophils. NETs as an aggressive defense mechanism are a double-edged sword. Timely and moderate NETs are beneficial in host defense against viruses; however, excessive and sustained NETs lead to ROS burst causing collateral lung damages (Barnes et al., 2020; Laforge et al., 2020; Schönrich, Raftery, & Samstag, 2020; Wu, 2020). Neutrophil infiltration has been shown in autopsied COVID-19 patients. Enhanced release of NETs occurs in severe cases of COVID-19 (Wang et al., 2020; Zuo et al., 2020a; Zuo et al., 2020b). Even sera from COVID-19 patients can cause NET release from control neutrophils in vitro (Zuo et al., 2020b).

c. *Evoking hypoxia-associated ROS production.* Pronounced hypoxia is a hallmark of severe SARS-CoV-2 infection (Potus et al., 2020). In COVID-19 patients, the severity of hypoxemia is independently associated with in-hospital mortality and an important predictor of intensive care unit (ICU) admission (Kashani, 2020; Xie et al., 2020). The lung is responsible for maintaining an adequate oxygenation in the organism. Hypoxia enhances the generation of superoxide anions and increases release of ROS from the inner mitochondrial membrane to the intermembrane space in the lung, resulting in disruption of redox balance (Araneda & Tuesta, 2012; Schumacker, 2011). Hypoxia also increases pulmonary ROS production via inducing NOX4, xanthine oxidase/reductase or endothelial/inducible nitric oxide synthases (Araneda & Tuesta, 2012). Hypoxia-induced pulmonary oxidative stress promotes vasoconstriction, edema, inflammation, vascular remodeling and pulmonary hypertension (Araneda & Tuesta, 2012; Fresquet et al., 2006; Hoshikawa et al., 2001; Liu, Zelko, Erbynn, Sham, & Folz, 2006).

Oxidative stress caused by SARS-CoV-2 not only promotes tissue damage but also accelerates virus replication. Monocytes from COVID-19 patients exhibited mitochondrial dysfunction (Gibellini et al., 2020). Age-related mitochondrial dysfunction is proposed as an enhancing factor in COVID-19 disease (Moreno Fernandez-Ayala, Navas, & Lopez-Luch, 2020). SARS-CoV-2-infected monocytes have increased mitochondrial ROS production. Treatment of the monocytes with

antioxidants such as mitoquinol or *N*-acetylcysteine almost fully inhibits SARS-CoV-2 replication (Codo et al., 2020). ROS are strong inducers of HIF-1α, which is a potent inducer of glycolysis. SARS-CoV-2-infected monocytes thus express high levels of HIF-1α and become highly glycolytic (Codo et al., 2020). Inhibition of rate-limiting enzyme of glycolysis (hexokinase) by 2-deoxy-D-glucose prevents SARS-CoV-2 replication (Bojkova et al., 2020; Codo et al., 2020). Likewise, HIF-1α inhibitor blocks SARS-CoV-2 replication, whereas HIF-1α stabilization increases SARS-CoV-2 replication (Codo et al., 2020). Concerning the ROS/HIF-1α/glycolysis axis pivotal for SARS-CoV-2 replication, modulation at each level has shown promising result.

Respiratory virus-induced oxidative damage and ROS-facilitated SARS-CoV-2 replication justify antioxidant therapeutic strategy for vulnerable COVID-19 patients (Laforge et al., 2020; Schönrich et al., 2020; Wu, 2020). *N*-acetylcysteine thus has been proposed to be used as preventive and adjuvant therapy of COVID-19 (De Flora, Balansky, & La Maestra, 2020). EGCG can directly scavenge multiple types of ROS and induce antioxidant and detoxifying enzymes, such as heme oxygenase 1, quinone reductase, glutamate cysteine ligase, GST, thioredoxin reductase, glutaredoxin, glutathione reductase, SOD, catalase and GPX (Dong et al., 2016; Na & Surh, 2008). In addition, EGCG can suppress NOX expression or activity in various disease models (Ahn, Kim, & Ha, 2010; Li et al., 2006; Nishikawa, Wakano, & Kitani, 2007; Sarkar, Chakraborti, Chowdhury, Bhuyan, & Chakraborti, 2019; Yao et al., 2009). Concerning viral infection, EGCG alleviates enterovirus 71-induced oxidative stress and impedes related enterovirus 71 reproduction in Vero cells (Ho, Cheng, Weng, Leu, & Chiu, 2009).

EGCG prevents mitochondrial dysfunction in diseases such as Down syndrome (Scala et al., 2021; Vacca & Valenti, 2015; Valenti et al., 2018). It has been reported that in primary cultures of rat neuronal cells, EGCG selectively accumulates in the mitochondria, where it acts locally as a free radical scavenger to protect cells from apoptosis induced by mitochondrial oxidative stress (Schroeder et al., 2009). Pre-treatment of rats with EGCG (30 mg/kg, i.g. for 21 days) prevents cardiac mitochondria from oxidative damage in isoproterenol-induced myocardial infarction (Devika & Stanely Mainzen Prince, 2008). Oxidative stress induced by hypoxia contributes to the development of pulmonary vascular remodeling and pulmonary hypertension (Araneda & Tuesta, 2012; Fresquet et al., 2006; Hoshikawa et al., 2001; Liu et al., 2006). EGCG (50, 100 or 200 mg/kg/d, i.g.) dose-dependently suppresses hypoxia-induced elevation of right ventricular systolic pressure, pulmonary vascular remodeling and right ventricular hypertrophy in rats (Zhu et al., 2017), suggesting that EGCG could ameliorate hypoxia-induced oxidative stress. Whether EGCG can impede SARS-CoV-2 triggered NETs and hypoxia associated oxidative stress in humans remains to be investigated.

