REVIEW

A comprehensive review on modulation of SIRT1 signaling pathways in the immune system of COVID-19 patients by phytotherapeutic melatonin and epigallocatechin-3-gallate

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Abstract

SARS-CoV-2 infection has now become the world's most significant health hazard, with the World Health Organization declaring a pandemic on March 11, 2020. COVID-19 enters the lungs through angiotensin-converting enzyme 2 (ACE2) receptors, alters various signaling pathways, and causes immune cells to overproduce cytokines, resulting in mucosal inflammation, lung damage, and multiple organ failure in COVID-19 patients. Although several antiviral medications have been effective in managing the virus, they have not been effective in lowering the inflammation and symptoms of the illness. Several studies have found that epigallocatechin-3-gallate and melatonin upregulate sirtuins proteins, which leads to downregulation of pro-inflammatory gene transcription and NF-κB, protecting organisms from oxidative stress in autoimmune, respiratory, and cardiovascular illnesses. As a result, the purpose of this research is to understand more about the molecular pathways through which these phytochemicals affect COVID-19 patients' impaired immune systems, perhaps reducing hyperinflammation and symptom severity.

Practical applications

Polyphenols are natural secondary metabolites that are found to be present in plants. EGCG a polyphenol belonging to the flavonoid family in tea has potent anti-inflammatory and antioxidative properties that helps to counter the inflammation and oxidative stress associated with many neurodegenerative diseases. Melatonin, another strong antioxidant in plants, has been shown to possess antiviral function and alleviate oxidative stress in many inflammatory diseases. In this review, we propose an alternative therapy for COVID-19 patients by supplementing their diet with these nutraceuticals that perhaps by modulating sirtuin signaling pathways counteract cytokine storm and oxidative stress, the root causes of severe inflammation and symptoms in these patients.

KEYWORDS
COVID-19, epigallocatechin-3-gallate, inflammation, melatonin, NF-κB, oxidative stress, sirtuins

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1 | INTRODUCTION

The new Coronavirus 2019 (COVID-19) illness caused by the Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) was discovered in December 2019 in the Chinese city of Wuhan. SARS-CoV-2, an enveloped single-stranded positive ribonucleic acid virus shows 82% similarity in its genome sequence with SARS-CoV-1 (Lu et al., 2020) and 52% similarity in its genome sequence with the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (Lu et al., 2020).

Coronavirus symptoms range from mild to severe, including fever, cough, cold, sore throat, headache, chest discomfort, shortness of breath, and viral pneumonia. Patients showing moderate to severe COVID-19 symptoms suffer from septic shock, acute respiratory distress syndrome (ARDS), and multiple organ failures (Harapan et al., 2020). These patients' bodies are unable to eliminate the virus, and their immune systems are dysregulated, resulting in the uncontrolled secretion of cytokines that lead to uncontrolled systemic inflammation (Ragab et al., 2020). Oxidative stress further enhances the severity of symptoms caused by SARS-Cov2 infection by activating NF-κB, which leads to an increase in the transcription of genes that drive cytokine synthesis, further enhancing the inflammatory process (Forcados et al., 2021).

Polyphenols are plant secondary metabolites (Pandey & Rizvi, 2009) that are found naturally in dietary plants and can help reduce inflammation in many degenerative and neurodegenerative diseases. Epigallocatechin-3-gallate (EGCG) is the most abundant polyphenolic catechin found in *Camellia sinensis* (L.) Kuntz (tea plant), and its anti-inflammatory, antiviral, and antioxidative properties are well documented (Hu et al., 2018; Khan et al., 2006; Zaveri, 2006). According to some reports, EGCG has antiviral activity at micromolar concentrations sufficient to inhibit the infection of viruses like herpes simplex virus, influenza A virus, and dengue virus (Calland et al., 2012; Ge et al., 2018; Sodagari et al., 2016), suggesting that this phytochemical could be used along with antiviral drugs to treat COVID-19 disease.

Another natural compound Melatonin (*N*-acetyl-5-methoxytryptamine), a potent scavenger for free radicals (Poeggeler et al., 2006), first identified as a neurohormone secreted by the pineal gland in the human body was later discovered to be present in many nonvertebrates and plant species (Hardeland & Poeggeler, 2003). Melatonin (MT) has been demonstrated to have neuroprotective, antioxidant, antiapoptotic, and anti-inflammatory properties in many cellular and animal models in addition to its function in sleep and circadian rhythms (R. Zhang et al., 2020). Several studies report Melatonin's beneficial role in severe cases of viral lung infections, such as ARDS and COVID-19, where it serves as a great antioxidative and anti-inflammatory agent (Bahrampour Juybari et al., 2020). Sirtuins are protein that plays an important role in essential physiological processes, including inflammation, stress, mitochondrial biogenesis, insulin secretion, and aging (Kitada et al., 2019; Poulose & Raju, 2015).

This paper gives us an overview of deregulated signaling pathways involved in the development of oxidative stress and cytokine storms leading to severe symptoms in COVID-19 patients and provides a safe alternative option for the treatment of the disease. This review gives us a concise sketch of signal transduction pathways underlying the SIRT1 activation by MT and EGCG that enables the prediction that these nutraceuticals may have on reducing the inflammation and respiratory difficulties associated with severe Coronavirus infection.

2 | PATHOBIOLOGY OF SARS-COV-2 INFECTION

2.1 | Dysregulated intracellular signaling pathways

The pathogenesis of SARS-CoV-2 infection involves the entry of this virus into the host cell through the binding of its spike protein (S-protein) with the ACE-2 receptor present on the cell surface of multiple cells such as lungs, heart, kidney, liver, testis, and intestine. Cellular proteases like transmembrane protease, serine2 (TMPRSS2), and another protein clathrin facilitate virus entry into the upper respiratory tract by endocytosis (Li et al., 2020). Upon entering the host cell, the virus replicates rapidly inside the nucleus leading to viremia. The host's innate immune system tries to eliminate the coronavirus with the help of cytokines and chemokines released by macrophages, neutrophils, and dendritic cells in the lung epithelial cells, which are later followed by activation of the adaptive immune response (Mehta et al., 2020). At this initial stage, the patient can be cured easily and can be asymptomatic. SARS-CoV-2 infection activates many downstream signaling pathways such as interleukin-6/Janus kinase/signal transducers and activators of transcription (IL-6/JAK/STAT) signaling pathway (Magro, 2020; C. Zhang et al., 2020), interferon (IFN) cell signaling pathway (Prokunina-Olsson et al., 2020), tumor necrosis factor-α–nuclear factor-kappa (TNF-α–NF-κB) pathway (Feldmann et al., 2020), toll-like receptor (TLR) pathway (Angelopoulou et al., 2020), T-cell receptor (TCR) pathway (de Biasi et al., 2020; C. Zhang et al., 2020), and JAK–STAT pathway (Luo et al., 2020). But in the later stages, when the body's adaptive immune system fails to control the virus, the dysregulation of these signaling pathways leads to overproduction of pro-inflammatory cytokines (IL-1β, IL-2R, IL-6, IL-7, IL-8, IL-17, and TNF-α) and chemokines (CCL2, CCL3, CCL5, CCL7, and CXCL-10) that lead to lung injury, acute respiratory distress syndrome (ARDS), and failure of multiple organs (Figure 1; Mehta et al., 2020).

Some reports suggest the role of inhibitors like Baricitinib in the impairment of JAK–STAT pathway mediated IFN and TNF signaling to mitigate SARS-CoV-2 infection (Favalli et al., 2020). In the case of patients with severe COVID-19 infection presence of impaired IFN-I signatures was observed compared to patients with milder infection (Hadjadj et al., 2020). Since NF-κB is a master regulator of inducing the expression of various pro-inflammatory cytokines and chemokine genes, deregulated NF-κB activation could be one of the main factors behind the etiology of several inflammatory diseases including COVID-19. Recently, its role is implicated in the regulation
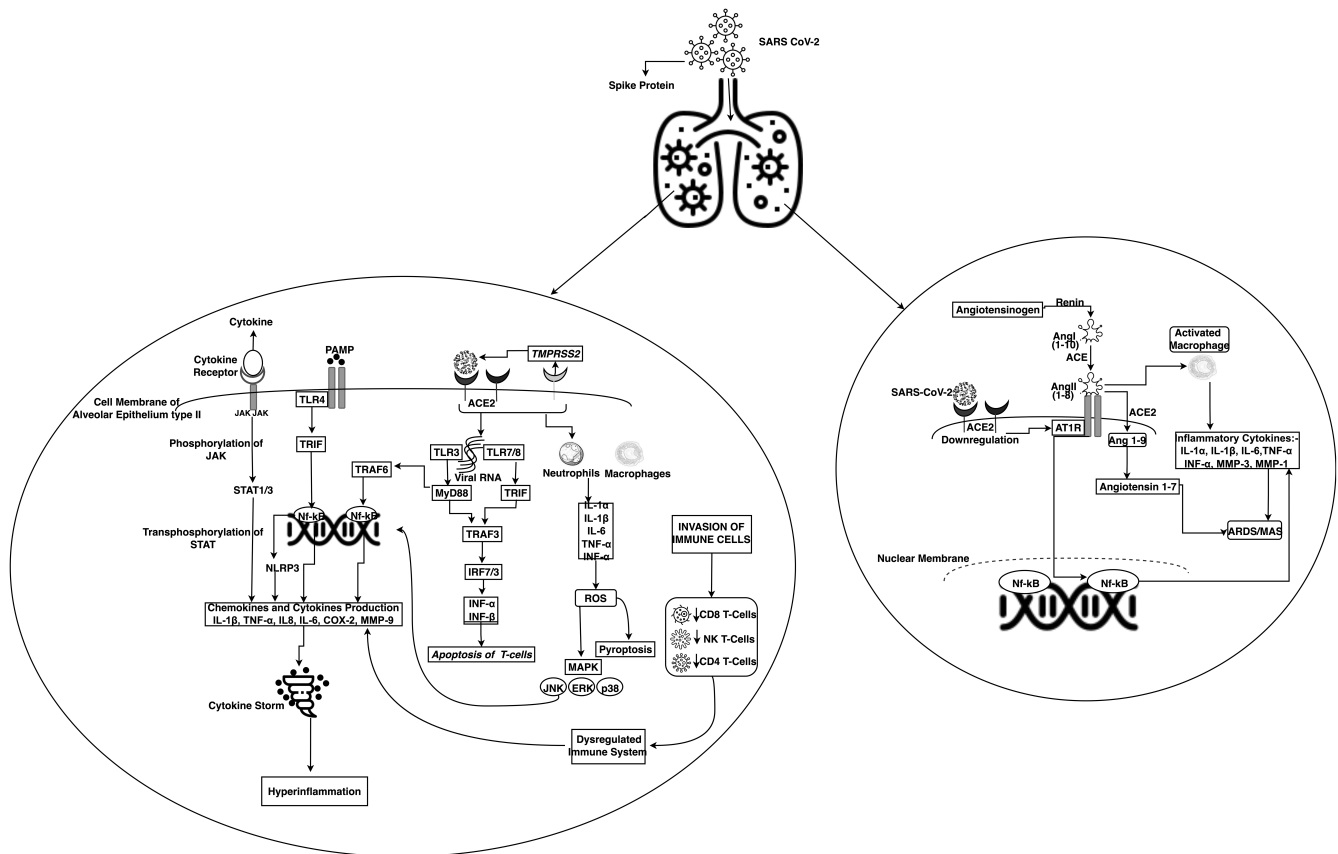
FIGURE 1 Modulation of signaling pathways by SARS-CoV-2 virus. Coronavirus disease occurs upon entry of the virus through the airway and mouth and affects the lung initially because of the presence of the ACE2 receptors on the surface of type II alveolar cells that bind to the spike protein. The virus multiplies rapidly within the host cell and infects other cells by the interaction of TLR to PAMPs present on the surface of microbial cells. This triggers the activation NF-κB pathway which is responsible for transcriptional induction of pro-inflammatory cytokines through the JAK/STAT signaling pathway. It also activates TLR and TCR pathways in different innate immune cells. High levels of cytokines lead to mitochondrial malfunction. The deregulated NF-κB pathway in these patients can cause extensive pulmonary endothelial cell injury and tissue damage that is central to the pathogenesis of ARDS. Also, when the virus binds to the ACE2 receptor on the host cell membrane, it causes downregulation of MAS and the ACE2 receptor in a COVID-19 patient. The failure of the ACE2/Ang-(1–7)/MAS pathway increases inflammation and contributes to tissue dysfunction, thrombosis, and fibrosis (Donoghue et al., 2000; Kuriakose et al., 2021).

of inflammasomes too. Therefore, mechanisms that underlie the NF-κB signaling could prove instrumental in controlling the immune responses to prevent autoimmunity and inflammatory diseases.

