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RESEARCH ARTICLE

Benefits of Ginger as Medicine for COVID-19: Literature Study

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) affects other systems, including the digestive, circulatory, urogenital, and even the central nervous systems, as its receptor Angiotensin-Converting Enzyme-2 (ACE-2) is expressed in several organs, such as lungs, intestine, heart, esophagus, kidneys, bladder, testes, liver and brain. Different mechanisms, in particular, massive virus replication, extensive apoptosis and necrosis of lung-related epithelial and endothelial cells, vascular leakage, hyperinflammatory responses, overproduction of proinflammatory mediators, cytokine storm, oxidative stress, the downregulation of ACE2 and impairment of the renin-angiotensin system contribute to the pathogenesis of COVID-19. Currently, COVID-19 is a global pandemic with no specific antiviral treatment. The favorable abilities of ginger were indicated in patients suffering from osteoarthritis, neurodegenerative disorders, rheumatoid arthritis, type 2 diabetes, respiratory distress, liver diseases, and primary dysmenorrhea. Ginger or its compounds exhibited strong anti-inflammatory and antioxidant influences in numerous animal models. This review provides evidence regarding the potential effects of ginger against SARS-CoV-2 infection and highlights its antiviral, anti-inflammatory, antioxidant, and immunomodulatory impacts in an attempt to consider this plant as an alternative therapeutic agent for the treatment of COVID-19.

Introduction

Ginger is a home remedy commonly used in food and drink mixes. In Islam, ginger is one of the plants enshrined in the Koran. Allah SWT said: "In Paradise you will be given a glass of (drink) mixed with ginger." (Quran surah al-Insan: 17). Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is an enveloped virus with positive-sense single-stranded RNA in its genome, which has affected more than 212 countries and territories [1]. SARS-CoV-2 has four fundamental structural proteins, which are called Spike (S), nucleocapsid, envelope, and membrane proteins, as well as a number of accessory proteins, including the surface-exposed S protein, which plays a major role in binding of the virus to its target cells [2]. Protein S has a Receptor-Binding Domain (RBD) that binds to its receptor, Angiotensin-Converting Enzyme 2 (ACE2), which is expressed in various organs, such as lungs, intestine, heart, esophagus, kidneys, bladder, testicles, liver and brain [3,4]. Cerebral vascular endothelial cells express ACE2, which provides a direct pathway for SARS-CoV-2 entry into this organ [5]. Therefore, in addition to the respiratory system, SARS-CoV-2 can infect the digestive, cardiovascular, urogenital, and nervous systems [3,6].

Symptoms of COVID-19, including dyspnea, fever, nonproductive cough, pneumonia, fatigue, and myalgia , emerge after an incubation stage of 2 to 14 days [7,8]. Clinically, the symptomatic types of COVID-19 include the following: the mild form (80.0%), which exhibits minor, nonspecific signs that do not progress to more

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severe disease; the moderate form (15.0%), which shows localized pulmonary inflammation and pneumonia with or without hypoxia; and severe infection (5.0%), exhibiting systemic hyperinflammation and acute Respiratory Distress Syndrome (ARDS) with risk of fatal outcome in critical cases (1-2%) [9]. Various pathways, in particular, massive virus replication, extensive apoptosis and necrosis of lung-associated epithelial and endothelial cells, vascular leakage, hyperinflammatory responses, overproduction of proinflammatory mediators, cytokine storm, oxidative stress, ACE2 downregulation, and impairment of the renin-angiotensin system all contribute to the pathogenesis of COVID-19 [10,11].

Currently, there are no specific therapies, such as relevant antiviral drugs, available for COVID-19. Herbs can provide valuable sources of compounds that have immunomodulatory, anti-inflammatory, antioxidant, and antiviral properties, exerting beneficial effects on systems affected by viruses [12]. Experimentally and clinically, ginger (the rhizome of *Zingiber officinale*) has exhibited numerous therapeutic activities, including anti-inflammatory, antioxidant, immunomodulatory, antimicrobial, antifungal, anticancer, neuroprotective, antimigraine, hepatoprotective, hypocholesterolemic, cardiovascular protective, respiratory protective, antiobesity , antidiabetics , anti-nausea and anti-emetics [13]. Ginger also shows direct antiviral effects [14-20], and may have a protective role against ARDS [20,21], which is the leading cause of mortality in patients with severe COVID-19. Therefore, ginger may have beneficial impacts on many organs that are affected by SARS-CoV-2 infection. This review provides evidence on the potential effects of ginger against SARS-CoV-2 infection and highlights its antiviral, anti-inflammatory, antioxidant, and immunomodulatory impacts in an effort to consider this plant as an alternative therapeutic agent for the treatment of COVID-19.

Ginger Bioactive Components

Ginger contains several components, including about 3.0%-6.0% fatty oil, 9.0% protein, 60.0%-70.0% carbohydrates, 3.0%-8.0% crude fiber, about 8.0% ash, 9.0%-12.0 % water and approximately 2.0% volatile oil [22]. Chemically, ginger contains more than 400 different compounds, however, the pharmacological effects of ginger are largely attributed to its terpenes and phenolic compounds [22,23]. Terpene ingredients in ginger include zingiberene, bisabolene, farnesene, sesquifellandrene, limonene, cineol, linalool, borneol, geranium, and cucumene [22]. Terpenes derived from ginger have various pharmacological properties such as anticancer effects, antioxidants, anti-inflammatory, antiviral, antibacterial, antidiabetic, antihyperalgesic, gastroprotective and neuroprotective [22]. Phenolic compounds derived from ginger include gingerols, paradols, shogaols, and zingerone. Ginger also contains other compounds related to gingerol or shogaol, such as 1-dehydrogynedone, 6-gingerdione, and 10-gingerdione, as well as gingerdiols and diarreptanoids [23]. The main pungent ingredients in fresh ginger are gingerols. Although 6-gingerol is the most abundant gingerol in ginger, other types of gingerols, such as 8-, 10-, and 12-gingerols, as well as 6-gingerdione, are also present [22]. Gingerols have anticancer, anti-inflammatory, antioxidant, antiangiogenesis, antimetastasis, antimicrobial, antifungal, neuroprotective, antiemetic and antihyperlipidemic [22].