6. Suppression of endoplasmic reticulum stress by EGCG

Coronavirus replication induces endoplasmic reticulum (ER) stress and the unfolded protein response in infected cells (Chan et al., 2006; Liao et al., 2013; Sureda et al., 2020; Versteeg, van de Nes, Bredenbeek, & Spaan, 2007). SARS-CoV-2 is known to simultaneously suppress the expression of *SELENOF*, *SELENOM*, *SELENOK* and *SELENOS* in Vero cells (Wang et al., 2021). Since hepatic SELENOP is essential for selenium delivery to other tissues for selenoprotein synthesis (Becker et al., 2014; Martitz et al., 2015), suppression of SELENOP in SARS-CoV-2 infection could cause synergistic suppression of ER-resident SELENOF, SELENOM, SELENOK and SELENOS via transcriptional and translational inhibition. SELENOF and SELENOM catalyze the reduction or rearrangement of disulfide bonds in ER-localized proteins and facilitate ER protein-folding. Impaired SELENOF and SELENOM increase misfolded proteins, causing ER stress. SELENOK and SELENOS promote ER-associated degradation (ERAD) of errant proteins. Impaired SELENOK and SELENOS attenuate ERAD of misfolded proteins (Labunskyy, Hatfield, & Gladyshev, 2014). Therefore, SARS-CoV-2 infection induces

a strong ER stress. This idea is supported by the observations that serum glucose-regulated protein 78 (GRP78), an ER stress marker, increases by 7-fold in SARS-COV-2 Infected patients compared to healthy controls (Köseler, Sabirli, Gören, Türkçüer, & Kurt, 2020), and GRP78 mRNA levels are four times higher in the blood of SARS-CoV-2 positive versus SARS-CoV-2 negative pneumonia patients (Palmeira et al., 2020).

GRP78, as a sensor of ER stress, has been recognized as an essential chaperone required for the life cycle of DNA or RNA viruses (Booth et al., 2016; Dimcheff, Faasse, McAtee, & Portis, 2004; Earl, Moss, & Doms, 1991; Goodwin et al., 2011; Rayner et al., 2020; Xu, Bellamy, & Taylor, 1998). ER stress induced by viral infection promotes GRP78 membrane translocation. Cell surface GRP78 mediates the entry of viruses, Ebola, and molecular docking shows that SARS-CoV-2 spike protein can bind cell surface GRP78 (Ibrahim, Abdelmalek, Elshahat, & Elfiky, 2020; Palmeira et al., 2020). During viral replication within cells, ER-localized GRP78, which is increased in response to high load of unfolded viral proteins, maintains ER homeostasis for proper folding, processing and assembly of viral proteins, such as spike protein (Chan et al., 2006; Yeung et al., 2008). However, mature virions hijack GRP78 as an accessory host factor for enhanced infectivity (Ha, Van Krieken, Carlos, & Lee, 2020). For these reasons, GRP78 is a promising therapeutic target for coronavirus infection (Wan, Song, Li, & He, 2020). Indeed, AR-12 (OSU-03012), which inhibits ATPase activity of GRP78 and decreases GRP78 protein expression, dose-dependently inhibits SARS-CoV-2 spike protein expression in transfected or infected cells (Rayner et al., 2020). Moreover, AR-12 suppresses replication of various viruses, and reduces liver injury and prolongs survival in rabbits infected with hemorrhagic fever viruses (Booth et al., 2016).

Direct and specific interaction between EGCG and GRP78 has been demonstrated in cell-free system and in cultured cells. EGCG binding at the ATP-binding site of GRP78 inhibits ATPase activity and changes GRP78 from active monomer to inactive dimer and oligomer forms (Ermakova et al., 2006). It has been suggested that, via inhibiting GRP78, EGCG suppresses Ebola virus replication (Reid et al., 2014) and avian reovirus S1133-induced apoptosis (Lin et al., 2015). Moreover, EGCG has been shown to downregulate GRP78 protein expression induced by cisplatin in mice (Chen et al., 2015), by amyloid β-induced in neuronal cells and in vivo (Du et al., 2018), by high glucose in podocytes and by hydrogen peroxide or calcium disterbance in mouse retinal pigment epithelial cells (Karthikeyan et al., 2017; Xiang et al., 2017). These interesting activities of EGCG in suppressing GRP78 protein levels and the catalytic activity, if can be demonstrated in humans, EGCG may be useful in protecting against SARS-CoV-2 infection.