Several downstream signaling pathways, including the extracellular signal-regulated kinase (ERK)-activator protein (AP-1) pathway, p65, and p38 mitogen-activated protein kinase (MAPK) pathway, with Jun NH$_2$-terminal kinase, activates various transcription factors downstream that further induce the expression of several pro-inflammatory cytokine genes (Huang et al., 2020). These cytokines then bind to their respective cytokine receptors and interact with JAK 1/2 and STAT 3/6 proteins Apoptosis is regulated by MAPK pathways, and there is crosstalk between the p38 MAPK pathway and other pathways that might cause cell death. To induce chronic infection with SARS-CoV2 (Battagello et al., 2020), the PI3 kinase/Akt pathway must be activated.

Further, based on several research studies, dysfunction of the renin–angiotensin–aldosterone system (RAAS) pathway caused by the downregulation of ACE-2 receptors is associated with regulation

of inflammation in COVID-19 patients (Kuba et al., 2005). Generally, ACE-2 leads to the conversion of angiotensin (Ang) I and angiotensin II into biologically active peptides Ang 1–9 and Ang 1–7 in the RAAS pathway (Hanff et al., 2020; Figure 1). Coronavirus infection downregulates the levels of ACE2 levels that lead to increased accumulation of toxic levels of Ang II that amplifies the production of pro-inflammatory cytokines. Further, angiotensin II stimulates angiotensin II type 1 receptor (AT1R) but inactivates angiotensin II type 2 receptor (AT2R). Thus, the reduction of AT2R/AT1R levels concomitant with the cytokine storm severely damage the lungs and induce ARDS (Donoghue et al., 2000) (Figure 1). High levels of angiotensin II promote oxidative stress and depletion of oxygen levels in these patients by increasing the generation of superoxide ions. Furthermore, these reactive oxygen species lead to the oxidation of cysteine residues present in the spike protein of the SARS-CoV-2 virus, forming disulfide that boosts the affinity of the Coronavirus to bind to its receptor leading to the development of COVID-19 disease (Ghasemitarei et al., 2022; Hati & Bhattacharyya, 2020).

Cardiac cells also express ACE-2 and so this virus could damage these cells resulting in myocardial infarction (Crackower et al., 2002). Some reports show high levels of D-dimers and thrombosis leading to cardiac arrhythmias in these patients, which results in multi-organ damage and eventually leads to death (Bansal et al., 2021).

Coronavirus can also infect the lung epithelial cells by binding through the Toll-Like receptors (like TLR3, TLR4, TLR7, and TLR-8) on the surface of plasmacytoid dendritic cells, so blocking of these receptors especially TLR4 by certain immunomodulators offers another promising target to prevent acute lung injury (ALI) (Sun et al., 2020). These receptors are further activated in immune cells by the presence of elevated levels of ROS or in injured or apoptotic cells stimulated by damage-associated molecular pattern molecules (DAMPs) (Figure 1) and will result in the generation of severe inflammation in COVID-19 patients (Land, 2015).

Coronavirus is expected to induce severe lung disease by triggering pyroptosis (Yang, 2020; Figure 1) and by activation of inflammasomes' Nod-like receptor, family pyrin domain containing 3 (NLRP3) (Shi et al., 2019) that leads to the production of pro-inflammatory cytokines like IL-1β and IL-18. Therefore, in the lungs, NLRP3s protective and harmful effects are likely to be balanced. It has also been discovered that oxidative stress triggered due to overproduction of free radical species further stimulates the generation of inflammatory cytokines in COVID-19 patients. TNF-α and IL-6 limit mitochondrial oxidative phosphorylation and, as a result, ATP generation while inducing ROS production in the cell (Saleh et al., 2020; Schofield & Schafer, 2021). Increased inflammatory/oxidative stress also can lead to ferroptosis, platelet destruction, and eventually organ damage in these patients.

3 | IMMUNOMODULATORY ROLE OF EGCG

3.1 | Antiviral property of EGCG

Green tea offers a variety of health benefits to mankind as it helps in the prevention and treatment of numerous infectious viral diseases. It has been one of the popular beverages consumed by people all over the world. It contains many polyphenols such as EGCG and Theaflavin that belong to the flavonoid family. One cup of tea has around 100–300 mg of EGCG which accounts for more than 80% of the catechin in them (Hu et al., 2018; Khan et al., 2006; Zaveri, 2006). The absorption of EGCG is relatively high, with a maximal plasma concentration of more than 1 g/ml (Zaveri, 2006). At micromolar concentrations, EGCG has been demonstrated to suppress infections caused by various viruses such as porcine reproductive and respiratory Syndrome Virus (PRRSV), Dengue virus, HIV-1, and hepatitis C virus (HCV) (Calland et al., 2012; Ge et al., 2018; Raekiansyah et al., 2018; Sodagari et al., 2016). When taken orally, EGCG, on the other hand, is unstable and has a low bioavailability. It is quickly oxidized before it reaches its destination. As a result, several scientists have proposed structural modifications of EGCG,

such as ester derivatives (Zhong & Shahidi, 2011), to improve its bio-availability. Combining EGCG with other antiviral medications can further boost its bioavailability. Some studies propose encapsulating EGCG with nanoparticles to improve its effectiveness (Munin & Edwards-Lévy, 2011). These polyphenols (EGCG and theaflavin) further inhibit the activity of SARS-CoV-2 3CL protease protein that is majorly responsible for the release of nonstructural proteins (nsps) from polyproteins that are required for the maintenance of the viral life cycle (Du et al., 2021; Jang et al., 2020). According to a recent report, the impact of EGCG on SARS-CoV-2 3CL Protease enzyme was found to be more profound compared with SARS 3CL protease which was in corroboration with the lower half-maximal inhibitory concentration (IC_{50}) dose of EGCG (0.847–16.5 μM) used for SARS-CoV-2 3CL protease with respect to a higher IC_{50} dose of EGCG (25–100 μM) for SARS 3CL protease. In addition, EGCG IC_{50} values for human coronaviruses (HCoV-OC43 and HCoV-229E) were higher than the IC_{50} for SARS-CoV-2 (Jang et al., 2021), suggesting the beneficial role of EGCG in preventing SARS-CoV-2 infection.

3.2 | Antioxidant role of EGCG

EGCG exhibits its antioxidant capability in two ways as follows: one by directly affecting ROS production and the other by boosting the body's defense mechanism (Frei et al., 2003; Shi et al., 2000). The potent free radicals scavenging activity of EGCG is due to the D ring in its galloyl group. Tea polyphenols prevent oxidative damage of DNA in cell cultures by lowering the expression of cytochromes P450 (Feng et al., 2002; Shibutani et al., 1991). This finding is supported by the lower amount of oxidative stress-induced DNA marker 8-oxoguanine. As a result, tea polyphenols may be able to treat oxidative stress-related illnesses by boosting antioxidant capacity and therefore reducing oxidative damage (Palmer et al., 1987; Ropero & Esteller, 2007). There are also some indirect methods in which tea polyphenols might protect against illness caused by oxidative stress. EGCG will function as a messenger molecule for downstream signaling pathways by creating reduced levels of ROS, particularly hydrogen peroxide (Engel, 2006). EGCG, on the other hand, enhances several other intracellular second messengers, such as Ca^{2+}, cAMP, and cGMP, by interacting with a particular receptor 67LR (67 kDa laminin receptors) (Umeda et al., 2008). These messengers, particularly cGMP, can further downstream induce the activation of PI3K/Akt/endothelial nitric oxide synthase (Akt/eNOS) (Palmer et al., 1987) signaling pathway. This reduces oxidative stress and heals the illnesses associated with it (Figure 2).

Several investigations have shown the anti-inflammatory properties of EGCG. Apart from lowering the STAT-1 activity, EGCG can also inhibit STAT3 activity which is activated by IL-6 cytokine thereby influencing many cellular processes (Figure 2). High levels of IL-6 cytokine produced during the inflammatory reactions in COVID-19 patients are one of the key factors determining the severity of the disease. So, drugs like tocilizumab that could inhibit IL-6 signaling can limit the development of the disease (C. Zhang
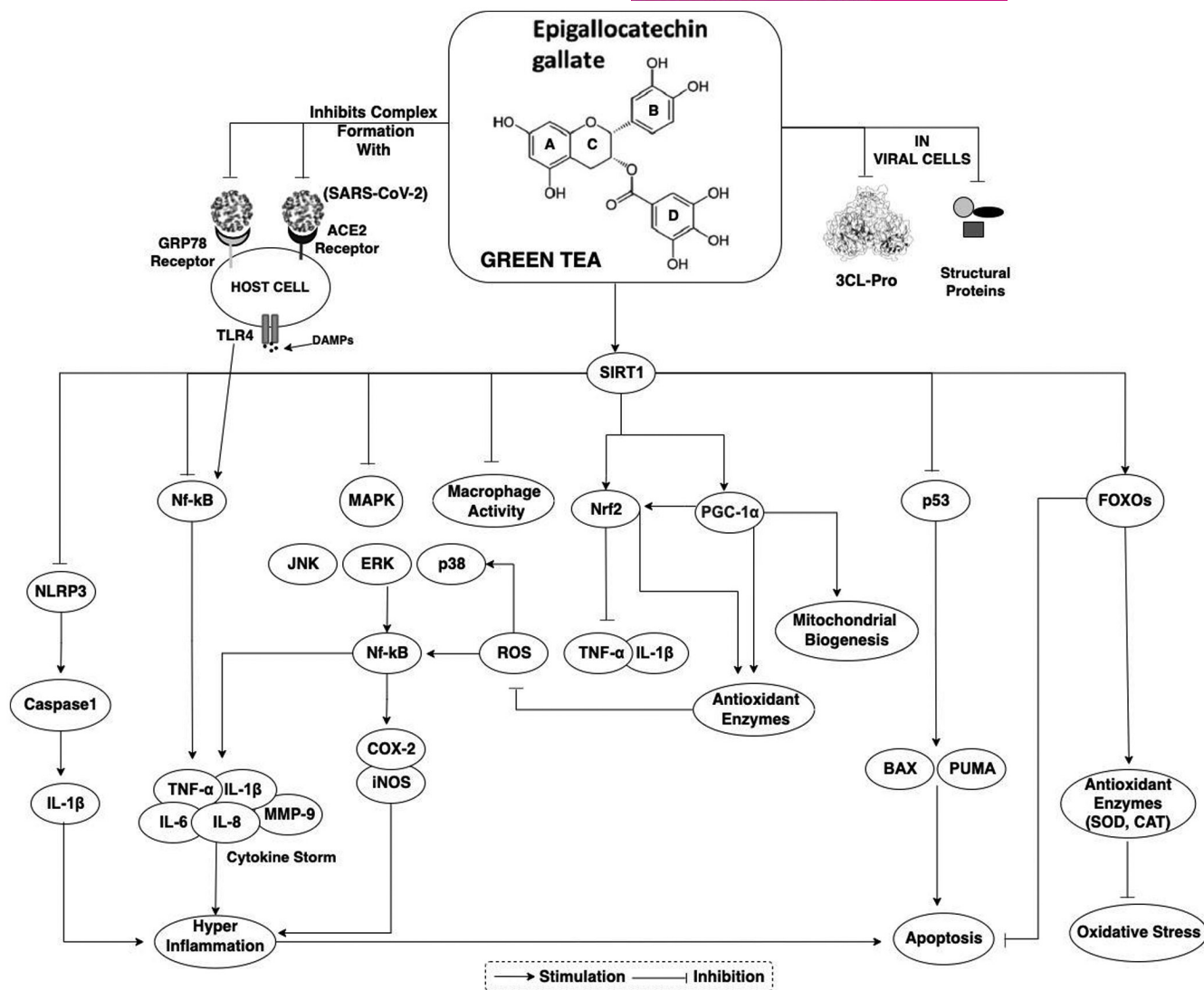
FIGURE 2 EGCG inhibits oxidative stress, apoptosis, and inflammation by boosting antioxidants and mitochondrial biogenesis via. SIRT1 activation. SIRT1 suppresses the transcription of several cytokine genes by directly regulating the NF-κB pathway. The SIRT1 activator EGCG inhibits the production of the inflammatory cytokine IL-1 by inhibiting the NLRP3 inflammasome signaling pathway. The severe COVID-19 infection leads to enhanced macrophage activity, that release high levels of pro-inflammatory cytokines resulting in cytokine storm. The EGCG suppresses the hyperinflammation and ROS production by upregulating SIRT1 to inhibit the production of these hyperinflammatory macrophages, inhibit the p38 MAPK pathway, and increase the levels of antioxidant enzymes SOD and CAT by deacetylating PGC1α and FOXO1 in the FOXO1-induced signaling cascade. EGCG-mediated SIRT1 activity can suppress the activation of the p53 protein that regulates pro-apoptotic proteins BAX and PUMA which are induced during DNA damage by ROS. 3CLpro, 3C-like protease; ACE2 Receptor, angiotensin-converting enzyme-2; BAX, Bcl-2-associated X protein; CAT, catalase; COX-2, cyclooxygenase 2; ERK, extracellular signal-regulated kinase; FOXO, Forkhead box transcription factors; JNK, Jun N-terminal kinase; IL-1β, interleukin 1 beta; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; MAPK, mitogen-activated protein kinase; MMP-9, matrix metallopeptidase 9; NF-kB, nuclear factor-kappa-light-chain-enhancer of activated B cells; NLRP3 inflammasome, NLR family pyrin domain containing 3 inflammasome; Nrf2, nuclear factor erythroid 2-related factor 2; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator 1 alpha; PUMA, p53 up-regulated modulator of apoptosis; ROS, reactive oxygen species; SARS-CoV-2 Virus, severe acute respiratory syndrome coronavirus 2; SIRT1, sirtuin 1; SOD, superoxide dismutase; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-alpha.