When ginger is dehydrated by drying or cooking, 6-gingerol is converted to 6-shogaol, which is more stable and has stronger pharmacological effects than 6-gingerol [24]. Shogaol has antioxidant, anti-inflammatory, anticancer, antiemetic, and neuroprotective effects [22]. 6-paradol is synthesized from 6-shogaol by microbial biotransformation through reduction of the double bond in shogaol that exhibits anticancer, anti-inflammatory, cardioprotective, and neuroprotective effects.

Zingerone is not found in fresh ginger, but can be synthesized from gingerols through reverse aldolization when ginger is dried, heated, or roasted [25]. Zingerone exhibits several properties, such as anti-inflammatory effects, antidiabetics, antioxidants, antidiarrheals, antispasmodics, antihiplipidemia, anticancer, anemetics, anxiolytics, antithrombotics, protectors of radiation and antimicrobials [25].

Antiviral Properties of Ginger

Fresh ginger exerts potent antiviral effects against Human Respiratory Syncytial Virus (HRSV) and rhinovirus, supporting its usefulness in treating viral respiratory tract infections [14]. Unlike dry ginger, the aqueous extract of fresh ginger inhibits the binding and penetration of HRSV to human laryngeal lung carcinoma cell lines, when administered 1–2 h before inoculation of the virus [14]. It has been proposed that fresh ginger may block viral attachment and penetration into host cells through interaction with G and F proteins [14,15]. Fresh ginger also stimulates Interferon (IFN)-α secretion and IFN-β from infected epithelial cells [14]. Therefore, fresh ginger may inhibit viral replication in the lower parts of the respiratory tract [14].

The existence of several terpenes with antirinoviral activity in the alcoholic extract of ginger has been demonstrated [16]. The aqueous extract of ginger also prevents the replication of the H9N2 avian influenza virus in the embryo of chicks [17]. *In vitro* experiments indicated that gingerenone inhibits the replication of the various influenza A virus subtypes (H1N1, H5N1, and H9N2) [19]. Influenza-A virus replication is also reduced in the lungs of mice treated with gingerenone [19]. In addition, some ginger-derived components exhibit anti-influenza activity and may prevent swine flu infection [26]. *Zingiber montanum* extract also reduces the infectivity of the H5N1 avian influenza virus *in vitro* [18].

The aqueous extract of ginger decreases the infectivity

of feline calicivirus in virus pretreatment, co-infection treatment, post-infection treatment, but not in target cell pretreatment [27]. Ginger extract contains a type of propanediol that has antiviral properties [27]. Furthermore, *in vitro* tests using a Vero cell line revealed that the aqueous extract of ginger shows powerful anti-chikungunya activity [28].

Ginger Essential Oil (GEO) inactivates Caprine Alphaherpesvirus-1 (CpHV-1) up to 100% by destroying the virus envelope and related structures required for virus attachment and entry into host cells [29]. GEO reduces HSV-2 activity by more than 90.0% when the virus is preincubated with ginger oil [30]. No inhibitory impact was found when GEO was added to target cells before infection with HSV-2 and CpHV-1 or after virus binding. Thus, GEO affects HSV-2 and CpHV-1 primarily prior to viral attachment, perhaps by disrupting virus envelope [29,30].

Results of *in vitro* experiments indicate that gingerol directly inactivates hepatitis A and Tulane viruses [31]. In addition, gingerol reduces the infectivity of murine norovirus-1 and inhibits replication of human norovirus in an infected cell line [32]. Zerumbone, a compound of *Zingiber zerumbet*, also acts as a powerful suppressor of an Epstein-Barr virus tumor promoter induced by tetradecanoylphorbol acetate [33].

In a clinical trial, the administration of ginger extract to patients infected with the Hepatitis C Virus (HCV) decreased the virus load, reduced the levels of α-fetoprotein and decreased the levels of functional enzymes related to the liver, such as alanine aminotransferase and aspartate aminotransferase [34].

In addition to direct antiviral impacts, ginger can boost antiviral innate immunity. IFNs are the first line of protection against viral infections, and an *in vitro* analysis indicated that gingerols promote IFN-γ secretion from activated T cells [35,36]. In addition, fresh ginger extract stimulates IFN-α and IFN-β secretion from HRSV-infected epithelial cells [14]. Aqueous extract of ginger also suppresses influenza virus replication through induction of Tumor Necrosis Factor α (TNF-α) production by macrophages [37].

Evidence of the Potentials of Ginger against COVID-19

The SARS-CoV-2-related Papain-like Polyprotein a/b (PP a/b) at different sites producing several proteins required for viral survival and replication [38]. SARS-CoV-2-related PLpro also interferes with the virus IFN type I response [38]. Therefore, PLpro can be considered as a suitable target of anti-SARS-CoV-2 drugs to effectively prevent virus replication and survival virus [39]. Molecular docking approaches indicated that 8-gingerol, 10-gingerol, 6-gingerol, and another class of ginger ingredients potently inhibit PLpro [40]. Consistent with molecular docking analyses, 6-gingerol was also found to exhibit high binding affinity with a number of virus proteins (major protease, SARS-CoV3C-like molecule, and cathepsin K) that are essential for the SARS-CoV-2 replication [41]. 6-gingerol also binds to protein S and several RNA-binding proteins of SARS-CoV-2 [42]. Docking analyzes also revealed that gingerol, geraniol, shogaol, zingiberene, zingiberenol, and zingerone interact with key residues in the catalytic domain of MPro [43]. Meanwhile, geraniol, shogaol, zingiberene, zingiberenol, and zingerone can interfere with S-ACE2 protein binding [43]. Docking studies indicated that 6-gingerol, 8-gingerol, 10-gingerol, 10-shogaol, 8-paradol, and 10-paradol interact with the virus protein S RBD, as well as with human ACE2, so they can inhibit the spread of SARS-CoV-2 [44]. The results of a computational analysis indicate that a ginger-derived terpene, namely sesquifellandrene, binds to protein S and thus interferes with protein S-ACE2 interaction [45]. It is obvious that these computational docking studies must be supported by *in vitro* and *in vivo* observations.