7. Impediment of cytokine storm by EGCG

The cytokine storm is characterized as a sudden acute increase in circulating levels of different pro-inflammatory cytokines. SARS-CoV-2 infection in some individuals induces a hyperactive and uncontrolled immune response. Several types of immune cells including T-lymphocytes, macrophages, dendritic cells and neutrophils secret immense amounts of pro-inflammatory cytokines (IFNα, IFNγ, IL-6, IL-1β, IL-12, IL-18, IL-33, TNFα, TGFβ, etc.) and chemokines (CXCL8, CXCL9, CXCL10, CCL2, CCL3, CCL5, etc.), leading to acute respiratory distress syndrome (ARDS) and systemic inflammatory responses (see Fig. 2). Cytokine storm is a life-threatening condition requiring immediate ICU admission. Cytokine storm is directly correlated with multi-organ failure and high case fatality rate. In addition to anti-viral therapies, anti-
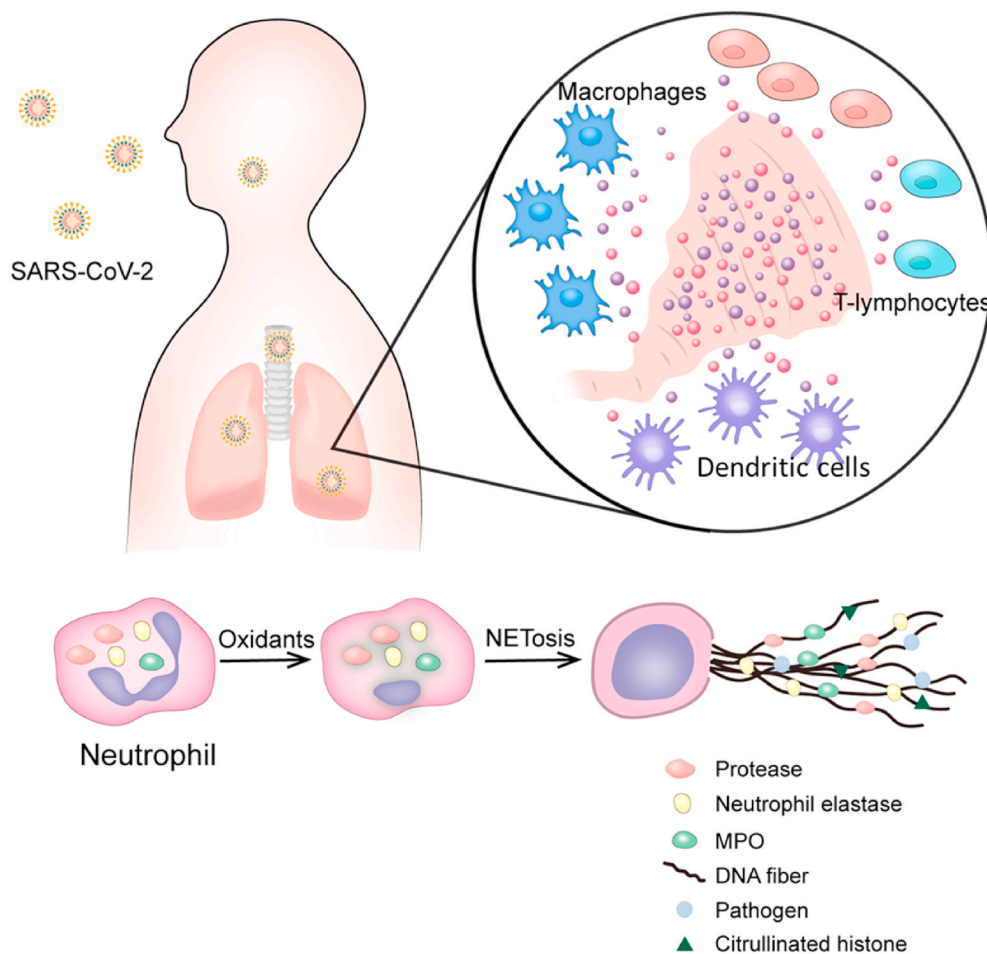
Fig. 2. Cytokine storm development after SARS-CoV-2 infection. SARS-CoV-2 induces a maladaptive and uncontrolled generalized immune response. Immune cells like T-lymphocytes, macrophages and dendritic cells secrete immense amounts of cytokines and chemokines. Neutrophils and neutrophil extracellular traps (NETs) further fuel the hyper-inflammation that again stimulates NETs, causing a feedback snowballing effect and eventually leading to ARDS. Modified from (Kalyanaraman, 2020) and (Coperchini et al., 2020).

inflammatory therapies that suppress cytokine storm are crucial for reducing mortality of severe and critical COVID-19 patients. IL-6 is frequently increased in COVID-19 patients, and its levels are positively associated to COVID-19 mortality. Tocilizumab (a recombinant humanized anti-human IL-6 receptor monoclonal antibody) has shown therapeutic results in severe and critical COVID-19 patients (Bohn et al., 2020; Coperchini, Chiovato, Croce, Magri, & Rotondi, 2020; Ragab, Salah Eldin, Taeimah, Khattab, & Salem, 2020; Tang, Liu, et al., 2020; Xu et al., 2020).

Many studies have shown that EGCG is highly effective in attenuating acute lung injury (ALI)/ARDS induced by virus, lipopolysaccharides (LPS) and other factors. Following the infection of H9N2 swine influenza virus in mice, administration of EGCG (10 mg/kg, i.g.) daily for 5 consecutive days significantly prolongs mouse survival and reduces death rate from 65% to 35%; attenuates lung histological lesions (inflammatory cell margination and infiltration, alveolar and interstitial edema, and bronchiolitis); decreases lung wet/dry ratio; suppresses total WBC count and leukocyte differential counts in bronchoalveolar lavage fluid; and lowers cytokines levels in the lung by downregulating TLR4 and NF-κB (Xu, Liu, et al., 2017). EGCG (40 mg/kg, i.g.) administered 3 days prior to influenza A virus infection in mice (followed with additional 2 daily EGCG treatments) significantly reduces death rate from 83.3% to 33.3%, decreases viral titers in the lung by 74-fold, and alleviates virus-evoked lung lesion (Ling et al., 2012).

In an LPS-induced mouse model of ALI, EGCG (15 mg/kg, i.p.) 1 h before and 3 h after LPS instillation mitigates ALI, neutrophils infiltration and the increase of M1/M2 macrophages subtype ratio (Almatroodi et al., 2020). In a similar model, EGCG (10 mg/kg, i.p.) administered 1 h before LPS injection in mice lowers the LPS-induced high PaCO$_2$/RR ratio; histological lesions; and the elevation of IL-6, TNFα and IL-1β in the lung, serum and bronchoalveolar lavage fluid (Wang, Fan, & Zhang, 2019). Similarly, EGCG (10 mg/kg, i.p.) 1 h before intratracheal administration of LPS in mice, reduces histological severities and the elevation of TNFα, MIP-2 and neutrophils in the lung (Bae et al., 2010).