et al., 2020). EGCG also seems to be a promising bioactive substance derived from plants for the treatment of COVID-19 disease as it inhibits IL6-JAK/STAT3 pathway. Further, EGCG can also block the activation of the transcription factor NF-κB (Shi et al., 2019; Sun et al., 2020), which plays a central role in many immunologic processes associated with inflammatory diseases (Hayakawa et al., 2019; Ohishi et al., 2016; Reygaert, 2018). NF-κB regulates

the production of various pro-inflammatory cytokines that are increased in the cytokines storm syndrome in COVID-19 (Khan et al., 2006; Reygaert, 2018; Zaveri, 2006). The capacity of EGCG to induce Nrf2 nuclear translocation and HO-1 activity results in anti-inflammatory effects, particularly on neuronal cells, arthritis (Singh et al., 2010), and atherosclerosis. In animal models, EGCG activation of Nrf2 at nontoxic doses has been documented (Dong et al., 2016;

Na et al., 2008; Sun et al., 2017; Yang et al., 2018). Infection with the respiratory syncytial virus reduces antioxidants, and 14 detoxification enzymes, including superoxide dismutase (SOD), catalase, glutathione peroxidase (GPX), and glutathione S-transferase (GST), inhibit Nrf2 expression in the lungs of mice. The infection severely lowers these enzymes in the airways of children with severe bronchiolitis. The degree of clinical illness in infected babies is connected to the decline in these enzymes (Hosakote et al., 2011). Similarly, the severity of the disease is connected to reduced SOD3 expression in the lungs of older COVID-19 patients (Laforge et al., 2020).

As previously indicated, EGCG at a nontoxic daily dose (less than 30 mg/kg i.p. or 300 mg/kg i.g.) in mice can ameliorate hypoxia-induced oxidative stress, s cytokine storm, and diabetes comorbidity while also lowering Glucose Regulated Protein 78 (GRP78) expression/activity, ER stress, thrombosis, sepsis, and lung fibrosis. These measures might benefit in the prevention or treatment of COVID-19 and associated disorders if they could be duplicated in people. As a consequence, EGCG might be utilized to treat COVID-19 patients with hyperinflammation (Zhang et al., 2021).

3.3 | Anti-inflammatory role of EGCG

According to Singh et al., EGCG can reduce inflammatory responses in Rheumatoid Arthritis by inhibiting numerous stages in the JAK/STAT pathway and the MAP Kinase signaling pathway, in addition to anti-ROS action (Singh et al., 2010). In another study, EGCG inhibited inflammation, sebum production, and growth of *P. acne* in Acne vulgaris, a skin disorder by activating AMPK and inhibiting insulin receptor substrate-1/PI3K/Akt, NF-κB, and AP1 signaling pathway (Yoon et al., 2013). A dose of 10 μmol/L of EGCG was observed to be protective for the primary culture of hepatocytes in vitro (Kucera et al., 2015). Because these green tea catechins including EGCG have several targets and work in a pleiotropic manner, these may be utilized to improve the quality of life of patients with inflammatory illnesses such as COVID-19 (Hayakawa et al., 2019; Kucera et al., 2015).

4 | IMMUNOMODULATORY ROLE OF MELATONIN

4.1 | Antiviral role of melatonin

Many viruses, particularly those that generate a cytokine storm, reduce melatonin production, which has a bad effect on the health and immunity of the host (Anderson & Reiter, 2020). The viral infections addressed in this review demonstrate the evasion of the host defense system by targeting the production and function of melatonin by depleting tryptophan (a melatonin precursor) and inhibiting the gene expression of enzymes synthesizing melatonin. Thus, many viral illnesses become more severe because of these melatonin-depleting effects.

According to recent research, SIRT1 inhibits the translocation of High Mobility Group Box 1 (HMGB1) from the nucleus that inhibits Dengue virus (DENV) replication via eliciting interferon (IFN)-stimulated genes (ISGs) (Morchang et al., 2021; Zainal et al., 2017). MT reduced DENV production in the early stages of the virus' reproduction according to our findings. Melatonin's antiviral action is thought to be due to the elicitation of ISGs, which activates the SIRT1 pathway.

Antiviral properties of MT have been utilized to treat lower respiratory tract illness caused by a respiratory syncytial virus (RSV), where bronchial epithelial cells are damaged by infiltration of immune cells overproducing cytokines and ROS leading to hyperinflammation.

RSV activates the TLR3, which activates NF-κB, and leads to increased production of pro-inflammatory cytokines. When RSV-infected macrophages were given melatonin, TLR3-mediated downstream gene expression was shown to be reduced. Further, melatonin supplementation in RSV-infected mice reduced the severity of damage to lung cells which was supported by increased levels of glutathione production and antioxidant enzymes (SOD) and decreased production of ROS and RNS (Boga et al., 2012).

Similarly, the influenza A virus is another virus that affects the respiratory tract and causes significant tissue damage. In all these illnesses, lymphocytes, neutrophils, and macrophages infiltrate the lung parenchyma, causing pro-inflammatory and nonspecific oxidative stress-related damage (Boga et al., 2012). Melatonin treatment significantly reduced the number of CD8+ T cells responsible for producing TNF-α in Influenza A-infected mice in the spleen and lungs, which might help to minimize the degree of lung damage (Huang et al., 2010).

Melatonin, through inhibiting calmodulin, prevents ACE-2 from interacting with the spike protein of Coronavirus and prevents its entry into the host cell. Melatonin inhibits the chymotrypsin-like protease, which aids in the cleavage of viral polyproteins (Cardinali, 2020). Melatonin was observed to influence the RAS pathway by promoting the activity of angiotensin 1–7 and inhibiting the activation of angiotensin II in treating various metabolic disorders (Campos et al., 2013). In the case of patients suffering from severe Coronavirus infection, MT inhibits the NLRP3 inflammasome, which inhibits pyroptosis and, as a result, has an anti-inflammatory impact (Yang, 2020) (Figure 3). Extensive clinical research has thus demonstrated that melatonin has preventative and clinical benefits for numerous diseases, including cancer, neurological disorders, and viral diseases like Coronaviruses.

4.2 | Immunoregulatory role of melatonin

Melatonin ameliorates both innate and adaptive immune responses by regulating the proliferation and maturation of immune cells like B and T lymphocytes, agranulocytes, and granulocytes in the bone marrow. It is a neurohormone secreted from the pineal gland which affects many organs of the body (Liu et al., 2020; Miller et al., 2006;
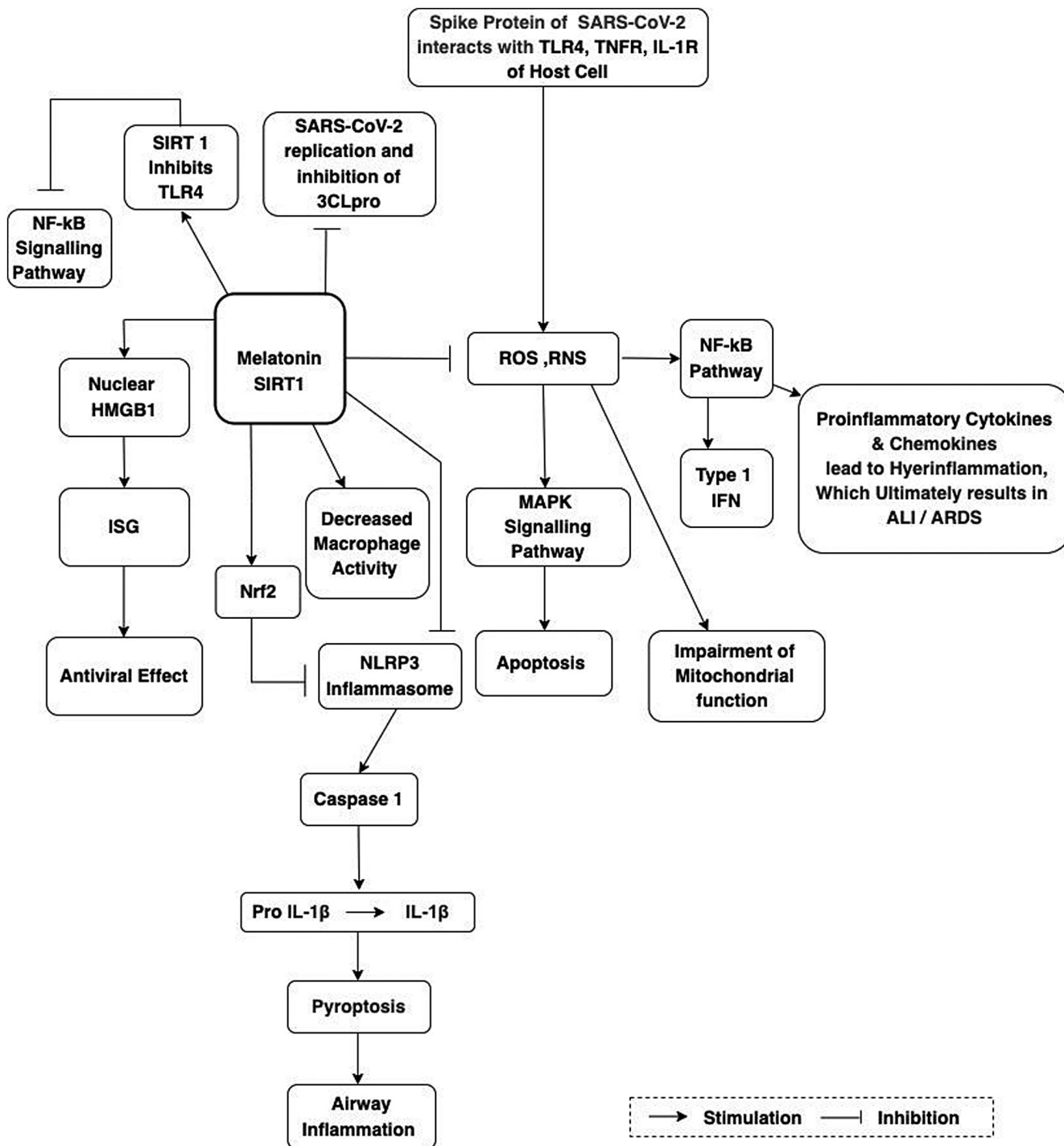
FIGURE 3 Melatonin inhibits oxidative stress, apoptosis, and inflammation by boosting antioxidants via activation of SIRT1. Melatonin inhibits early virus replication or 3CLpro which aids in fighting against viral infection. Melatonin exerts its anti-inflammatory properties by stimulating sirtuin proteins, inhibiting activation of TLR4, and reducing the levels of pro-inflammatory cytokines from hyperinflammatory macrophages through downregulation of NF-kB signaling. SIRT1 in association with melatonin scavenges the production of ROS and RNS by increasing antioxidants and thereby reduces the damage produced by oxidative stress. Melatonin leads to the downregulation of inducible nitric oxide synthase and cyclooxygenase-2 which further decreases inflammation via. the NF-kB signaling pathway. Sirtuins, an Nrf2 promoter, in the presence of melatonin inhibit the inflammasome NLRP3 activity, inhibiting pyroptosis and preventing airway inflammation. SIRT1 activates interferon-stimulated genes (ISG), which activates nuclear HMGB1, resulting in the generation of the antiviral effect of melatonin. 3CLpro, 3C-like protease; ACE2 Receptor, angiotensin-converting enzyme-2; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; IL-1R, interleukin-1 receptor; IL-1β, interleukin 1 beta; IL-6, interleukin 6; ISG, interferon-stimulated genes; MAPK pathway, mitogen-activated protein kinase; NF-kB, nuclear factor-kappa-light-chain-enhancer of activated B cells; NLRP3 Inflammasome, NLR family pyrin domain containing 3 inflammasome; Nrf2, nuclear factor erythroid 2-related factor 2; Nuclear HMGB1, nuclear high mobility group box protein 1; Pro IL-1β, pro interleukin 1 beta; RNS, reactive nitrogen species; ROS, reactive oxygen species; SARS-CoV-2 Virus, severe acute respiratory syndrome coronavirus 2; SIRT1, sirtuin 1; TLR4, toll-like receptor 4; TNFR, tumor necrosis factor receptor; TNF-α, tumor necrosis factor-alpha; Type 1 IFN, type I interferons.