Results from a study in Saudi Arabia indicate that ginger consumption by COVID-19 patients increased from 36.2% before infection to 57.6% after infection. The proportion of patients hospitalized for COVID-19 treatment was also lower among ginger users (28.0%) than among non-users (38.0%) [46]. In a study from Bangladesh, some cases of patients cured of COVID-19 who consumed home medicines containing ginger in mixtures of various herbs with or without the use of additional treatments were described [47]. According to the results of a Tunisian study, the treatment of some cases of COVID-19 with home medicines containing ginger in combination with other herbs reduced the symptoms of the disease [48]. In some parts of Africa, acclaimed remedies containing ginger in mixtures of various herbs have also been used for the management of COVID-19 [49]. Results from a clinical trial study from Iran indicate that a combination therapy with ginger and echinacea in suspected COVID-19 outpatients attenuated some of their clinical symptoms (shortness of breath, cough, and muscle pain) compared to those treated with a standard protocol using hydroxychloroquine, alone [50]. In addition, the hospitalization rate in the intervention group (2.0%) was lower than that in the control group (6.0%) [50]. Results from a randomized controlled study showed that patients with ARDS who were fed an enteral diet enriched with ginger extract for 21 days exhibited higher oxygenation , lower serum concentrations of IL-1, IL-6, and TNF-α, and spent less time on mechanical ventilation compared to the control group. However, organ failure, barotrauma, and mortality rate occurred similarly in patients treated with ginger and in the control group [20]. Ginger may have beneficial impacts on patients suffering from pulmonary complications such as ARDS, pulmonary fibrosis, and pneumonia, as well as sepsis, all of which are signs seen in COVID-19 [51]. Overall, the above evidence indicates that more high-quality controlled trials are needed to confirm the effectiveness and safety of ginger or its compound in patients with COVID-19. A clinical

trial is underway in Iran, in which a total of 84 COVID-19 patients were randomized into two groups each with 42 participants, including intervention and control groups. The intervention group will be given the standard treatment protocol plus 1,000 mg ginger three times a day for seven days, while the control group will be given the standard treatment plus placebo tablets at the same dose and time [52].

Anti-Inflammatory, Immunomodulatory and Antioxidant Potentials of Ginger

Potentials of ginger to modulate neutrophil responses

COVID-19 activation and degranulation may promote inflammation and hemorrhagic lesions in the pulmonary system of COVID-19 patients [53]. Lymphopenia and an increased neutrophil-to-lymphocyte ratio also occur in patients with severe COVID-19 [54]. COVID-19 patients exhibited high circulating levels of calprotectin (a marker of neutrophil activation), and its amounts were higher in patients who had progressed to the severe form of the disease [55]. During viral respiratory infections, the amounts of CXC Motif Chemokine Ligand (CXCL8), which is a neutrophil-recruiting chemokine, in airway secretions were positively related to neutrophil count, amount of elastase derived from neutrophils and clinical scores [56,57]. Activated neutrophils showed NETosis, autophagy, and generation of Reactive Oxygen Species (ROS) leading to lung injury, thus promoting ARDS [56]. Interaction of viral TLR4 triggers netosis consisting of large, network-like, extracellular structures [56,58].

In an experimental inflammatory model, aqueous extract of ginger dose-dependently attenuates neutrophil infiltration and activation as assessed by Myeloperoxidase (MPO) production [59]. Aqueous extract of ginger also reduced leukocyte infiltration in an animal model of allergic asthma [60]. GEO potently suppresses ROS production by human neutrophils stimulated by Phorbol Myristate Acetate (PMA) [61]. In a mouse model of Acute Lung Injury (ALI), zingerone pretreatment decreased lung histopathologic changes, alveolar hemorrhage, as well as neutrophil accumulation and MPO activity [21]. Ginger extract inhibits CXCL8 production by fibroblast- like synovial cells collected from patients with Rheumatoid Arthritis (RA) and osteoarthritis [62].

Potentials of ginger to modulate macrophage responses

SARS-CoV-infected human macrophages express CC Chemokine Ligand (CCL2), CCL3 (macrophage inflammatory protein 1α, MIP1α), CCL8 (MCP2), CCL7 (MCP3), and CXCL10 [63,64]. Treatment of human monocytes with purified protein S from SARS-CoV promotes the expression of CCL15, CCL16, CCL19, CXCL10, and CXCL11 [65,66]. Similarly, human macrophages infected with Middle East respiratory syndrome coronavirus (MERS-CoV) express CCL2, CCL3, CCL5, interleukin (IL-2), and IL-3 [67]. SARS-CoV-2 can infect various subsets of monocytes and macrophages through ACE2-related and/or non-ACE2-related pathways [68]. SARS-CoV-2-infected monocytes/macrophages secrete large concentrations of proinflammatory mediators that cause local organ inflammation and cytokine storms. Elevated amounts of IFN-γ, TNF-α, Granulocyte-Colony Stimulating Factor (G-CSF), Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), CXCL8, CXCL10, IL-1β, IL-2 were observed, IL-7, IL-9, IL-10, IL-17, MCP1, MIP1A and MIP1B in patients with COVID-19, especially those who required ICU services [69]. Both localized organ inflammation and cytokine storm play a critical role in exacerbating SARS-CoV-2-related consequences [68].