EGCG is also effective in other rodent models of ALI/ARDS: 1) EGCG (10 mg/kg, i.v.), immediately after the infliction of thermal injury in rats, significantly reduces plasma concentrations of inflammatory mediator and severity of ARDS (Liu et al., 2017). 2) EGCG (10 mg/kg, i. p.) 10 min before inflicting hip fracture in rats significantly reduces the elevated lung injury (Zhang et al., 2010; Zhao, Liu, Li, Gong, & Zhang, 2017) and infiltration of inflammatory cells in the bronchoalveolar lavage fluid (Zhao et al., 2017). 3) EGCG (20 mg/kg, i.p.), 1, 24 and 48 h after paraquat administration in mice, attenuates ALI, the activation of NF-κB and upregulation of toll-like receptor 2, 4 and 9, as well as their adaptors MyD88 and TRAF6 in the lung (Shen, Wu, Liu, Zhao, & Zhao, 2017). 4) EGCG (10 mg/kg, i.p.) 30 min before seawater instillation into the lung in rats significantly reduces hypoxia, pulmonary edema, lung vascular leak, and levels of TNFα and IL-1 (Liu et al., 2014). 5) EGCG (25 mg/kg, administered as green tea extract i.p.) 1 h prior to pleural injection of carrageenan in mice, reduces acute inflammatory responses (interstitial haemorrhage, polymorphonuclear leukocyte infiltration, increased TNFα and activated STAT1) in lung tissues (Di Paola et al., 2005). Altogether, low to moderate doses of EGCG have consistently shown an inhibitory effect of ALI/ARDS in rodent models initiated by various challenges including RNA viruses. If such activities can be demonstrated in humans, EGCG may be useful to curb SARS-CoV-2 triggered cytokine storm and ARDS.

8. Sepsis prevention by EGCG

Sepsis, an infection-triggered systemic inflammatory response syndrome, is a common complication of severe and critical COVID-19 patients. High mobility group box 1 (HMGB1), released by activated monocytes, macrophages or neutrophils, acts as a late mediator of sepsis and is a crucial therapeutic target for preventing sepsis-triggered lethality (Yang et al., 2004). Administration of antibodies against

HMGB1 attenuates endotoxin lethality in mice (Wang et al., 1999). Elevated serum levels of HMGB1 at hospital admission are correlated with inferior clinical outcomes in COVID-19 patients (Chen et al., 2020). HMGB1 has been postulated as a therapeutic target of COVID-19 (Andersson, Ottestad, & Tracey, 2020; Menegazzi et al., 2020; Street, 2020; Tang, Comish, & Kang, 2020).

HMGB1 is a redox-sensitive protein containing three conserved cysteine residues at the amino acid sequence of 23, 45 and 106. Redox modification of these cysteines affects its extracellular chemokine- or cytokine-inducing properties (Yang et al., 2015). Specifically, fully reduced HMGB1 binds to CXCL12 and stimulates immune cell infiltration; disulfide HMGB1 (with a Cys23-Cys45 disulfide bond and a reduced Cys106) activates immune cells to produce cytokines/chemokines; and sulfonyl HMGB1 (all three cysteines are oxidized) loses its activity in modulating chemokines and cytokines (Venereau et al., 2012; Yang et al., 2015). EGCG can conjugate with purified HMGB1 protein to form quinone proteins, which can be visualized by nitrobluetetrazolium staining. In the presence of dithiothreitol, quinone protein formation is prevented, suggesting that free cysteines of HMGB1 participate in the covalent conjugation (Li et al., 2011). EGCG also reduces cytoplasmic HMGB1 levels in endotoxin-stimulated macrophages (Li et al., 2011). In addition to the redox modification of cysteines, the inhibitory effect of EGCG on STAT1 activation (Menegazzi et al., 2001, 2020; Townsend et al., 2004) may also play a role in reducing cytoplasmic HMGB1. JAK/STAT1 pathway regulates HMGB1 cytoplasmic accumulation (Lu et al., 2014). JAK/STAT1 inhibition decreases HMGB1 release and enhances survival in animal models of lethal sepsis and endotoxemia (Kim et al., 2009; Lu et al., 2014).

There are two studies demonstrating that treatment with as low as 4 mg/kg EGCG (i.p.), following the onset of sepsis (induced by cecal ligation and puncture) in mice, effectively reduces mortality, possibly involving HMGB1 inhibition (Li et al., 2007, 2011). Another study in rodent models found that treatment with EGCG, after cecal ligation and puncture, significantly improve survival and septic shock, as indicated by hypotension (Wheeler et al., 2007). In mouse model of LPS-induced lethal endotoxemia, EGCG (4 mg/kg, i.p) or green tea polyphenols (500 mg/kg, i.g.) significantly increase survival rate (Li et al., 2007; Yang, de Villiers, McClain, & Varilek, 1998). These results need to be further substantiated in rodent models and humans before considering studies in COVID-19 patients.

9. Thrombosis inhibition by EGCG

Coagulation activation and thrombotic events are common in COVID-19 patients (Katneni et al., 2020). Endotheliopathy has been identified in COVID-19 patients (Goshua et al., 2020; O'Sullivan, Gonagle, Ward, Preston, & O'Donnell, 2020). Coagulation factor III, an important mediator for coagulopathy, interacts with circulating coagulation factor VII to trigger extrinsic coagulation (DiNicolantonio & McCarty, 2020). Thrombotic complications of COVID-19 may reflect an upregulation of endothelial tissue factor expression via activation of NOX (DiNicolantonio & McCarty, 2020). Indeed, NOX2 is activated in COVID-19 patients, especially those with thrombotic events (Violi et al., 2020). Increased plasma levels of tissue factors have been detected in COVID-19 patients (Skendros et al., 2020). Circulating platelet-neutrophil, -monocyte and -T-cell aggregates are significantly elevated in COVID-19 patients. Platelets from COVID-19 patients aggregate faster (Manne et al., 2020). SARS-CoV-2 and its spike protein directly activate platelets, which contribute to thrombus formation and inflammatory responses in COVID-19 patients (Zhang, Liu, et al., 2020).