Rogers et al., 2018). It is also involved the defense mechanism of plants and protects them against oxidative damage and many biotic and abiotic stresses. Melatonin therapy may enhance antigen presentation of macrophages and microglia of rat brain by upregulating their class I and class II MHC receptors, complement receptor 3 antigens, and cluster of differentiation 4 (CD4) antigens.

Melatonin decreases inflammation by inhibiting activation of TLR4 and NF-κB, downregulating the synthesis of enzymes like iNOS and COX-2, which result in lower levels of pro-inflammatory cytokines (Figure 3). MT increase the level of anti-inflammatory IL-10 cytokine and lowers cytokine production from hyperinflammatory glycolytic macrophages by transforming them into macrophages that are anti-inflammatory and that perform oxidative phosphorylation. This holds true in COVID-19 patients where melatonin stimulates the protein sirtuin 1, which suppresses the formation of hyperinflammatory (Martin Gimenez et al., 2020; Niu & Li, 2020; Öztürk et al., 2020). On the other hand, some research suggests that melatonin may have an inhibiting impact on immune responses. More comprehensive experiments are needed, according to conflicting research, to fully comprehend the molecular pathways modulated by MT in the immune system (Niu & Li, 2020).

4.3 | Antioxidant role of melatonin in countering oxidative stress and inflammation

Melatonin is a potent antioxidant and a free radical scavenger (Reiter et al., 1997). It can bind up to ten free radicals per molecule in comparison to traditional antioxidant molecules like vitamins C and E which can only bind one (Tan et al., 2007). MT can easily pass through membranes of various cells and mechanical barriers like the blood–brain barrier or the placental membrane because of its amphiphilic nature and high bioavailability (Reppert et al., 1979). MT enhances mitochondrial function by increasing complex I and IV activity and suppressing electron leakage (Juybari et al., 2019).

MT has been shown in several studies to have the ability to reduce inflammation in vivo and in vitro by regulating various pathways (Xu et al., 2007). Supplementation of melatonin in foodstuff may boost the production of the anti-inflammatory cytokine IL-1R and the negative acute-phase protein (APP) fibrinogen (Yu et al., 2017). Melatonin has been shown to have an anti-inflammatory effect in a variety of high- and medium-grade inflammatory diseases. MT was shown to decrease LPS-induced TNF-α in human blood cells (Silva et al., 2004). MT inhibited the production of IL-6 from IL-2 stimulated human lymphocytes and monocytes in vitro. MT has an anti-inflammatory impact on the NLRP3 inflammasome (Figure 3). In recent research, Zhang et al. (2016) showed that melatonin is a strong inhibitor of the Inflammasome NLRP3 in an ALI mouse model triggered by LPS. Melatonin's positive impact decreases the flow of neutrophils and macrophages into the lungs and improves pulmonary damage (Zhang et al., 2016).

Recently, several studies suggested that sirtuin is associated with diverse actions of melatonin. The idea that melatonin exerts indirect

effects on RORα via the circadian system has recently gained traction. SIRT1 increases the amplitude of the rhythm by increasing transcription of the core oscillator genes *Bmal1* and *Clock* through deacetylation of PGC-1α, making it easier for RORα to bind to RORE sequences (Chang & Guarente, 2013).

5 | IMMUNOMODULATORY ROLES OF SIRTUINS

5.1 | Modulation of inflammation by SIRT1 proteins

Sirtuins are proteins belonging to the class III histone deacetylase (HDACs) family that are ubiquitously found in all forms of life including humans. It was called after the Saccharomyces cerevisiae gene silent information regulation-2 and was known to be involved in the regulation of multiple processes like premature aging, inflammation, DNA damage, or any kind of genomic instability. A total of seven sirtuins (SIRT1–SIRT7) are present in humans (Frye, 2000). Among the seven sirtuins, silent information regulation-1 (SIRT1) has prominent anti-inflammatory, antiapoptotic, and antiaging effects (Nakagawa & Guarente, 2011) in several chronic diseases.

SIRT1 deacetylates histone proteins at specific residues (like H3 and H4) and nonhistone proteins like tumor suppressor p53, forkhead box protein O (FOXO) transcription factors, NF-κB, PARP, peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α), and hypoxia-inducible factor (HIF)-1α (Brunet, 2004; Jeong et al., 2007; Lim et al., 2010).

SIRT1 can lead to reduced inflammation in COVID-19 patients by directly modulating the immune response in macrophages and suppressing the activity of NF-κB by deacetylating Lys310 of the RelA/p65 subunit (Rajendrasozhan et al., 2008; Yeung et al., 2004). The p53 signaling pathway was shown to be upregulated in SARS-CoV-2-infected people's peripheral blood mononuclear cells, suggesting a role for cell death in COVID-19 pathogenesis. However, in COVID-19 patients with severe and intermediate illnesses, the role of p53 in lymphocyte homeostasis is unknown. According to a recent study, reduced expression of the deacetylase SIRT1 led to lower transcription levels of p53, compromising B and T cell signaling hemostasis and leading to B and T cell death, one of the main explanations for the severe symptoms of COVID-19 illness (Bordoni et al., 2021).

SIRT1 through modulation of NF-κB activation reduces poly (ADP-ribose) polymerase-1 (PARP-1) activity (Beneke, 2012; Rajamohan et al., 2009). Studies have shown that knocking down the SIRT1 in macrophages of mice increases LPS-stimulated TNF-α (Yoshizaki et al., 2010). SIRT1 deacetylates c-Fos and inhibits activator protein-1 (AP-1) and leads to the downregulation of COX-2 gene expression in macrophages (Zhang et al., 2010). The COX-2 enzyme is expressed by cells involved in inflammation and helps the cells in the conversion of arachidonic acid into prostaglandins and other eicosanoids (Sellers et al., 2010).

SIRT1 influence the RAAS pathway by reducing the expression levels of AGTR1 in aged transgenic mice overexpressing SIRT1

compared with control mice (Diaz-Ruiz et al., 2015). SIRT1, therefore, reduces hypoxia by deacetylating hypoxia-inducible factor (HIF)-1α at residue LYS674 (Lim et al., 2010).

5.2 | SIRT1 controls the biogenesis of mitochondria

SIRT1-stimulated deacetylation of PGC-1α acts as a chief regulator of mitochondrial metabolism and biogenesis (Amat et al., 2009; Guo et al., 2014). SIRT1promotes translocation of PGC-1α to the nucleus where it leads to coactivation of Nrf1/Nrf2 and mitochondrial transcription factor A (TFAM) to regulate the expression of genes responsible for encoding proteins involved in transcription and replication of mitochondrial DNA and the multienzyme complexes of the mitochondrial respiratory chain.

5.3 | SIRT1 modulation of oxidative stress

SIRT1 has been exhibited to control ROS levels by modulating the mitochondrial electron transport chain. Inhibition of NF-κB transcriptional activation by and reduction of expression of gp91phox and p22phox encoding for NADPH oxidase subunits by SIRT1, therefore prevents the production of reactive oxygen and nitrogen radicals by phagocytes (Anrather et al., 2006; Manea et al., 2007; Xie et al., 1994). NFE2L2, also referred to as Nrf2 in literature is known to bind to the antioxidant response element (ARE) sequences in promoters of the antioxidant genes and plays a crucial role in the activation of cellular antioxidant defense. Melatonin signals SIRT1-dependent transcriptional activation of Nrf2 to exert anti-oxidative effects have been reported in the developing rat brain and BV2 cells, and SIRT1 inhibitor remarkably decreased the SIRT1 and Nrf2 expression in BV2 cells (Shah et al., 2017). SIRT1 was also demonstrated to add to the activation of the Nrf2/ARE antioxidant pathway and hamper the apoptosis of type II alveolar epithelial cells (Ding et al., 2016).

5.4 | SIRT1 protein working in tandem with MT in COVID-19 patients

According to new retrospective research, COVID-19 infection may be much less prevalent in people who take supplementary melatonin (36–72 mg/day given in four divided doses). It was observed that a daily dose of MT led to decreased mortality rate, avoids ventilation problems, and decreased the duration of hospital stay of these patients. This effect might be explained by the fact that MT can upregulate type 1 interferon production by Coronavirus and activate polyubiquitination of the mitochondrial antiviral signaling (MAVS) protein through activation of SIRT1. In COVID-19 patients where there is oxidative stress due to uncontrolled production of cytokines and reactive oxygen species by the infected immune cells, SIRT1 helps to mount an effective antiviral response mediated by upregulating genes transcribing the Type I IFN (IFNβ) and by preventing the

release of high mobility group box 1 (HMGB1) (Bonaldi, 2003) from the nucleus by avoiding its acetylation. SIRT1 was reported to upregulate NFE2L2 protein that can inhibit the activation of the NLRP3 inflammasome, reducing the pro-inflammatory cytokine secretion of IL1 and IL18 and inhibiting the NF-κB activity, which is downstream of the MAVS protein, responsible for inducing the IFNβ through interferon regulatory factor 3 (IRF3) (Dinicolantonio et al., 2021; Li et al., 2020). If these theories are accurate, a nutraceutical regimen containing sirtuin activator melatonin may be useful in COVID-19 treatment that helps to alleviate severe inflammatory reactions in these patients by regulating the MAVS/IRF3/IFNβ, NF-κB, NRF2, HMGB1/ISG signaling pathways and boosting an antiviral effect.

5.5 | Association of SIRT1 protein with polyphenol EGCG in viral diseases

According to several studies, supplementation of EGCG in diet may protect against complex neurodegenerative, cardiovascular, inflammatory, and cancer disorders by increasing SIRT1 deacetylase activity, (Niu et al., 2013). SIRT1 inhibits the transcription activity of activator protein-1 (AP-1), resulting in the downregulation of COX-2 gene expression, according to recent research (Zhang et al., 2010). EGCG was shown to decrease hepatic cholesterol synthesis by binding to the sterol regulatory element-binding protein (SREBP)-2 and by upregulating SIRT1, FOXO1 expression, SOD activity, and total antioxidant activity (TAOC) and decreasing malondialdehyde (MDA) content (Li & Wu, 2018). It was also shown to possess anti-inflammatory effects and enhanced disposal of glucose in adipocyte cells by phosphorylating AMPK in the presence of SIRT1 (Xiao et al., 2014). EGCG stimulates SIRT1 protein which induced Akt and inhibits the NF-κB by phosphorylation of its p65 subunit. Another study reported the influence of the antioxidant property of EGCG on decreasing age-associated inflammation and liver injury by regulating the FOXO3a/SIRT1 signaling pathway through downregulation of the expression of NF-κB activity (Niu et al., 2013).

As a result, targeting the SIRT1 signaling pathways might be a viable treatment strategy for a variety of viral illnesses. The highest promising SIRT1-binding capability was found in EGCG, hence, it can be hypothesized to be a propitious pathway to treat viral diseases like COVID 19.

5.6 | Clinical studies of EGCG in humans with moderate and severe SARS-CoV-2 infection

Tea has been linked to the prevention and treatment of COVID-19 in three recent trials (Chowdhury & Barooah, 2020; Menegazzi et al., 2020; Mhatre et al., 2021). Early stages of viral infection, including attachment, entry, and membrane fusion, are inhibited by epigallocatechin-3-gallate (EGCG) (Hoffmann et al., 2020; Kaihatsu et al., 2018; Mhatre et al., 2021; Steinmann et al., 2013; Xu et al., 2017). The majority of these studies were carried out in

vitro in circumstances that may differ significantly from those found in people, therefore the findings should be regarded with caution.