Elevated amounts of neutrophil recruitment chemokines (including CCL7 and CCL2, CXCL10, CXCL8, CXCL1, and CXCL2) and monocyte/lymphocyte recruitment chemokines (such as CCL20, CCL8, CCL7, CCL4, CCL3, CCL2, as well as CXCL11 and CXCL6) in Bronchoalveolar Lavage Fluid (BALF) samples collected from patients with COVID-19 [9]. Chemokines recruit leukocytes in the lungs, thus playing an essential role in the development of pulmonary abnormalities [9]. Patients suffering from severe and moderate COVID-19 show higher frequencies of M1-like macrophages in BALF and higher amounts of circulating CXCL9, CXCL10, and CXCL11 than healthy individuals [70].

Two major subsets of macrophages, including M1 and M2 macrophages, generate large amounts of proinflammatory mediators (such as TNF-α, IFN-γ, IL-6, IL-12, Nitric oxide (NO), and ROS) and anti-inflammatory cytokines (especially IL-10, TGF-β and il-1 receptor antagonist), respectively [13,71]. Higher proportions of FCN1- and FCN1 + lo SPP1 macrophages (type M1) were detected in BALF samples collected from patients with severe COVID-19, whereas BALF samples collected from patients with COVID-19 and healthy individuals had an increased number of FABP4 macrophages (type M2) [70]. In animal models of Respiratory Syncytial Virus (RSV) infection, differentiation of lung macrophages to an M1-like phenotype limits virus replication [72]. Strong depletion of M1-like macrophages occurs during SARS and influenza A infections, supporting viral expansion [72]. Inappropriate activation of M2 macrophages leads to pulmonary fibrosis, while hyperactivation of M1 macrophages exacerbates damaging inflammatory responses [73,74]. However, mitigation of the immunopathological consequences linked to RSV requires a balanced induction of M1- and M2-like macrophages [72,75].

Ginger extract [76-79] shogaols including 6, 8, and 10-shogaol, [79-82] gingerols including 8- and 10-gingerol [79], 1-dehydro-10-gingerdione [80], and 6-dehydrogynedone [83] suppress the production of TNF-α, IL-1β, IL-6, IL-12, MCP-1, RANTES, Cyclooxygenase (COX)-2, inducible Nitric Oxide Synthase (iNOS), and NO in

Lipopolysaccharide (LPS) -induced mouse macrophages . Ginger extract, 6-gingerol, and 6-shogaol downregulate IL-6, IL-8, PGE2, and iNOS in an LPS-stimulated human colonic epithelial cell line through downregulation of Nuclear Factor kappa B (NF-κB) [84]. Zerumbone prevents NF-κB activation and downregulates COX-2, IL-6, TLR2, TLR4, and MyD88 in LPS-activated human macrophages [85].

In a mouse model with fibromyalgia, feeding powdered ginger ameliorates the symptoms of the disorder and decreases the production of IL-1β, NO, Thromboxane B2 and PGE2 by macrophages [86]. In an animal periodontitis model, treatment with 6-shogaol reduces macrophage number, prevents bone destruction, inhibits osteoclast maturation and activation and downregulates IL-1β, TNF-α and ROS [87]. Similarly, 6-gingerol prevents osteoclast differentiation and represses IL-1-induced PGE2 synthesis in mouse osteoblasts [88]. Moreover, zingerone restores renal functions and decreases the generation of TNF-α, IL-1β, IL-6 and ROS in animal models of nephropathy [89,90]. In addition, zerumbone downregulates TNF-α, IL-1β, and IL-6 in an animal neuropathic pain model [91]. Further, gingerols decreased the serum quantities of TNF-α, IL-1β, and IL-6 in rats with ulcerative colitis [92]. Aforementioned studies indicate that ginger and its components exert suppressive impacts on the M1 macrophage-related inflammatory parameters.

Concerning the chemokines, ginger extract downregulates CXCL10 in a human macrophage cell line [93]. 6-shogaol reduces CCL17 generation in a model of allergic dermatitis [94]. CCL22 and its receptor CCR4 are downregulated by ginger extract in experimental autoimmune Encephalomyelitis (EAE) mice [95]. Ginger extract also dampens the production of CCL2 and CCL5, thus decreasing monocyte/macrophage migration [59,96]. In addition to chemokines, cell adhesion molecules play a major role in leukocyte migration to inflamed organs. Zerumbone and gingerenone inhibit the expression of ICAM-1 and VCAM-1 [97,98].

IL-6 and TNF-α are two powerful players among the cytokine storm associated with COVID-19 [99]. Ginger consumption reduces circulating amounts of TNF-α, IL-1, and IL-6 in patients with osteoarthritis [100], and in endurance runners [101]. In addition, oral administration of ginger in subjects with type 2 diabetes reduces serum concentrations of TNF-α, IL-6, and C-reactive protein [102]. Collectively, ginger and its bioactive ingredients effectively modulate macrophage activation and attenuate the generation of proinflammatory mediators that lead to mitigation of inflammatory responses. As a result, they can relieve inflammation related to COVID-19.

Potentials of ginger to modulate TLR-mediated responses

TLRs are components of innate immunity that recognize ligands derived from microbes called Pathogen-Associated Molecular Patterns (PAMPs) and ligands of endogenous origin called Danger-Associated Molecular Patterns (DAMPs) [103,104]. Single-stranded RNA, double-stranded RNA, CpG DNA, lipoproteins, peptidoglycans, Lipopolysaccharides (LPS), and flagellin are examples of PAMPs [103,104]. Heat Shock Protein (HSP) [70], HSP90, and High Mobility Group Box 1 (HMGB1) are examples of DAMPs that are released after cell damage [104].