EGCG inhibits TNFα - or histamine-induced tissue factor expression in cultured human aortic endothelial cells in a concentration-dependent manner (up to 30 μM). EGCG also decreases TNFα-induced tissue factor expression in cultured human aortic vascular smooth muscle cells and human umbilical venous endothelial cells. EGCG administration at the dose of 30 mg/kg (i.p.) daily for 7 days in mice inhibits tissue factor

activity of carotid arteries (Holy et al., 2010). EGCG can inhibit ADP, collagen, epinephrine or calcium ionophore A23187 induced human platelet aggregation in a dose-dependent manner (Kang et al., 1999). EGCG also has antithrombotic activities in mice: 1) oral administration of a single dose of EGCG (10 or 50 mg/kg), 90 min prior to tail vein injection of epinephrine plus collagen, protects against death caused by pulmonary thrombosis in a dose-dependent manner; and 2) i.p. injection of EGCG (4 and 10 mg/kg) dose-dependently prolongs tail bleeding time of conscious mice by 2- and 3-fold, respectively (Kang et al., 1999). If the inhibition of tissue factor upregulation and anti-platelet activity of EGCG can be demonstrated in humans, EGCG may be useful in the prevention against thrombosis formation in COVID-19 patients.

10. Inhibition of lung fibrosis by EGCG

A systematic review of pathophysiological timeline in COVID-19 shows three main histological patterns in the lung, namely epithelial, vascular and fibrotic with interstitial fibrosis. The epithelial and vascular patterns can be found in all stages, while interstitial fibrous changes generally appear at 3 weeks after the onset of symptoms (Polak, Van Gool, Cohen, von der Thüsen, & van Paassen, 2020). Emerging evidence shows that many patients have persistent respiratory symptoms months after their initial illness (Fraser, 2020), and suggests that SARS-CoV-2 infection may have pulmonary fibrosis sequelae (George, Wells, & Jenkins, 2020).

The bleomycin-induced pulmonary fibrosis model is characterized by initial inflammation and secondary fibrosis, being similar to the pathological features of COVID-19. EGCG (20 mg/kg, i.p.) exhibits antifibrotic property in a rat model of pulmonary fibrosis induced by bleomycin (Sriram, Kalayarasan, Manikandan, Arumugam, & Sudhandiran, 2015; Sriram, Kalayarasan, & Sudhandiran, 2008, 2009a, 2009b). The mechanisms include augmenting Nrf2 defense and suppressing NF-κB activation. EGCG treatment (25 mg/kg, i.p.) also significantly inhibits irradiation-induced pulmonary fibrosis in rats (You et al., 2014). Oral administration of green tea extract in drinking water (equivalent to EGCG doses of 300–400 mg/kg) to mice significantly reduces pulmonary fibrosis induced by intratracheal challenge of fluorescein isothiocyanate; interstitial and peribronchial fibrosis is nearly completely prevented (Donà et al., 2003). In rats, green tea extract (150 mg/kg, i.g.) prevents cyclophosphamide-induced pulmonary fibrosis in rats (Hamdy, El-Maraghy, & Kortam, 2012) and green tea extract (1% in diet) ameliorates paraquat-induced pulmonary fibrosis (Kim et al., 2006). In cultured precision-cut lung slices from explants of patients with idiopathic pulmonary fibrosis undergoing transplantation, EGCG attenuates TGFβ1 signaling and new collagen accumulation, activates matrix metalloproteinase-dependent collagen I turnover (Wei et al., 2021). EGCG (600 mg given orally for 14 days) to patients with idiopathic pulmonary fibrosis, reverses profibrotic biomarkers in their diagnostic biopsies and serum samples (Chapman et al., 2020). Overall, with demonstrated activities in alleviating pulmonary fibrosis in rodent models and humans, EGCG and green tea extract may be useful for the prevention and treatment of pulmonary fibrosis in COVID-19 patients.

11. Reduction of COVID-19 diabetes comorbidity risk by EGCG

It is known that COVID-19 severity is magnified in people with underlying medical conditions. COVID-19 patients with diabetes comorbidity are at great risk of lengthy hospitalization and dire consequences, including ICU admission and mortality. Hyperglycemia upregulates receptors for advanced glycation end products (RAGE) and increases RAGE ligands such as HMGB1 (Le Bagge, Fotheringham, Leung, & Forbes, 2020). Most healthy tissues express low basal levels of RAGE, while pulmonary tissues have very high basal levels of RAGE (Rojas, Gonzalez, & Morales, 2020). RAGE is a major mediator of pulmonary inflammatory responses (Oczypok, Perkins, & Oury, 2017). RAGE regulates a positive feed-forward loop of RAGE and NF-κB, resulting in a

sustained NF-κB activation (Bierhaus et al., 2001). RAGE may play a pivotal role in SARS-CoV-2-mediated inflammatory response in the lung (Rojas et al., 2020) and has been suggested to be a therapeutic target for inhibition in COVID-19 patients with diabetes (De Francesco, Vella, & Belfiore, 2020). As outlined in Fig. 3, SARS-CoV-2 increases extracellular HMGB1 (Chen et al., 2020), which binds pulmonary RAGE to participate in triggering cytokine storm, sepsis and thrombosis (Yang et al., 2004). In diabetic conditions, hyperglycemia increases RAGE expression and HMGB1 levels (Le Bagge et al., 2020), amplifying SARS-CoV-2/HMGB1/RAGE axis. Moreover, hyperglycemia increases SARS-CoV-2 replication via reshaping cell metabolism in favor of glycolysis (Codo et al., 2020). Therefore, hyperglycemia and SARS-CoV-2 can synergistically enhance HMGB1-RAGE signaling transduction, leading to far worse outcomes. In addition, type 2 diabetic patients have an increased level of NETs (Carestia et al., 2016; Menegazzo et al., 2015; Park et al., 2016; Wang et al., 2018; Wong et al., 2015). SARS-CoV-2-evoked NETs together with high basal NETs in diabetic patients also increase risk of ICU admission and mortality of COVID-19 patients with diabetes comorbidity.