In human HepG2 cells, the Nrf2-activator PB125® suppresses both ACE2 and TMPRSS2 production (McCord et al., 2020). In renal proximal tubule cells, genetic deletion of Nrf2 or pharmacological suppression of Nrf2 upregulates ACE2 expression, whereas its activator, oltipraz, downregulates ACE2 expression (Zhao et al., 2018). Genes connected to Nrf2-dependent antioxidant response are considerably reduced in COVID-19 patients' lung biopsies, and Nrf2 inducers (4-octyl-itaconate and dimethyl fumarate) reduce SARS-CoV-2 replication and inflammatory response (Cuadrado et al., 2020; Olagnier et al., 2020). These findings suggest that activating Nrf2 might help prevent SARS-CoV-2 infection and reduce COVID-19n severity (Zhang et al., 2021).

In an LPS-induced mouse model of ALI, EGCG (15 mg/kg, i.p.) administered 1 hr before and 3 hr after LPS instillation lowers ALI, neutrophil infiltration, and the rise in the M1/M2 macrophage subtype ratio (Almatroodi et al., 2020). If similar effects can be demonstrated in humans, EGCG might be useful in avoiding the cytokine storm and ARDS induced by SARS-CoV-2. In one study, the initial salivary concentrations of EGCG were 10–50 μM, with elimination $t_{1/2}$ values of 10–20 min, after drinking 200 ml of warm tea (containing 1200 mg of green tea extracts) and rinsing the mouth violently 10 times (Yang et al., 1999). Saliva samples (taken similarly) initially contained 120–300 μM EGCG after participants kept 96 mg EGCG in 60 ml in their mouth for 2 min and then fell to 25–65 μM after 30 min.

These data suggest that after drinking or gargling tea, the levels of EGCG and other catechins in the oral/nasal/pharyngeal cavity may be high enough to protect against viral infection. It was observed in Japan that gargling a tea catechin solution on a daily basis lowered the incidence of influenza infection in the elderly (Yamada et al., 2006). These exciting findings should be reproduced with a larger number of people and used to further antiviral studies in humans.

In another study by Bettuzzi et al., 10 SARS-COV-2 patients with positive swabs were treated at home for 15 days with two sessions of inhalation and three capsules each day (total catechins: 840 mg; total EGCG: 595 mg). All patients recovered fully and had no symptoms after a median of 9 days, with a range of 7–15 days. Seven patients had a negative SARS CoV-2 nasopharyngeal swab test after a median of 9 days and a range of 6–13 days (Bettuzzi et al., 2021). At the end of the therapy, the following inflammatory markers viz. α-1 antitrypsin, C-reactive protein, and eosinophils were significantly lowered in all patients, whereas 7 out of 10 also showed decreased levels of IL-6 and erythrocyte sedimentation rate. A bigger number of people must be engaged in a research study to establish if green tea polyphenols might assist COVID-19 patients to recover faster and prevent a fatality.

6 | CONCLUSION

The Coronavirus disease-19 pandemic is currently the world's most significant health concern. There is currently no single effective drug for the treatment of COVID-19 infection, but the inclusion of a variety of nutraceuticals derived from medicinal plants could provide a promising adjunct therapy for COVID-19 disease. Identifying the conditions in which SIRT1 or other sirtuins mediate or operate in tandem with Melatonin and/or with EGCG, therefore supporting or enhancing melatonin's and/or EGCG activities, will be a critical effort in near future. As evidenced by data from various viral illnesses with the enhanced cytokine release and inflammation, this relates to their common effects on TCR, TLR4, NF-κB, and inflammasomes as well as several newly found or investigated pathways.

In this review, we propose how SIRT1-dependent and -independent pathways could work along with MT and EGCG in preventing the entry and growth of Coronavirus 2 inside the host cell and modulate underlying signaling pathways specially NF-κB protein to alleviate the inflammation, oxidative stress, and lung injury in patients with severe COVID-19 infection. To support our hypothesis, more clinical trials need to be set up to standardize the dose and time of administration of this phytotherapeutics.

We propose that the NF-κB signaling pathway is one of the common pathways involved in the pathogenesis of the disease known to be suppressed by SIRT1 activators EGCG and MT in patients with severe SARS-CoV2 infection. Thus, the inclusion of these phytochemicals as dietary supplements may help in combating Coronavirus 2 infection in the host by strengthening their immune system. However, the crosstalk between these phytochemicals, SIRT1 and NF-κB, and their mechanism of action should be further validated through clinical studies and that may prove beneficial for the prevention and recovery of COVID-19 patients.

AUTHOR CONTRIBUTIONS

Vineeta Chattree: conceptualization, writing—reviewing, editing, and supervision. Kamana Singh: reviewing and editing. Kanishk Singh: resources, writing—original draft, reviewing, and editing. Aayush Goel: methodology, writing—original draft preparation, and data curation. Amritaparna Maity: resources, writing—original draft preparation and editing. Asif Lone: investigation, writing—original draft, visualization.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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REFERENCES

Almatroodi, S. A., Almatroudi, A., Alsahli, M. A., Aljasir, M. A., Syed, M. A., & Rahmani, A. H. (2020). Epigallocatechin-3-gallate (EGCG), an active compound of green tea attenuates acute lung injury regulating macrophage polarization and Krüpple-like-factor 4 (KLF4) expression. *Molecules*, 25(12), 2853. https://doi.org/10.3390/molecules25122853

Amat, R., Planavila, A., Chen, S. L., Iglesias, R., Giralt, M., & Villarroya, F. (2009). SIRT1 controls the transcription of the peroxisome proliferator-activated receptor-γ co-activator-1α(PGC-1α) gene in skeletal muscle through the PGC-1α autoregulatory loop and interaction with MyoD. *Journal of Biological Chemistry*, 284(33), 21872–21880. https://doi.org/10.1074/jbc.M109.022749

Anderson, G., & Reiter, R. J. (2020). Melatonin: Roles in influenza, Covid-19, and other viral infections. *Reviews in Medical Virology*, 30(3), e2109. https://doi.org/10.1002/rmv.2109

Angelopoulou, A., Alexandris, N., Konstantinou, E., Mesiakaris, K., Zanidis, C., Farsalinos, K., & Poulas, K. (2020). Imiquimod—A toll like receptor 7 agonist—Is an ideal option for management of COVID 19. *Environmental Research*, 188. https://doi.org/10.1016/j.envres.2020.109858

Anrather, J., Racchumi, G., & Iadecola, C. (2006). NF-κB regulates phagocytic NADPH oxidase by inducing the expression of gp91phox. *Journal of Biological Chemistry*, 281(9), 5657–5667. https://doi.org/10.1074/jbc.M506172200

Bahrampour Juybari, K., Pourhanifeh, M. H., Hosseinzadeh, A., Hemati, K., & Mehrzadi, S. (2020). Melatonin potentials against viral infections including COVID-19: Current evidence and new findings. *Virus Research*, 287, 198108. https://doi.org/10.1016/j.virusres.2020.198108

Bansal, A., Singh, A. D., Jain, V., Aggarwal, M., Gupta, S., Padappayil, R. P., Nadeem, M., Joshi, S., Mian, A., Greathouse, T., Wells, D., Gupta, M., & Khan, M. Z. (2021). The association of D-dimers with mortality, intensive care unit admission or acute respiratory distress syndrome in patients hospitalized with coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *Heart and Lung*, 50(1), 9–12. https://doi.org/10.1016/j.hrtlng.2020.08.024

Battagello, D. S., Dragunas, G., Klein, M. O., Ayub, A. L. P., Velloso, F. J., & Correa, R. G. (2020). Unpuzzling COVID-19: Tissue-related signaling pathways associated with SARS-CoV-2 infection and transmission. *Clinical Science*, 134(16), 2137–2160. https://doi.org/10.1042/CS20200904

Beneke, S. (2012). Regulation of chromatin structure by poly(ADP-ribosyl)ation. *Frontiers in Genetics*, 3, 169. https://doi.org/10.3389/fgene.2012.00169

Bettuzzi, S., Gabba, L., & Cataldo, S. (2021). Efficacy of a polyphenolic, standardized green tea extract for the treatment of COVID-19 syndrome: A proof-of-principle study. *COVID*, 1(1), 2–12. https://doi.org/10.3390/covid1010002

Boga, J. A., Coto-Montes, A., Rosales-Corral, S. A., Tan, D.-X., & Reiter, R. J. (2012). Beneficial actions of melatonin in the management of viral infections: A new use for this "molecular handyman"? *Reviews in Medical Virology*, 22(5), 323–338. https://doi.org/10.1002/rmv.1714

Bonaldi, T. (2003). Monocytic cells hyperacetylate chromatin protein HMGB1 to redirect it towards secretion. *The EMBO Journal*, 22(20), 5551–5560. https://doi.org/10.1093/emboj/cdg516

Bordoni, V., Tartaglia, E., Sacchi, A., Fimia, G. M., Cimini, E., Casetti, R., Notari, S., Grassi, G., Marchioni, L., Bibas, M., Capobianchi, M. R., Locatelli, F., Maeurer, M., Zumla, A., Antinori, A., Nicastri, E., Ippolito, G., & Agrati, C. (2021). The unbalanced p53/SIRT1 axis may impact lymphocyte homeostasis in COVID-19 patients. *International Journal of Infectious Diseases*, 105, 49–53. https://doi.org/10.1016/j.ijid.2021.02.019

Brunet, A. (2004). Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. *Science*, 303(5666), 2011–2015. https://doi.org/10.1126/science.1094637

Calland, N., Albecka, A., Belouzard, S., Wychowski, C., Duverlie, G., Descamps, V., Hober, D., Dubuisson, J., Rouillé, Y., & Séron, K. (2012). (−)-Epigallocatechin-3-gallate is a new inhibitor of hepatitis C virus entry. *Hepatology*, 55(3), 720–729. https://doi.org/10.1002/hep.24803

Campos, L. A., Cipolla-Neto, J., Amaral, F. G., Michelini, L. C., Bader, M., & Baltatu, O. C. (2013). The angiotensin-melatonin axis. *International Journal of Hypertension*, 2013, 521783. https://doi.org/10.1155/2013/521783

Cardinali, D. P. (2020). High doses of melatonin as a potential therapeutic tool for the neurologic sequels of covid-19 infection. *Melatonin Research*, 3(3), 311–317. https://doi.org/10.32794/mr11250064

Chang, H.-C., & Guarente, L. (2013). SIRT1 mediates central circadian control in the SCN by a mechanism that decays with aging. *Cell*, 153(7), 1448–1460. https://doi.org/10.1016/j.cell.2013.05.027

Chowdhury, P., & Barooah, A. K. (2020). Tea bioactive modulate innate immunity: In perception to COVID-19 pandemic. *Frontiers in Immunology*, 11, 590716. https://doi.org/10.3389/fimmu.2020.590716

Crackower, M. A., Sarao, R., Oudit, G. Y., Yagil, C., Kozieradzki, I., Scanga, S. E., Oliveira-dos-Santos, A. J., da Costa, J., Zhang, L., Pei, Y., Scholey, J., Ferrario, C. M., Manoukian, A. S., Chappell, M. C., Backx, P. H., Yagil, Y., & Penninger, J. M. (2002). Angiotensin-converting enzyme 2 is an essential regulator of heart function. *Nature*, 417(6891), 822–828. https://doi.org/10.1038/nature00786

Cuadrado, A., Pajares, M., Benito, C., Jiménez-Villegas, J., Escoll, M., Fernández-Ginés, R., Garcia Yagüe, A. J., Lastra, D., Manda, G., Rojo, A. I., & Dinkova-Kostova, A. T. (2020). Can activation of NRF2 be a strategy against COVID-19? *Trends in Pharmacological Sciences*, 41(9), 598–610. https://doi.org/10.1016/j.tips.2020.07.003

de Biasi, S., Meschiari, M., Gibellini, L., Bellinazzi, C., Borella, R., Fidanza, L., Gozzi, L., Iannone, A., lo Tartaro, D., Mattioli, M., Paolini, A., Menozzi, M., Milić, J., Franceschi, G., Fantini, R., Tonelli, R., Sita, M., Sarti, M., Trenti, T., … Cossarizza, A. (2020). Marked T cell activation, senescence, exhaustion and skewing towards TH17 in patients with COVID-19 pneumonia. *Nature Communications*, 11(1), 3434. https://doi.org/10.1038/s41467-020-17292-4