Each TLR molecule has an extracellular area that recognizes PAMP/DAMP and an intracellular part consisting of the Toll/IL-1 Receptor (TIR) domain, which initiates signaling [103,104]. Following TLR ligation, MyD88 binds to the intracellular TIR domain and subsequently recruits an IL-1 Receptor-Associated Kinase (IRAK) complex [105]. The MyD88-IRAK4 interaction phosphorylates IRAK4 and then attracts IRAK1, IRAK2, and Tumor Necrosis Factor Receptor-Associated Factor 6 (TRAF-6) to construct a transient MyD88-IRAKs-TRAF-6 complex [106]. TRAF-6 is subsequently released into the cytoplasm, where it creates a signaling complex with TGF-Activated Kinase 1 (TAK1), TAK1-binding protein (TAB) 1, TAB2, and TAB3 [107].

This signaling complex activates the IKK complex contributing to the degradation of an inhibitor of NF-κB called IκB [106]. NF-κβ is activated and migrates to the cell nucleus, where it initiates gene expression of several proinflammatory parameters, such as TNF-α, IL-1β, IL-6, IL-8, IL-12, IL-17, IFN-γ and iNOS [108]. TAK1-induced activation of MAPK and AP-1 also increases cytokine gene expression [109]. In plasmacytoid Dendritic Cells (DCs), a myeloid differentiation factor 88 (MyD88)-related pathway upregulates type I IFNs through IRAK1-stimulated activation [109].

All TLRs except TLR3 require MyD88 to initiate signaling [110]. TlR3 and TLR4 use TLR3 and TLR4 to initiate β signaling and recruit TRAF6 and TRAF3. TRAF6 then triggers the activation of RIP kinase-1 and NF-κB, while TRAF3 triggers type I IFN production by inducing TBK-1-related activation of IRF3 [106,109].

IL-6 and TNF-α as the most effective players in the COVID-19-associated cytokine storm are produced through TLR signaling [111]. The SARS-CoV S molecule uses TLR2 to promote IL-8 production in monocytes through NF-κB activation [66]. The SARS-CoV-2-TLR interaction causes the release of pro-IL-1β which ultimately converts to active IL-1β and contributes to lung inflammation [112]. According to molecular docking, the SARS-CoV-2 S molecule can interact with TLR1, TLR4, and TLR6; however, the TLR4-S protein interaction shows the strongest affinity compared to TLR6 and TLR1 [113]. TLR4 may be important in recognizing SARSCoV2 molecular patterns and inducing inflammatory responses in COVID-19 [113]. Therefore, targeting the S-TLR4 protein interaction may provide new approaches for the treatment of COVID-19. TLR5 may bind to a candidate COVID-19 vaccine [114].

Ginger derivatives such as 6-shogaol suppress TRIF-, MyD88-, and IKK-linked signaling in murine macrophages, thereby downregulating the activities of TBK1, IRF3, and NF-κB [81,82]. In addition, 6-shogaol inactivates ERK1/2 and prevents the expression of MyD88, NOS2, and Matrix Metalloproteinase 2 (MMP2) and MMP9 in LPS-treated chondrocytes [96]. 6-shogaol protects microglia against LPS-induced toxicity by inhibiting the expression of MAPK, NF-κB, NOS, and COX-2.[115] TLR4 dimerization, NF-κB induction, and COX-2 expression are also prevented by 6-shogaol [116]. In animals with oral carcinoma, 6-shogaol treatment confers anticancer impacts through mitigation of AP-1 and NF-κB activity, as well as downregulation of IL-1, TNF-α, IL -6 and COX-2 [117].

Furthermore, zingerone was found to inhibit several elements that contribute to TLR-related signaling, such as TRIF, MyD88, MAPK, IRF-3, and NF-κB in various animal models [118,119]. Zingerone decreases HMGB1 release from stimulated and damaged cells, and downregulates TLR2, TLR4, and RAGE that act as HMGB1 receptors [120]. Zingerone decreases HMGB1-induced NF-κB and ERK1/2 activation and downregulates HMGB1-induced adhesion molecule, as well as decreases neutrophil migration [120].

1-Dehydro-10-gingerdione suppresses LPS binding to a TLR4-related co-receptor called MD2, downregulates IL-6, iNOS, and COX-2, and prevents NF-κB activation in macrophages induced by LPS [121,122]. NF-κB induction and translocation to the cell nucleus are also prevented by 6-dehydrogindione [83]. Galangin, a flavonoid derived from ginger, has antioxidant, anti-inflammatory, and anti-apoptotic activities [123]. In a model of nephrotoxicity, galangin improves renal function and downregulates NF-κB, p38 MAPK, ERK1/2, and JNK [123].

Taken together, ginger and its bioactive ingredients may mitigate inflammation by decreasing DAMPs released from injured cells, preventing TLR ligation, inhibiting TLR-mediated signals, and ultimately downregulating inflammation-promoting parameters.

Potentials of ginger to downregulate inflammasome-induced responses

Inflammasomes are amplifiers of inflammation consisting of a sensor molecule that recognizes a stimulator, an adapter element (called ASC), and an effector component called pro-caspase-1 [124]. Various types of DAMPs and PAMPs activate inflammasomes, resulting in cleavage of pro-IL-1β and pro-IL-18 into their active forms, as well as pyroptosis that allows release of IL-1β and IL-18 [124,125].

The NOD-Like Receptor 3 (NLRP3) inflammasome is induced during some pulmonary viral infections, such as RSV and influenza A virus infections [126,127]. Sustained NLRP3 inflammasome induction causes massive discharge of DAMP (such as HMGB1), infiltration and stimulation of macrophages and neutrophils, massive generation of cytokines (such as IFN-γ, IL-1β, IL-2, IL-6, IL-17, TNF-α, G-CSF, GM-CSF, CCL2, CCL3 and CXCL10) and fibrosis [128,129]. In influenza virus infection, a positive association has been suggested between HMGB1 amounts and severity of pneumonia, as well as ALI-related death, which can be blocked by HMGB1-specific antibody [128,130]. NLRP3 inflammasome -deficient mice showed lower lung lesions and a higher survival rate after influenza infection, suggesting that this inflammasome and IL-1β contribute to lung inflammation and ARDS [131].