Mounting evidence demonstrates that EGCG is helpful in controlling blood glucose in diabetic subjects (Chen et al., 2009; Kao, Chang, Lee, & Chen, 2006; Sae-tan, Grove, & Lambert, 2011; Wolfram et al., 2006; Yang, Zhang, Zhang, Huang, & Wang, 2016; Zhao, Wu, Wang, Yang, & Zhang, 2020). Moreover, several studies in animal models and humans have shown that EGCG suppresses RAGE signaling pathway; specifically, 1) treatment with EGCG (10 mg/kg and 50 mg/kg, i.p.) reduces pulmonary injury and airway remodeling in PM2.5-exposed asthmatic rats, partially via regulation of the HMGB1/RAGE signaling pathway (Li et al., 2019); 2) EGCG dose-dependently (75, 150 and 300 mg/kg, i.g.) downregulates pancreatic RAGE in diabetic mice (Feng, Hou, Zhu, Zhu, & Jiang, 2019); 3) EGCG (2 mg/kg and 4 mg/kg, i.p.) improves restenosis in a rat model of carotid artery balloon injury via inhibiting HMGB1/RAGE and NF-κB activation (Yang et al., 2017); 4) EGCG (75 mg/kg, i.p. 3 times per week) alleviates hyperglycemia, downregulates RAGE expression and reduces advanced glycation end products in mice with high fat diet-induced obesity (Sampath, Rashid, Sang, & Ahmedna, 2017); 5) in patients with type II diabetes, EGCG at doses from 300 to 900 mg/day dose-dependently increases plasma levels of soluble RAGE, a RAGE variant acting as a ligand decoy that competes with RAGE (Huang et al., 2013). These inhibitory activities of EGCG, in rodent models and humans, suggest that EGCG could reduce the risk of ICU admission and mortality of COVID-19 patients with diabetes comorbidity.

12. Dose and safety issues of EGCG for COVID-19 prevention and treatment

The biological activities and toxic effects of EGCG in mice have been extensively studied. Generally, the effect of an i.p. dose approximates that of a 10-fold oral dose. For example, 55–75 mg/kg (i.p.) or 600 mg/kg (i.g.) for five consecutive days caused hepatoxicity and elevated hepatic Nrf2 response, while one dose of 200 mg/kg (i.p.) or 2000 mg/kg (i.g.) caused lethal consequence associated with suppression of hepatic Nrf2, in the same mouse species (Wang, Wang, Wan, Yang, & Zhang, 2015). The maximum non-toxic dose of EGCG by i.p. injection was 45 mg/kg (Wang, Wang, et al., 2015; Wang, Wei, et al., 2015; Wang, Wang, et al., 2019; Wang, Yang, et al., 2019) or 400–450 mg/kg by i.g. administration in mice (Lambert et al., 2010). Accordingly, the non-toxic doses of EGCG at 10–40 mg/kg (i.p.) or 100–400 mg/kg (orally) are extensively used for elucidating functions of EGCG in mice (Bose et al., 2008; Gan et al., 2015; Kumazoe et al., 2013; Siddiqui et al., 2009; Yan, Zhao, Suo, Liu, & Zhao, 2012).

To prevent SARS-CoV-2 infection, the key step is to prevent the binding of viral spike proteins to cellular receptors (ACE2) and to inhibit cell host proteases (TMPRSS2). The activation of Nrf2 by EGCG at non-toxic doses, which has been demonstrated in animal models (Dong et al.,
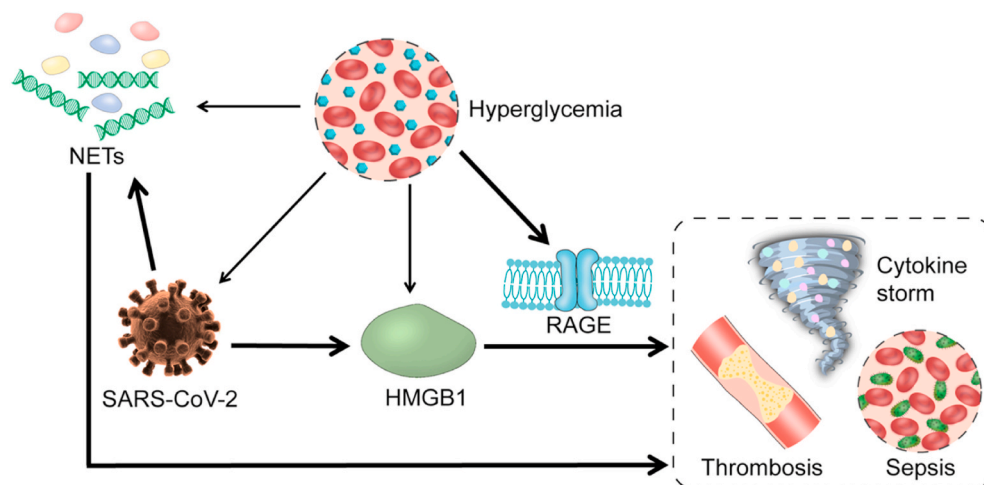
Fig. 3. Proposed mechanism by which COVID-19 is aggravated in diabetic conditions. The main feature of diabetes, hyperglycemia, promotes the replication of SARS-CoV-2 and the development of neutrophil extracellular traps (NETs). Hyperglycemia also strongly upregulates receptor for advanced glycation end products (RAGE) and increases the RAGE ligands — high mobility group box 1 (HMGB1). SARS-CoV-2 also strongly stimulates the formation of NETs and synthesis of HMGB1. Upon activation by its receptor (HMGB1), the RAGE signaling and NETs both induce cytokine storm, sepsis and thrombosis.