Diaz-Ruiz, C., Rodriguez-Perez, A. I., Beiroa, D., Rodriguez-Pallares, J., & Labandeira-Garcia, J. L. (2015). Reciprocal regulation between sirtuin-1 and angiotensin-II in the substantia nigra: Implications for aging and neurodegeneration. *Oncotarget*, 6(29), 26675–26689. https://doi.org/10.18632/oncotarget.5596

Ding, Y. W., Zhao, G. J., Li, X. L., Hong, G. L., Li, M. F., Qiu, Q. M., Wu, B., & Lu, Z. Q. (2016). SIRT1 exerts protective effects against paraquat-inducedinjury in mouse type II alveolar epithelial cellsby deacetylating NRF2 in vitro. *International Journal of Molecular Medicine*, 37(4), 1049–1058. https://doi.org/10.3892/ijmm.2016.2503

Dinicolantonio, J. J., McCarty, M., & Barroso-Aranda, J. (2021). Melatonin may decrease risk for and aid treatment of COVID-19 and other RNA viral infections. *Open Heart*, 8(1), e001568. https://doi.org/10.1136/openhrt-2020-001568

Dong, R., Wang, D., Wang, X., Zhang, K., Chen, P., Yang, C. S., & Zhang, J. (2016). Epigallocatechin-3-gallate enhances key enzymatic activities of hepatic thioredoxin and glutathione systems in selenium-optimal mice but activates hepatic Nrf2 responses in selenium-deficient mice. *Redox Biology*, 10, 221–232. https://doi.org/10.1016/j.redox.2016.10.009

Donoghue, M., Hsieh, F., Baronas, E., Godbout, K., Gosselin, M., Stagliano, N., Donovan, M., Woolf, B., Robison, K., Jeyaseelan, R., Breitbart, R. E., & Acton, S. (2000). A novel angiotensin-converting

enzyme–related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. *Circulation Research*, *87*(5), E1-9. https://doi.org/10.1161/01.RES.87.5.e1

Du, A., Zheng, R., Disoma, C., Li, S., Chen, Z., Li, S., Liu, P., Zhou, Y., Shen, Y., Liu, S., Zhang, Y., Dong, Z., Yang, Q., Alsaadawe, M., Razzaq, A., Peng, Y., Chen, X., Hu, L., Peng, J., ... Xia, Z. (2021). Epigallocatechin-3-gallate, an active ingredient of traditional Chinese medicines, inhibits the 3CLpro activity of SARS-CoV-2. *International Journal of Biological Macromolecules*, *176*, 1–12. https://doi.org/10.1016/j.ijbiomac.2021.02.012

Engel, R. H. (2006). Oxidative stress and apoptosis: A new treatment paradigm in cancer. *Frontiers in Bioscience*, *11*(1), 300–312. https://doi.org/10.2741/1798

Favalli, E. G., Biggioggero, M., Maioli, G., & Caporali, R. (2020). Baricitinib for COVID-19: A suitable treatment? *The Lancet Infectious Diseases*, *20*(9), 1012–1013. https://doi.org/10.1016/S1473-3099(20)30262-0

Feldmann, M., Maini, R. N., Woody, J. N., Holgate, S. T., Winter, G., Rowland, M., Richards, D., & Hussell, T. (2020). Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. *The Lancet*, *395*(10234), 1407–1409. https://doi.org/10.1016/S0140-6736(20)30858-8

Feng, Q., Torii, Y., Uchida, K., Nakamura, Y., Hara, Y., & Osawa, T. (2002). Black tea polyphenols, theaflavins, prevent cellular DNA damage by inhibiting oxidative stress and suppressing cytochrome P450 1A1 in cell cultures. *Journal of Agricultural and Food Chemistry*, *50*(1), 213–220. https://doi.org/10.1021/jf010875c

Forcados, G. E., Muhammad, A., Oladipo, O. O., Makama, S., & Meseko, C. A. (2021). Metabolic implications of oxidative stress and inflammatory process in SARS-CoV-2 pathogenesis: Therapeutic potential of natural antioxidants. *Frontiers in Cellular and Infection Microbiology*, *11*, 654813. https://doi.org/10.3389/fcimb.2021.654813

Frei, B., & Higdon, J. V. (2003). Antioxidant activity of tea polyphenols in vivo: Evidence from animal studies. *The Journal of Nutrition*, *133*(10), 3275S–3284S. https://doi.org/10.1093/jn/133.10.3275S

Frye, R. A. (2000). Phylogenetic classification of prokaryotic and eukaryotic Sir2-like proteins. *Biochemical and Biophysical Research Communications*, *273*(2), 793–798. https://doi.org/10.1006/bbrc.2000.3000

Ge, M., Xiao, Y., Chen, H., Luo, F., Du, G., & Zeng, F. (2018). Multiple antiviral approaches of (–)-epigallocatechin-3-gallate (EGCG) against porcine reproductive and respiratory syndrome virus infection in vitro. *Antiviral Research*, *158*, 52–62. https://doi.org/10.1016/j.antiviral.2018.07.012

Ghasemitarei, M., Privat-Maldonado, A., Yusupov, M., Rahnama, S., Bogaerts, A., & Ejtehadi, M. R. (2022). Effect of cysteine oxidation in SARS-CoV-2 receptor-binding domain on its interaction with two cell receptors: Insights from atomistic simulations. *Journal of Chemical Information and Modeling*, *62*(1), 129–141. https://doi.org/10.1021/acs.jcim.1c00853

Guo, P., Pi, H., Xu, S., Zhang, L., Li, Y., Li, M., Cao, Z., Tian, L., Xie, J., Li, R., He, M., Lu, Y., Liu, C., Duan, W., Yu, Z., & Zhou, Z. (2014). Melatonin improves mitochondrial function by promoting mt1/sirt1/pgc-1 alpha-dependent mitochondrial biogenesis in cadmium-induced hepatotoxicity in vitro. *Toxicological Sciences*, *142*(1), 182–195. https://doi.org/10.1093/toxsci/kfu164

Hadjadj, J., Yatim, N., Barnabei, L., Corneau, A., Boussier, J., Smith, N., Péré, H., Charbit, B., Bondet, V., Chenevier-Gobeaux, C., Breillat, P., Carlier, N., Gauzit, R., Morbieu, C., Pène, F., Marin, N., Roche, N., Szwebel, T.-A., Merkling, S. H., ... Terrier, B. (2020). Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science*, *369*(6504), 718–724. https://doi.org/10.1126/science.abc6027

Hanff, T. C., Harhay, M. O., Brown, T. S., Cohen, J. B., & Mohareb, A. M. (2020). Is there an association between COVID-19 mortality and the renin-angiotensin system? A call for epidemiologic investigations. *Clinical Infectious Diseases*, *71*(15), 870–874. https://doi.org/10.1093/cid/ciaa329

Harapan, H., Itoh, N., Yufika, A., Winardi, W., Keam, S., Te, H., Megawati, D., Hayati, Z., Wagner, A. L., & Mudatsir, M. (2020). Coronavirus disease 2019 (COVID-19): A literature review. *Journal of Infection and Public Health*, *13*(5), 667–673. https://doi.org/10.1016/j.jiph.2020.03.019

Hardeland, R., & Poeggeler, B. (2003). Non-vertebrate melatonin. *Journal of Pineal Research*, *34*(4), 233–241. https://doi.org/10.1034/j.1600-079X.2003.00040.x

Hati, S., & Bhattacharyya, S. (2020). Impact of thiol–disulfide balance on the binding of Covid-19 spike protein with angiotensin-converting enzyme 2 receptor. *ACS Omega*, *5*(26), 16292–16298. https://doi.org/10.1021/acsomega.0c02125

Hayakawa, S., Oishi, Y., Tanabe, H., Isemura, M., & Suzuki, Y. (2019). Tea, coffee and health benefits. In J. M. Mérillon & K. Ramawat (Eds.), *Bioactive molecules in good*. Reference Series in Phytochemistry. (pp. 991–1047). Springer. https://doi.org/10.1007/978-3-319-78030-6_14

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T. S., Herrler, G., Wu, N.-H., Nitsche, A., Müller, M. A., Drosten, C., & Pöhlmann, S. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*, *181*(2), 271–280.e8. https://doi.org/10.1016/j.cell.2020.02.052

Hosakote, Y. M., Jantzi, P. D., Esham, D. L., Spratt, H., Kurosky, A., Casola, A., & Garofalo, R. P. (2011). Viral-mediated inhibition of antioxidant enzymes contributes to the pathogenesis of severe respiratory syncytial virus bronchiolitis. *American Journal of Respiratory and Critical Care Medicine*, *183*(11), 1550–1560. https://doi.org/10.1164/rccm.201010-1755OC

Hu, J., Webster, D., Cao, J., & Shao, A. (2018). The safety of green tea and green tea extract consumption in adults—Results of a systematic review. *Regulatory Toxicology and Pharmacology*, *95*, 412–433. https://doi.org/10.1016/j.yrtph.2018.03.019

Huang, S. H., Cao, X. J., Liu, W., Shi, X. Y., & Wei, W. (2010). Inhibitory effect of melatonin on lung oxidative stress induced by respiratory syncytial virus infection in mice. *Journal of Pineal Research*, *48*(2), 109–116. https://doi.org/10.1111/j.1600-079X.2009.00733.x

Huang, W., Berube, J., McNamara, M., Saksena, S., Hartman, M., Arshad, T., Bornheimer, S. J., & O'Gorman, M. (2020). Lymphocyte subset counts in COVID-19 patients: A meta-analysis. *Cytometry Part A*, *97*(8), 772–776. https://doi.org/10.1002/cyto.a.24172

Jang, M., Park, R., Park, Y. I., Cha, Y. E., Yamamoto, A., Lee, J. I., & Park, J. (2021). EGCG, a green tea polyphenol, inhibits human coronavirus replication in vitro. *Biochemical and Biophysical Research Communications*, *547*, 23–28. https://doi.org/10.1016/j.bbrc.2021.02.016

Jang, M., Park, Y. I., Cha, Y. E., Park, R., Namkoong, S., Lee, J. I., & Park, J. (2020). Tea polyphenols EGCG and theaflavin inhibit the activity of SARS-CoV-2 3CL-protease in vitro. *Evidence-Based Complementary and Alternative Medicine*, *2020*, 5630838. https://doi.org/10.1155/2020/5630838

Jeong, J., Juhn, K., Lee, H., Kim, S.-H., Min, B.-H., Lee, K.-M., Cho, M.-H., Park, G.-H., & Lee, K.-H. (2007). SIRT1 promotes DNA repair activity and deacetylation of Ku70. *Experimental & Molecular Medicine*, *39*(1), 8–13. https://doi.org/10.1038/emm.2007.2

Juybari, K. B., Hosseinzadeh, A., Ghaznavi, H., Kamali, M., Sedaghat, A., Mehrzadi, S., & Naseripour, M. (2019). Melatonin as a modulator of degenerative and regenerative signaling pathways in injured retinal ganglion cells. *Current Pharmaceutical Design*, *25*(28), 3057–3073. https://doi.org/10.2174/1381612825666190829151314

Kaihatsu, K., Yamabe, M., & Ebara, Y. (2018). Antiviral mechanism of action of epigallocatechin-3-O-gallate and its fatty acid esters. *Molecules*, *23*(10), 2475. https://doi.org/10.3390/molecules23102475

Khan, N., Afaq, F., Saleem, M., Ahmad, N., & Mukhtar, H. (2006). Targeting multiple signaling pathways by green tea polyphenol (−)-epigallocatechin-3-gallate. *Cancer Research, 66*(5), 2500–2505. https://doi.org/10.1158/0008-5472.CAN-05-3636

Kitada, M., Ogura, Y., Monno, I., & Koya, D. (2019). Sirtuins and type 2 diabetes: Role in inflammation, oxidative stress, and mitochondrial function. *Frontiers in Endocrinology, 10,* 187. https://doi.org/10.3389/fendo.2019.00187

Kuba, K., Imai, Y., Rao, S., Gao, H., Guo, F., Guan, B., Huan, Y., Yang, P., Zhang, Y., Deng, W., Bao, L., Zhang, B., Liu, G., Wang, Z., Chappell, M., Liu, Y., Zheng, D., Leibbrandt, A., Wada, T., ... Penninger, J. M. (2005). A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nature Medicine, 11*(8), 875–879. https://doi.org/10.1038/nm1267