In a mouse model of respiratory viral infection, suppression of the NLRP3 inflammasome early in the disease increased mortality, whereas its inhibition during peak infection protected mice [132]. Therefore, inflammasomes may have protective and detrimental impacts during various phases of a virus infection.

COV-derived viroporin 3a directly stimulates the NLRP3 inflammasome [133]. The viroporin 3a gene has been found in the SARS-CoV-2 genome, suggesting that SARS-CoV-2 may similarly trigger the NLRP3 inflammasome [134]. The SARS-CoV-related proteins E, ORF3a, and ORF8b induce the NLRP3 inflammasome [135-137] and their sequences have also been mapped to the SARS-CoV-2 genome, so they may play a role in the pathogenesis of SARS-CoV-2 [138].

After inhalation, SARS-CoV-2 activates P2RX7, which stimulates the NLRP3 inflammasome, causing pyroptosis and the release of IL-18 and IL-1 [138]. TNF-α and IL-1β secreted by alveolar macrophages cause cell death and DAMP release, leading to excessive activation of the NLRP3 inflammasome, resulting in a positive inflammatory feedback loop [138]. Damage to type II alveolar epithelial cells expressing ACE2 also triggers the NLRP3 inflammasome [138]. The elevation of angiotensin II may be caused by SARS-CoV-2-mediated downregulation of ACE2, which may lead to activation of the NLRP3 inflammasome [68,139]. Angiotensin II-mediated activation of the NLRP3 inflammasome can promote smooth muscle cell expansion vascular, vascular remodeling, hypertension and pulmonary fibrosis [138,140,141]. Irregular stimulation of the NLRP3 inflammasome reinforces the cytokine storm, exacerbating the severity of COVID-19 [134].

Th17 cell activation, neutrophil infiltration, HMGB1 release, macrophage activation, and cytokine storm are the results of NLRP3 inflammasome hyperactivation [134]. The NLRP3 inflammasome exacerbates the severity of MERS and SARS while promoting ARDS and cytokine storm, indicating that this inflammasome has an important role in the pathogenesis of COVID-19 [138].

Suppression of NLRP3 inflammasome downstream elements, such as caspase-1, il-1, and IL-18, can be used to control COVID-19 related hyperinflammation [134]. Due to the high inflammatory capacity of inflammasomes, they are suitable therapeutic candidates for the treatment of inflammatory abnormalities. Some ginger- derived

phytochemicals suppress NLRP3 and IL-1β inflammasome expression. Pretreatment of a shogaol-stimulated human macrophage cell line prevents conversion of pro-caspase-1 to active caspase-1 [142]. Gingerols and shogaols also downregulate the NLRP3 inflammasome and IL-1β in LPS-induced human macrophages [142]. *In vitro* experiments have revealed that high glucose concentrations initiate calcification in human vascular smooth muscle cells through upregulation of the inflammasome-IL-1β NLRP3 axis [143]. 6-shogaol reduces calcification through attenuation of ROS production and downregulation of the NLRP3 inflammasome [143]. Ginger - derived Exosome-Like Nanoparticles (ELNs) also inhibit NLRP3 inflammasome assembly, IL-1β and IL-18 production, as well as pyroptosis in mouse macrophages [144]. ELN-related suppressive activity was largely attributed to its lipid fraction [144].

Potential ginger to downregulate oxidative stress

Oxidative stress (SG) is a prooxidant-antioxidant imbalance that results from the excessive production of reactive intermediates such as ROS, Reactive Nitrogen Species (RNS), and free radicals. It damages DNA, proteins, lipids, and polysaccharides, disrupting cellular physiological functions, eventually leading to cell death [145]. SG also contributes to inflammatory responses through the activation of NF-κB [146]. In addition, NO provokes the expression of COX-2, promoting the generation of prostaglandin E2 (PGE2) [146].

Nuclear erythroid factor 2-related factor 2 (Nrf2) has cellular protection mechanisms against GS. Nrf2 maintains cellular homeostasis by triggering the production of various antioxidant factors such as NADPH-quinone oxidoreductase, Glutathione Synthetase (GSH-S), heme oxygenases, and the enzyme thioredoxin [145].

Viral infections generally deplete antioxidant stores and enhance oxidant production [145]. A number of pulmonary viral infections promote ROS generation as a result of leukocyte recruitment to the site of infection. ROS overproduction coupled with antioxidant depletion increases viral replication and virus-associated complications [147]. Respiratory viral infections have been linked to repression of Nrf2 pathways and/or activation of NF-κB-related signaling, which cause inflammation and oxidative injury [147,148].

Like other RNA viruses, SARS-CoV2 can trigger GS [149]. The severity and mortality risks of COVID-19 increase in old age when antioxidant degradation occurs along with prooxidant accumulation [150,151]. In elderly patients with COVID-19, an inverse association has been postulated between low expression of an antioxidant factor called Superoxide Dismutase 3 (SOD3) in the lungs and disease severity [152].

In animal models of lung inflammation, treatment with ginger extract reduces inflammation, lung structural alterations, tissue concentrations of TNF-α, IL-1β and IL-6, total oxidant status, lowers Malondialdehyde (MDA) and MPO levels. It also prevents DNA oxidation and enhances endogenous antioxidants [153,154]. In various animal models of neurotoxicity and brain damage, ginger treatment improves levels of antioxidant elements such as Glutathione S-Transferase (GST), Catalase (CAT), GSH, SOD, Glutathione Peroxidase (GPx), Glutathione Reductase (GR) and Quinine Reductase (QR), stops lipid peroxidation, prevents NO generation, scavenges the hydroxyl radical, and reduces iNOS expression, caspase-3 expression, and apoptosis [155-157]. These ginger-related antioxidant properties are due to shogaols, gingerols, and other ketone-phenolic derivatives that attenuate SG [155].