2016; Na et al., 2008; Sun et al., 2017; Yang et al., 2018), may reach a magnitude that can downregulate both ACE2 and TMPRSS2. However, these remain to be demonstrated. As described above, many studies in rodent models have demonstrated that EGCG at a non-toxic daily dose (under 30 mg/kg, i.p. or 300 mg/kg, i.g.) in mice can ameliorate hypoxia-induced oxidative stress, cytokine storm, and diabetes comorbidity as well as decrease GRP78 expression/activity, ER stress, thrombosis, sepsis, and lung fibrosis. These activities, if could be manifested in humans, would be beneficial in the prevention or alleviation of COVID-19 and associated syndromes.

The rodent dose can be converted to a human equivalent dose based on body weight divided by conversion factor of 12.9, because the mouse has a larger body surface area and higher metabolic rate per unit body weight (Reagan-Shaw, Nihal, & Ahmad, 2008). The above describes effective concentration of oral 300 mg/kg EGCG in mice is equal to 1392 mg EGCG daily for an adult with body weight of 60 kg. It was reported recently that daily 600 mg EGCG given orally to patients with idiopathic pulmonary fibrosis reversed profibrotic biomarkers in their diagnostic biopsies and serum samples, while FDA-approved drugs showed no beneficial effects (Chapman et al., 2020).

Two to 4 h following oral administrator of green tea polyphenols at a dose of 500 mg/kg in mice, the serum level of polyphenols reaches maximum value at 9–10 μg/mL (Yang et al., 1998). This level is higher than the IC_{50} (2.8 μg of green tea extract per mL) for the inhibition of M^{pro} activity of SARS-CoV-2 in vitro (Zhu & Xie, 2020). The inhibition of M^{pro} activity of SARS-CoV-2 by EGCG shows an IC_{50} of 7.5 μM (Zhu & Xie, 2020). In human studies, after ingesting 375 to 1200 mg of EGCG (as green tea extract or Polyphenon E) under fasting conditions, the maximum levels of EGCG were 4.3–5.6 μM (Chow et al., 2005; Nakagawa, Okuda, & Miyazawa, 1997). These human blood levels of EGCG approach, but are still lower than, the effective inhibitory concentration of EGCG against M^{pro} observed in vivo. There is also a possibility that some products formed from EGCG oxidation in vivo can inhibit M^{pro} activity of SARS-CoV-2 (Jang et al., 2020). The extrapolation of results from studies in vitro to situations in vivo, and the translation of animal studies to humans, are challenging issues. More studies on the dose response relationship of EGCG in humans are needed.

Following ingestion of tea catechins, the concentration of EGCG and other catechins can be rather high in the oral cavity. For example, in a study with volunteers, after each drinking 200 mL of warm tea (containing 1,200 mg of green tea extracts), followed by rinsing the mouth rigorously 10 times, the initial salivary concentrations of EGCG were 10–50 μM with elimination $t_{1/2}$ values of 10–20 min. EGC and EC, were present in slightly higher concentrations (Yang, Lee, & Chen, 1999). In a second experiment, after subjects holding 96 mg EGCG in 60 mL in the

mouth for 2 min, the saliva samples (collected similarly) initially contained 120–300 μM EGCG and decreased to 25–65 μM after 30 min. These results suggest that after drinking or gargling tea, the levels of EGCG and other catechins in the oral/nasal/pharyngeal cavity could be high enough to protect against viral infection. It has been shown in Japan that daily gargling a tea catechin solution significantly lowered the incidence of influenza infection in elderly (Yamada, Takuma, Daimon, & Hara, 2006). In a randomized double-blind trial of 200 healthcare workers, consumption of catechin capsules for 5 months had a protective effect against influenza virus compared to the placebo group (Matsumoto, Yamada, Takuma, Niino, & Sagesaka, 2011). These interesting studies need to be repeated in studies with more subjects and extended to other anti-viral studies in humans.

If higher doses of catechins are needed for alleviating the symptoms of COVID-19 disease, a concern is hepatotoxicity, which has been observed in animal models and individuals taking green tea extract-based dietary supplements for the purpose of weight reduction (Yang & Zhang, 2019). For long-term supplementation, a tolerable upper intake level was set at 300 mg of EGCG per day for humans in some European countries, such as France and Italy (Yates, Erdman, Shao, Dolan, & Griffiths, 2017). If tea is consumed as a beverage throughout the day, the tolerable upper intake level should be much higher (Yang & Zhang, 2019). Reversible hepatotoxicity caused by therapeutics for a period of a few months may be acceptable for a deadly disease. For example, in a study on the treatment of chronic lymphocytic leukemia (CLL), a high dose of Polyphenon E (containing 2000 mg EGCG, twice daily) was used for up to six months. Side effects, including transaminitis, abdominal pain and fatigue, were observed in some patients and some had to be switched to a lower dose. However, because of the clinical benefits (e.g. durable decline in absolute lymphocyte count), such side effects were considered to be tolerable (Shanafelt et al., 2013). Individuals that are susceptible to or already infected with SARS-CoV-2 are probably taking medications for prevention of chronic diseases or receiving anti-COVID-19 therapeutic drugs. One concern is that high dose of EGCG may interfere the transport, metabolism and efficacy of some of these drugs (Huang et al., 2020; Liu et al., 2020; Yang & Pan, 2012). However, such EGCG-drug interactions only occur with certain drugs, prior knowledge of such interactions could avoid complications.