Kucera, O., Mezera, V., Moravcova, A., Endlicher, R., Lotkova, H., Drahota, Z., & Cervinkova, Z. (2015). In vitro toxicity of epigallocatechin gallate in rat liver mitochondria and hepatocytes. *Oxidative Medicine and Cellular Longevity, 2015,* 476180. https://doi.org/10.1155/2015/476180

Kuriakose, J., Montezano, A. C., & Touyz, R. M. (2021). ACE2/Ang-(1-7)/Mas1 axis and the vascular system: Vasoprotection to COVID-19-associated vascular disease. *Clinical Science, 135*(2), 387–407. https://doi.org/10.1042/CS20200480

Laforge, M., Elbim, C., Frère, C., Hémadi, M., Massaad, C., Nuss, P., Benoliel, J.-J., & Becker, C. (2020). Tissue damage from neutrophil-induced oxidative stress in COVID-19. *Nature Reviews Immunology, 20*(9), 515–516. https://doi.org/10.1038/s41577-020-0407-1

Land, W. G. (2015). The role of damage-associated molecular patterns (DAMPs) in human diseases: Part II: DAMPs as diagnostics, prognostics and therapeutics in clinical medicine. *Sultan Qaboos University Medical Journal, 15*(2), e157–e170 http://www.ncbi.nlm.nih.gov/pubmed/26052447

Li, X., Geng, M., Peng, Y., Meng, L., & Lu, S. (2020). Molecular immune pathogenesis and diagnosis of COVID-19. *Journal of Pharmaceutical Analysis, 10*(2), 102–108. https://doi.org/10.1016/j.jpha.2020.03.001

Li, Y., & Wu, S. (2018). Epigallocatechin gallate suppresses hepatic cholesterol synthesis by targeting SREBP-2 through SIRT1/FOXO1 signaling pathway. *Molecular and Cellular Biochemistry, 448*(1–2), 175–185. https://doi.org/10.1007/s11010-018-3324-x

Lim, J. H., Lee, Y. M., Chun, Y. S., Chen, J., Kim, J. E., & Park, J. W. (2010). Sirtuin 1 modulates cellular responses to hypoxia by deacetylating hypoxia-inducible factor 1α. *Molecular Cell, 38*(6), 864–878. https://doi.org/10.1016/j.molcel.2010.05.023

Liu, Y., Yang, Y., Zhang, C., Huang, F., Wang, F., Yuan, J., Wang, Z., Li, J., Li, J., Feng, C., Zhang, Z., Wang, L., Peng, L., Chen, L., Qin, Y., Zhao, D., Tan, S., Yin, L., Xu, J., ... Liu, L. (2020). Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Science China Life Sciences, 63*(3), 364–374. https://doi.org/10.1007/s11427-020-1643-8

Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Wang, W., Song, H., Huang, B., Zhu, N., Bi, Y., Ma, X., Zhan, F., Wang, L., Hu, T., Zhou, H., Hu, Z., Zhou, W., Zhao, L., ... Tan, W. (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. *The Lancet, 395*(10224), 565–574. https://doi.org/10.1016/S0140-6736(20)30251-8

Luo, W., Li, Y. X., Jiang, L. J., Chen, Q., Wang, T., & Ye, D. W. (2020). Targeting JAK-STAT signaling to control cytokine release syndrome in COVID-19. *Trends in Pharmacological Sciences, 41*(8), 531–543. https://doi.org/10.1016/j.tips.2020.06.007

Magro, G. (2020). SARS-CoV-2 and COVID-19: Is interleukin-6 (IL-6) the 'culprit lesion' of ARDS onset? What is there besides Tocilizumab? SGP130Fc. *Cytokine: X, 2*(2), 100029. https://doi.org/10.1016/j.cytox.2020.100029

Manea, A., Manea, S. A., Gafencu, A. V., & Raicu, M. (2007). Regulation of NADPH oxidase subunit p22phox by NF-kB in human aortic smooth muscle cells. *Archives of Physiology and Biochemistry, 113*(4–5), 163–172. https://doi.org/10.1080/13813450701531235

Martin Gimenez, V. M., Prado, N., Diez, E., Manucha, W., & Reiter, R. J. (2020). New proposal involving nanoformulated melatonin targeted to the mitochondria as a potential COVID-19 treatment. *Nanomedicine, 15*(29), 2819–2821. https://doi.org/10.2217/nnm-2020-0371

McCord, J. M., Hybertson, B. M., Cota-Gomez, A., Geraci, K. P., & Gao, B. (2020). Nrf2 activator PB125® as a potential therapeutic agent against COVID-19. *Antioxidants, 9*(6), 518. https://doi.org/10.3390/antiox9060518

Mehta, P., McAuley, D. F., Brown, M., Sanchez, E., Tattersall, R. S., & Manson, J. J. (2020). COVID-19: Consider cytokine storm syndromes and immunosuppression. *The Lancet, 395*(10229), 1033–1034. https://doi.org/10.1016/S0140-6736(20)30628-0

Menegazzi, M., Campagnari, R., Bertoldi, M., Crupi, R., di Paola, R., & Cuzzocrea, S. (2020). Protective effect of epigallocatechin-3-gallate (EGCG) in diseases with uncontrolled immune activation: Could such a scenario be helpful to counteract COVID-19? *International Journal of Molecular Sciences, 21*(14), 5171. https://doi.org/10.3390/ijms21145171

Mhatre, S., Srivastava, T., Naik, S., & Patravale, V. (2021). Antiviral activity of green tea and black tea polyphenols in prophylaxis and treatment of COVID-19: A review. *Phytomedicine, 85,* 153286. https://doi.org/10.1016/j.phymed.2020.153286

Miller, S. C., Pandi, P. S. R., Esquifino, A. I., Cardinali, D. P., & Maestroni, G. J. M. (2006). The role of melatonin in immuno-enhancement: Potential application in cancer. *International Journal of Experimental Pathology, 87*(2), 81–87. https://doi.org/10.1111/j.0959-9673.2006.00474.x

Morchang, A., Malakar, S., Poonudom, K., Noisakran, S., Yenchitsomanus, P. T., & Limjindaporn, T. (2021). Melatonin inhibits dengue virus infection via the sirtuin 1-mediated interferon pathway. *Viruses, 13*(4), 659. https://doi.org/10.3390/v13040659

Munin, A., & Edwards-Lévy, F. (2011). Encapsulation of natural polyphenolic compounds; a review. *Pharmaceutics, 3*(4), 793–829. https://doi.org/10.3390/pharmaceutics3040793

Na, H.-K., Kim, E.-H., Jung, J.-H., Lee, H.-H., Hyun, J.-W., & Surh, Y.-J. (2008). (−)-Epigallocatechin gallate induces Nrf2-mediated antioxidant enzyme expression via activation of PI3K and ERK in human mammary epithelial cells. *Archives of Biochemistry and Biophysics, 476*(2), 171–177. https://doi.org/10.1016/j.abb.2008.04.003

Nakagawa, T., & Guarente, L. (2011). Sirtuins at a glance. *Journal of Cell Science, 124*(6), 833–838. https://doi.org/10.1242/jcs.081067

Niu, Y., Na, L., Feng, R., Gong, L., Zhao, Y., Li, Q., Li, Y., & Sun, C. (2013). The phytochemical, EGCG, extends lifespan by reducing liver and kidney function damage and improving age-associated inflammation and oxidative stress in healthy rats. *Aging Cell, 12*(6), 1041–1049. https://doi.org/10.1111/acel.12133

Niu, Z., & Li, R. (2020). Clinical study of novel coronavirus pneumonia prevention by melatonin. *Reproductive BioMedicine Online, 41*(6), 1156. https://doi.org/10.1016/j.rbmo.2020.09.003

Ohishi, T., Goto, S., Monira, P., Isemura, M., & Nakamura, Y. (2016). Anti-inflammatory action of green tea. *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry, 15*(2), 74–90. https://doi.org/10.2174/1871523015666160915154443

Olagnier, D., Farahani, E., Thyrsted, J., Blay-Cadanet, J., Herengt, A., Idorn, M., Hait, A., Hernaez, B., Knudsen, A., Iversen, M. B., Schilling, M., Jørgensen, S. E., Thomsen, M., Reinert, L. S., Lappe, M., Hoang, H.-D., Gilchrist, V. H., Hansen, A. L., Ottosen, R., ... Holm, C. K. (2020). SARS-CoV2-mediated suppression of NRF2-signaling reveals potent antiviral and anti-inflammatory activity of 4-octyl-itaconate and dimethyl fumarate. *Nature Communications, 11*(1), 4938. https://doi.org/10.1038/s41467-020-18764-3

Öztürk, G., Akbulut, K. G., & Güney, Ş. (2020). Melatonin, aging, and COVID-19: Could melatonin be beneficial for COVID-19 treatment

in the elderly? *Turkish Journal of Medical Sciences*, *50*(6), 1504–1512. https://doi.org/10.3906/sag-2005-356

Palmer, R. M. J., Ferrige, A. G., & Moncada, S. (1987). Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature*, *327*(6122), 524–526. https://doi.org/10.1038/327524a0

Pandey, K. B., & Rizvi, S. I. (2009). Plant polyphenols as dietary antioxidants in human health and disease. *Oxidative Medicine and Cellular Longevity*, *2*(5), 270–278. https://doi.org/10.4161/oxim.2.5.9498

Poeggeler, B., Saarela, S., Reiter, R. J., Tan, D.-X., Chen, L.-D., Manchester, L. C., & Barlow-Walden, L. R. (2006). Melatonin-A highly potent endogenous radical scavenger and electron donor: New aspects of the oxidation chemistry of this indole accessed in vitroa. *Annals of the New York Academy of Sciences*, *738*(1), 419–420. https://doi.org/10.1111/j.1749-6632.1994.tb21831.x

Poulose, N., & Raju, R. (2015). Sirtuin regulation in aging and injury. *Biochimica et Biophysica Acta (BBA)—Molecular Basis of Disease*, *1852*(11), 2442–2455. https://doi.org/10.1016/j.bbadis.2015.08.017

Prokunina-Olsson, L., Alphonse, N., Dickenson, R. E., Durbin, J. E., Glenn, J. S., Hartmann, R., Kotenko, S. V., Lazear, H. M., O'Brien, T. R., Odendall, C., Onabajo, O. O., Piontkivska, H., Santer, D. M., Reich, N. C., Wack, A., & Zanoni, I. (2020). COVID-19 and emerging viral infections: The case for interferon lambda. *Journal of Experimental Medicine*, *217*(5), e20200653. https://doi.org/10.1084/jem.20200653

Raekiansyah, M., Buerano, C. C., Luz, M. A. D., & Morita, K. (2018). Inhibitory effect of the green tea molecule EGCG against dengue virus infection. *Archives of Virology*, *163*(6), 1649–1655. https://doi.org/10.1007/s00705-018-3769-y

Ragab, D., Salah Eldin, H., Taeimah, M., Khattab, R., & Salem, R. (2020). The COVID-19 cytokine storm; what we know so far. *Frontiers in Immunology*, *11*, 1446. https://doi.org/10.3389/fimmu.2020.01446

Rajamohan, S. B., Pillai, V. B., Gupta, M., Sundaresan, N. R., Birukov, K. G., Samant, S., Hottiger, M. O., & Gupta, M. P. (2009). SIRT1 promotes cell survival under stress by deacetylation-dependent deactivation of poly(ADP-ribose) polymerase 1. *Molecular and Cellular Biology*, *29*(15), 4116–4129. https://doi.org/10.1128/mcb.00121-09

Rajendrasozhan, S., Yang, S. R., Kinnula, V. L., & Rahman, I. (2008). SIRT1, an antiinflammatory and antiaging protein, is decreased in lungs of patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, *177*(8), 861–870. https://doi.org/10.1164/rccm.200708-1269OC

Reiter, R., Tang, L., Garcia, J. J., & Muñoz-Hoyos, A. (1997). Pharmacological actions of melatonin in oxygen radical pathophysiology. *Life Sciences*, *60*(25), 2255–2271. https://doi.org/10.1016/S0024-3205(97)00030-1

Reppert, S. M., Chez, R. A., Anderson, A., & Klein, D. C. (1979). Maternal-fetal transfer of melatonin in the non-human primate. *Pediatric Research*, *13*(6), 788–791. https://doi.org/10.1203/00006450-197906000-00015

Reygaert, W. C. (2018). Green tea catechins: Their use in treating and preventing infectious diseases. *BioMed Research International*, *2018*, 9105261. https://doi.org/10.1155/2018/9105261

Rogers, M. C., Williams, J., & v. (2018). Quis Custodiet Ipsos Custodes? Regulation of cell-mediated immune responses following viral lung infections. *Annual Review of Virology*, *5*(1), 363–383. https://doi.org/10.1146/annurev-virology-092917-043515

Ropero, S., & Esteller, M. (2007). The role of histone deacetylases (HDACs) in human cancer. *Molecular Oncology*, *1*(1), 19–25. https://doi.org/10.1016/j.molonc.2007.01.001

Saleh, J., Peyssonnaux, C., Singh, K. K., & Edeas, M. (2020). Mitochondria and microbiota dysfunction in COVID-19 pathogenesis. *Mitochondrion*, *54*, 1–7. https://doi.org/10.1016/j.mito.2020.06.008

Schofield, J. H., & Schafer, Z. T. (2021). Mitochondrial reactive oxygen species and mitophagy: A complex and nuanced relationship.