In a chlorpyrifos-induced toxicity model, administration of a 6-gingerol-rich fraction decreases H2O2, MPO, NO, and MDA levels, as well as caspase-3 expression in various organs (such as the brain , uterus and ovary), while improving the amounts of antioxidant factors such as SOD, GPx, GST, CAT and GSH [158]. 6-gingerol also exhibits protective influences against ischemia-mediated intestinal damage by suppressing ROS generation [159]. In an ulcerative colitis model, treatment with gingerols reduces MPO activity and MDA production [92].

Some effective antioxidant activities were also attributed to 6-shogaol, such as suppression of ROS, iNOS, COX-2 production, and upregulation of antioxidant molecules such as Nrf2, GSH, quinone-1, and hemeoxygenase-1 [94,160,161]. Similarly, zingerone enhances the activity of GPx, SOD, and CAT, and promotes GSH production, while decreasing the expression of NF-κB, IL-1β, IL-6, TNF-α, COX-2 and iNOS in a model of cisplatin-mediated toxicity [162]. Zingerone also attenuates GS and age-associated inflammation through repression of MAPK/NF-κB signaling [163]. Like shogaols, paradols exhibit antioxidant impacts [164,165].

Together, ginger and its compounds are able to decrease oxidative elements and act as powerful stimulators for GS-attenuating proteins. Therefore, the antioxidant activity of ginger may have beneficial effects in patients with COVID-19.

Potentials of ginger to downregulate prostaglandins and Leukotrienes (LT)

PGs are proinflammatory mediators generated through the COX pathway from Arachidonic Acid (AA) [166]. Some leukocyte subsets constitutively express COX-1, whereas COX-2 is expressed during inflammation, promoting PGE2 production [166].

PGE2 can increase viral pathogenicity in a number of infections such as Cytomegalovirus (CMV), RSV, Herpes Simplex Virus (HSV), enterovirus [71], and Coxsackie virus B2 infections by influencing viral replication [167]. In pulmonary microvascular endothelial cells, PGE2 promotes

inflammation through upregulation of COX-2 expression and also increases CXCL8 production [168]. SARS-CoV increases PGE2 production by binding to COX-2 [169]. PGE2 has been postulated to play an important role in the pathogenesis of COVID-19 [167]. During acute inflammation, COX-2 expression and PGE2 production are increased more in men compared to women, thus increased PGE2 production in men causes more severe COVID-19 [167]. The increased severity of COVID-19 in older and obese people was also attributed to higher levels of PGE2 [170,171]. PGE2 also contributes to intravascular thrombosis, which is a crucial complication in patients with COVID-19 [172].

During SARS-CoV-2, AA is released by various types of leukocytes. AA, as an antiviral component, can inactivate enveloped viruses, such as SARS-CoV-2 [173]. Thus, AA deficiency promotes human susceptibility to SARS-CoV-2 [171,173]. Suppression of mPGES-1 reduces PGE2 generation and may promote the immune response against SARS-CoV-2 [171,173]. Selective suppression of mPGES-1 stimulates antiviral immunity and improves survival rates in influenza A virus-infected mice [174].

LTs, including LTB4, LTC4, LTD4, and LTE4, are produced from AA *via* the 5-lipoxygenase (5-LOX) pathway [166]. Influenza virus promotes 5-LOX expression in the lungs, and LTB4 suppresses influenza virus expansion [175]. Neutrophils exposed to LTB4 exhibit a strong virucidal response against RSV, influenza virus, and rhinovirus [171,176].

The COX and LOX enzymes are inactivated by gingerols and shogaols [177]. Ginger extract, 6-shogaol, and 6-gingerol prevent COX-2 activation and PGE2 generation through various cell types, such as microglia and LPS-stimulated colonic epithelial cells *in vitro*. [84,115,178]. COX-2 expression was also repressed in macrophages stimulated using gingerols, 8-paradol, and dehydrogynedone [179,180]. In patients with Rheumatoid Arthritis (RA) and osteoarthritis, ginger supplementation prevents PG and LT production [181]. Ginger prevents the synthesis of PG and LT by inactivating the enzymes COX-1/2 and 5-LOX, respectively [177]. Double repression of PG and LT generation by ginger could mitigate hyperinflammation in COVID-19 patients.

Potentials of ginger to modulate T-cell mediated responses

5.7.1. **Potentials of ginger to modulate Th1 cell-mediated responses:** CD4 Th1 effector cells secrete several cytokines, particularly IFN-γ, IL-2, and TNF-α, which provide help to CD8 T cells as well as Natural Killer (NK) cells to kill virally infected cells and reduce the viral load [182-184]. The eradication of SARS-CoV-2 appears to require timely and adequate activation of Th1 cells. However, Th1 cells may play various roles during different periods of COVID-19. During SARS, Th1 and Th2 cell responses appear to be related to resistance and disease progression, respectively [185]. All virus- specific CD4 T cells in individuals who recovered from mild COVID-19 were subsets of Th1 cells [186]. CD4 Th cells were decreased in COVID-19 patients who did not respond to antigenic stimulation with major SARS-CoV-2 proteins [187]. Older age and a higher rate of comorbidity were also associated with a lower number of IFN-γ-producing cells [187].

Immunopathological reactions can be caused by unbalanced and excessive responses mediated by Th1 cells [188,189]. In COVID-19 patients suffering from ARDS, virus-specific T cells mainly generated Th1-cell-related cytokines, while Th17- and Th2-cell-related cytokines were also produced [190]. Patients with severe COVID-19 showed higher proportions of Th1 cells in their secondary lymphoid organs, which were associated with reduced numbers of Tfh cells [191]. In transgenic mice expressing human ACE2, SARS-CoV-2 infection results in the accumulation of macrophages and lymphocytes in the lungs with predominant Th1 cell activity, as well as large amounts of proinflammatory cytokines/chemokines [192]. Importantly, elevated amounts of TNF-α, IFN-γ, IFN-γ-inducible protein 10 (IP-10), and MCP-1 correlated with severity of COVID-19 [69,193].