13. Concluding remarks

As discussed above, EGCG has shown many redox and specific inhibitory activities, in cell lines and rodent models, which may be applicable for the prevention and treatment of COVID-19. The possible anti-COVID-19 activities of EGCG are outlined in Fig. 4. EGCG may
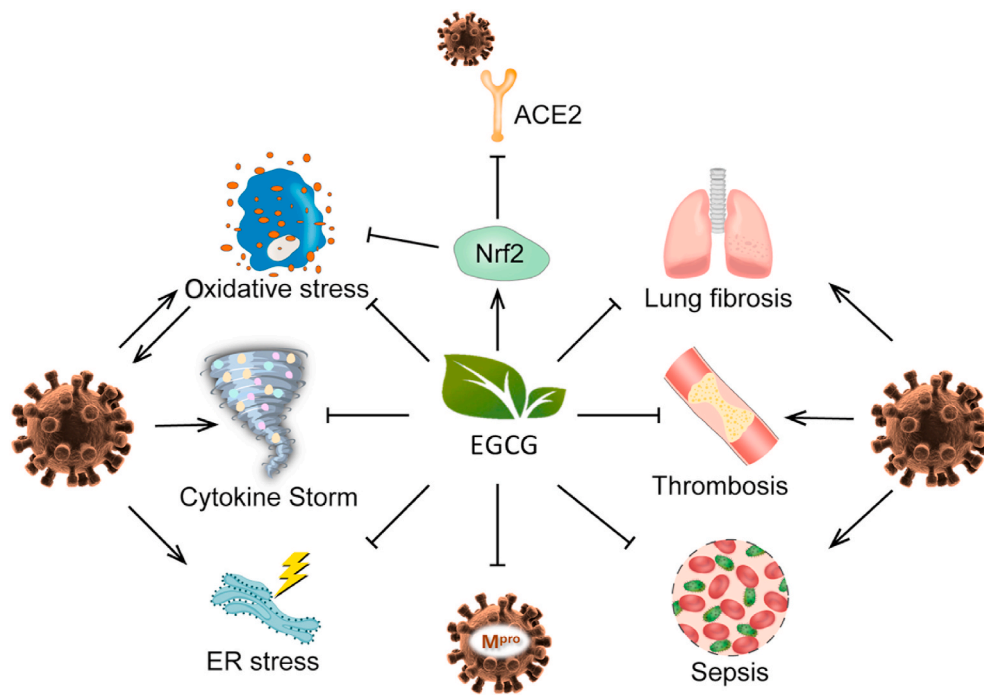
Fig. 4. Proposed multiple-target actions by EGCG to prevent or alleviate COVID-19. EGCG via its direct antioxidant activity and induction of Nrf2 prevents or suppresses oxidative stress and inflammation. Through its downregulation of angiotensin-converting enzyme 2 (ACE2) via Nrf2 and direct inhibition of main protease (M^pro), EGCG inhibits the infection and replication of SARS-CoV-2. These activities in combination with direct inhibition of key enzymes or proteins, contribute to the prevention or alleviation of cytokine storm, ER stress, sepsis, thrombosis and lung fibrosis that are caused by SARS-CoV-2 infection.

suppress SARS-CoV-2 infection via suppressing the expression of cell surface ACE2 and TMPRSS2 via activating Nrf2. EGCG may also inhibit SARS-CoV-2 M^pro — a protease essential for viral reproduction. EGCG has direct and indirect antioxidant activities to possibly protect against SARS-CoV-2 evoked oxidative stress. EGCG could reduce ER stress and SARS-CoV-2 life cycle via inhibiting ER-resident GRP78 activity and expression. EGCG could also protect against cytokine storm-associated ALI/ARDS, thrombosis, sepsis and lung fibrosis. Overall, EGCG has shown activities with the potential to prevent against SARS-CoV-2 infection, suppress SARS-CoV-2 life cycle, and curb SARS-CoV-2 triggered cytokine storm, oxidative stress, ER stress, thrombosis, sepsis, and lung fibrosis. These possible concerted activities of EGCG suggest the importance of further studies in relevant animal models and humans. To our knowledge, such human studies have not been registered or conducted. Other catechins in green tea may have similar, but slightly lower, activities of EGCG. Tea consumption has been shown to decrease the risk for obesity, diabetes and cardiovascular diseases (Yang & Hong, 2013; Yang & Zhang, 2019), which enhance the risk of and aggravate COVID-19. It is important to conduct epidemiological studies to determine whether regular tea consumption (and the amount required) could decrease risk for SARS-CoV-2 infection and associated syndromes.

Author contributions

Conception of idea: J.Z. Design of review outline: W.Y., C.S.Y. and J.Z. Sourcing literature of clinical symptoms and molecular pathology of COVID-19: Z.Z. and W.Y. Sourcing literature of EGCG and tea: X.Z., K.B., Y.H., C.S.Y. and J.Z. Drafting the article: Z.Z., X.Z., W.Y., C.S.Y. and J.Z. Preparing the figures: Z.Z. (Figs. 2–4) and C.S.Y. (Fig. 1). Reviewing and revising the manuscript: C.S.Y. and J.Z. Editing the manuscript: K.B. and Y.H.

Declaration of competing interest

The authors declare no conflict of interest.

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