Antioxidants and Redox Signaling, *34*(7), 517–530. https://doi.org/10.1089/ars.2020.8058

Sellers, R. S., Radi, Z. A., & Khan, N. K. (2010). Pathophysiology of cyclooxygenases in cardiovascular homeostasis. *Veterinary Pathology*, *47*(4), 601–613. https://doi.org/10.1177/0300985810364389

Shah, S. A., Khan, M., Jo, M. H., Jo, M. G., Amin, F. U., & Kim, M. O. (2017). Melatonin stimulates the SIRT1/Nrf2 signaling pathway counteracting lipopolysaccharide (LPS)-induced oxidative stress to rescue postnatal rat brain. *CNS Neuroscience and Therapeutics*, *23*(1), 33–44. https://doi.org/10.1111/cns.12588

Shi, C. S., Nabar, N. R., Huang, N. N., & Kehrl, J. H. (2019). SARS-Coronavirus Open Reading Frame-8b triggers intracellular stress pathways and activates NLRP3 inflammasomes. *Cell Death Discovery*, *5*(1), 101. https://doi.org/10.1038/s41420-019-0181-7

Shi, X., Ye, J., Leonard, S., Ding, M., Vallyathan, V., Castranova, V., Rojanasakul, Y., & Dong, Z. (2000). Antioxidant properties of (–)-epicatechin-3-gallate and its inhibition of Cr(VI)-induced DNA damage and Cr(IV)- or TPA-stimulated NF-κB activation. *Molecular and Cellular Biochemistry*, *206*(1/2), 125–132. https://doi.org/10.1023/A:1007012403691

Shibutani, S., Takeshita, M., & Grollman, A. P. (1991). Insertion of specific bases during DNA synthesis past the oxidation-damaged base 8-oxodG. *Nature*, *349*(6308), 431–434. https://doi.org/10.1038/349431a0

Silva, S. O., Rodrigues, M. R., Ximenes, V. F., Bueno-Da-Silva, A. E. B., Amarante-Mendes, G. P., & Campa, A. (2004). Neutrophils as a specific target for melatonin and kynuramines: Effects on cytokine release. *Journal of Neuroimmunology*, *156*(1–2), 146–152. https://doi.org/10.1016/j.jneuroim.2004.07.015

Singh, R., Akhtar, N., & Haqqi, T. M. (2010). Green tea polyphenol epigallocatechi3-gallate: Inflammation and arthritis. *Life Sciences*, *86*(25–26), 907–918. https://doi.org/10.1016/j.lfs.2010.04.013

Sodagari, H. R., Bahramsoltani, R., Farzaei, M. H., Abdolghaffari, A. H., Rezaei, N., & Taylor-Robinson, A. W. (2016). Tea polyphenols as natural products for potential future management of HIV infection—An overview. *Journal of Natural Remedies*, *16*(2), 60. https://doi.org/10.18311/jnr/2016/4782

Steinmann, J., Buer, J., Pietschmann, T., & Steinmann, E. (2013). Anti-infective properties of epigallocatechin-3-gallate (EGCG), a component of green tea. *British Journal of Pharmacology*, *168*(5), 1059–1073. https://doi.org/10.1111/bph.12009

Sun, W., Liu, X., Zhang, H., Song, Y., Li, T., Liu, X., Liu, Y., Guo, L., Wang, F., Yang, T., Guo, W., Wu, J., Jin, H., & Wu, H. (2017). Epigallocatechin gallate upregulates NRF2 to prevent diabetic nephropathy via disabling KEAP1. *Free Radical Biology and Medicine*, *108*, 840–857. https://doi.org/10.1016/j.freeradbiomed.2017.04.365

Sun, X., Wang, T., Cai, D., Hu, Z., Chen, J., Liao, H., Zhi, L., Wei, H., Zhang, Z., Qiu, Y., Wang, J., & Wang, A. (2020). Cytokine storm intervention in the early stages of COVID-19 pneumonia. *Cytokine and Growth Factor Reviews*, *53*, 38–42. https://doi.org/10.1016/j.cytogfr.2020.04.002

Tan, D. X., Manchester, L. C., Terron, M. P., Flores, L. J., & Reiter, R. J. (2007). One molecule, many derivatives: A never-ending interaction of melatonin with reactive oxygen and nitrogen species? *Journal of Pineal Research*, *42*(1), 28–42. https://doi.org/10.1111/j.1600-079X.2006.00407.x

Umeda, D., Yano, S., Yamada, K., & Tachibana, H. (2008). Green tea polyphenol epigallocatechin-3-gallate signaling pathway through 67-kDa laminin receptor. *Journal of Biological Chemistry*, *283*(6), 3050–3058. https://doi.org/10.1074/jbc.M707892200

Xiao, N., Mei, F., Sun, Y., Pan, G., Liu, B., & Liu, K. (2014). Quercetin, luteolin, and epigallocatechin gallate promote glucose disposal in adipocytes with regulation of AMP-activated kinase and/or sirtuin 1 activity. *Planta Medica*, *80*(12), 993–1000. https://doi.org/10.1055/s-0034-1382864

Xie, Q. W., Kashiwabara, Y., & Nathan, C. (1994). Role of transcription factor NF-κB/Rel in induction of nitric oxide synthase. _Journal of Biological Chemistry, 269_(7), 4705–4708. https://doi.org/10.1016/s0021-9258(17)37600-7

Xu, D. X., Wang, H., Ning, H., Zhao, L., & Chen, Y. H. (2007). Maternally administered melatonin differentially regulates lipopolysaccharide-induced proinflammatory and anti-inflammatory cytokines in maternal serum, amniotic fluid, fetal liver, and fetal brain. _Journal of Pineal Research, 43_(1), 74–79. https://doi.org/10.1111/j.1600-079X.2007.00445.x

Xu, J., Xu, Z., & Zheng, W. (2017). A review of the antiviral role of green tea catechins. _Molecules, 22_(8), 1337. https://doi.org/10.3390/molecules22081337

Yamada, H., Takuma, N., Daimon, T., & Hara, Y. (2006). Gargling with tea catechin extracts for the prevention of influenza infection in elderly nursing home residents: A prospective clinical study. _The Journal of Alternative and Complementary Medicine, 12_(7), 669–672. https://doi.org/10.1089/acm.2006.12.669

Yang, C. S., Ho, C.-T., Zhang, J., Wan, X., Zhang, K., & Lim, J. (2018). Antioxidants: Differing meanings in food science and health science. _Journal of Agricultural and Food Chemistry, 66_(12), 3063–3068. https://doi.org/10.1021/acs.jafc.7b05830

Yang, C. S., Lee, M. J., & Chen, L. (1999). Human salivary tea catechin levels and catechin esterase activities: Implication in human cancer prevention studies. _Cancer Epidemiology, Biomarkers & Prevention, 8_(1), 83–89.

Yang, M. (2020). Cell Pyroptosis, a potential pathogenic mechanism of 2019-nCoV infection. _SSRN Electronic Journal_. https://doi.org/10.2139/ssrn.3527420

Yeung, F., Hoberg, J. E., Ramsey, C. S., Keller, M. D., Jones, D. R., Frye, R. A., & Mayo, M. W. (2004). Modulation of NF-κB-dependent transcription and cell survival by the SIRT1 deacetylase. _EMBO Journal, 23_(12), 2369–2380. https://doi.org/10.1038/sj.emboj.7600244

Yoon, J. Y., Kwon, H. H., Min, S. U., Thiboutot, D. M., & Suh, D. H. (2013). Epigallocatechin-3-gallate improves acne in humans by modulating intracellular molecular targets and inhibiting _P. acnes. Journal of Investigative Dermatology, 133_(2), 429–440. https://doi.org/10.1038/jid.2012.292

Yoshizaki, T., Schenk, S., Imamura, T., Babendure, J. L., Sonoda, N., Ju Bae, E., Young Oh, D., Lu, M., Milne, J. C., Westphal, C., Bandyopadhyay, G., & Olefsky, J. M. (2010). SIRT1 inhibits inflammatory pathways in macrophages and modulates insulin sensitivity. _American Journal of Physiology. Endocrinology and Metabolism, 298_(8), 419–428. https://doi.org/10.1152/ajpendo.00417.2009.-Chronic

Yu, G. M., Kubota, H., Okita, M., & Maeda, T. (2017). The anti-inflammatory and antioxidant effects of melatonin on LPS-stimulated bovine mammary epithelial cells. _PLoS One, 12_(5), e0178525. https://doi.org/10.1371/journal.pone.0178525

Zainal, N., Chang, C. P., Cheng, Y. L., Wu, Y. W., Anderson, R., Wan, S. W., Chen, C. L., Ho, T. S., Abubakar, S., & Lin, Y. S. (2017). Resveratrol treatment reveals a novel role for HMGB1 in regulation of the type 1 interferon response in dengue virus infection. _Scientific Reports, 7_, 42998. https://doi.org/10.1038/srep42998

Zaveri, N. T. (2006). Green tea and its polyphenolic catechins: Medicinal uses in cancer and noncancer applications. _Life Sciences, 78_(18), 2073–2080. https://doi.org/10.1016/j.lfs.2005.12.006

Zhang, C., Wu, Z., Li, J. W., Zhao, H., & Wang, G. Q. (2020). Cytokine release syndrome in severe COVID-19: Interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. _International Journal of Antimicrobial Agents, 55_(5), 105954. https://doi.org/10.1016/j.ijantimicag.2020.105954

Zhang, R., Wang, X., Ni, L., Di, X., Ma, B., Niu, S., Liu, C., & Reiter, R. J. (2020). COVID-19: Melatonin as a potential adjuvant treatment. _Life Sciences, 250_, 117583. https://doi.org/10.1016/j.lfs.2020.117583

Zhang, R., Chen, H. Z., Liu, J. J., Jia, Y. Y., Zhang, Z. Q., Yang, R. F., Zhang, Y., Xu, J., Wei, Y. S., Liu, D. P., & Liang, C. C. (2010). SIRT1 suppresses activator protein-1 transcriptional activity and cyclooxygenase-2 expression in macrophages. _Journal of Biological Chemistry, 285_(10), 7097–7110. https://doi.org/10.1074/jbc.M109.038604

Zhang, Y., Li, X., Grailer, J. J., Wang, N., Wang, M., Yao, J., Zhong, R., Gao, G. F., Ward, P. A., Tan, D. X., & Li, X. (2016). Melatonin alleviates acute lung injury through inhibiting the NLRP3 inflammasome. _Journal of Pineal Research, 60_(4), 405–414. https://doi.org/10.1111/jpi.12322

Zhang, Z., Zhang, X., Bi, K., He, Y., Yan, W., Yang, C. S., & Zhang, J. (2021). Potential protective mechanisms of green tea polyphenol EGCG against COVID-19. _Trends in Food Science & Technology, 114_, 11–24. https://doi.org/10.1016/j.tifs.2021.05.023

Zhao, S., Ghosh, A., Lo, C.-S., Chenier, I., Scholey, J. W., Filep, J. G., Ingelfinger, J. R., Zhang, S.-L., & Chan, J. S. D. (2018). Nrf2 deficiency upregulates intrarenal angiotensin-converting Enzyme-2 and angiotensin 1-7 receptor expression and attenuates hypertension and nephropathy in diabetic mice. _Endocrinology, 159_(2), 836–852. https://doi.org/10.1210/en.2017-00752

Zhong, Y., & Shahidi, F. (2011). Lipophilized epigallocatechin gallate (EGCG) derivatives as novel antioxidants. _Journal of Agricultural and Food Chemistry, 59_(12), 6526–6533. https://doi.org/10.1021/jf201050j