Th1 cell-mediated responses may be regulated by ginger, as it inhibits the production of IL-12 (an inducer of Th1 cells) and downregulates MHC class II molecules as well as costimulatory molecules (such as CD80 and CD86) by Antigen Presenting Cells (APC) [76]. Ginger can modulate antigen presentation, CD4 T cell response, as well as IFN-γ and IL-2 secretion by T cells [76]. Ginger extract also reduces IL-12 production and IFN-γ in EAE mice [194,195].

In an allergic dermatitis model, 6-shogaol attenuates allergy symptoms and modulates the generation of Th1 cell cytokines (including IL-12, IFN-γ, and TNF-α), as well as Th2 cell cytokines (IL-4) and IL-13) [94]. Gingerols reduce T cell activation and proliferation, as well as IFN γ and IL-2 secretion by activated T cells [196]. In a potent Th1-polarizing milieu, 6-gingerol also has a direct effect on TCR-mediated signaling and suppresses Th1 cell development [197].

However, in a mouse model of tuberculosis, 6-gingerol increased the counts of splenic IFN-γ and IL-17-producing CD4 T cells, while reducing the counts of splenic FOXP3 regulatory T cells (Treg) [198]. In immunocompromised mice, treatment with ginger extract increases serum amounts of Th1 cytokines, such as ifn-γ and TNF-α [199]. Collectively, ginger and some of its bioactive compounds may modulate Th1 cell responses.

Potentials of ginger to modulate Th2 cell-mediated responses: Th2 cells produce cytokines, including IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13, providing helper signals for B cells to produce antiviral antibodies [13,200]. Adequate antibody responses to parts of the S protein, particularly the RBD, can block SARS-CoV-2 binding to ACE2-expressing cells [201]. Although the exact role of Th1/Th2 cells in

the different stages of SARS-CoV-2 infection is obscure, balanced Th1/Th2-dependent responses appear to be necessary for successful virus control. Th2 cell responses, rather than Th1 responses, are induced against SARS-CoV-2 in patients requiring intensive care [202]. Indeed, large amounts of Th2 cell cytokines were identified in fatal cases of COVID-19 compared to cured patients [203].

In mouse models of airway allergy, ginger extract and 6-gingerol suppress Th1 and Th2 cell expansion and differentiation, downregulate Th1 and Th2 cell-related cytokines, suppress the generation of IgE and block the accumulation of mast cells [60,197,204]. 6-gingerol also directly inhibits Th2 cell polarization in a strong Th2-polarizing medium [197]. A better understanding of Th2 cell-dependent responses in COVID-19 needs further study. If the contribution of Th2 cells to the pathogenesis of COVID-19 is identified, ginger has a potent ability to regulate these cells.

Potentials of ginger to modulate Th17 cell-mediated responses: Th17 cells produce many types of cytokines, such as IL-17A, IL-17F, IL-21, IL-22, IL-26, TNF-α, CCL20 and GM-CSF [13,205]. TNF-α, IL-1β, IL-6, CXCL1, CXCL8 (IL-8), CXCL6 , CCL2, GM-CSF and G-CSF are generated by different lymphoid and nonlymphoid cell types in response to IL -17A.

Hyperactivation of Th1/Th17 cells results in the generation of many proinflammatory cytokines that promote pulmonary dysfunction. Robust Th17 cell-related responses occur in patients infected with SARS-CoV and MERS-CoV [206,207]. Higher blood concentrations of Th17 cells have been reported in severe patients with COVID-19 [208]. A number of risk factors associated with COVID-19, including obesity, Chronic Kidney Disease (CKD), hypertension, aging, diabetes, and male gender, have been linked to powerful Th17 cell activity [209]. Hypoxia and downregulation of ACE2 also potentiate Th17 cell activities in COVID-19 [209].

Many of the cytokines in the COVID-19-associated cytokine storm are derived from activated Th17 cells. As a result, uncontrolled Th17 cell responses lead to hyperinflammatory reactions and tissue damage in patients with severe COVID-19. In patients with ARDS, alveolar inflammation, lung damage, organ dysfunction, and poor outcome have been associated with increased levels of IL-17A in BALF. 210 In patients infected with SARS-CoV-2 and SARS-CoV, IL-22 increases the generation of life-threatening edema filled with fibrin and mucins [211].

Ginger extract decreases the generation of IL-23 (complete activator of Th17 cells) and IL-17 in EAE mice [212]. In addition, ginger extract decreases the production of IL-17, IFN-γ, and IL-4 in mice with arthritis [213]. Ginger extract downregulates ROR-γt, T-bet, and GATA-3 (transcription factors of Th17, Th1, and Th2 cells, respectively) in PBMC collected from asthmatic patients [214]. In microglial cells exposed to LPS, 6-shogaol downregulates the expression of IL-1β and TNF-α (as promoters of Th17 polarization) [115]. Collectively, ginger may attenuate deleterious inflammatory reactions in COVID-19 patients by suppressing Th17 cell-related responses.

Potentials of ginger to modulate responses mediated by Treg cells

Treg cells generate immunomodulatory cytokines TGF-β, IL-10, and IL-35, which play a key role in maintaining tolerance to self-antigens and preventing harmful uncontrolled immune responses during infections [13,205]. However, hyperactivation of Treg cells may aid pathogen persistence [205,215]. Treg cells may play different roles during the various phases of COVID-19. Hyperactivation of Treg cells in the initial stages of infection may result in SARS-CoV-2 persistence, while their activation during later stages may minimize immunopathological reactions.

In patients with severe COVID-19, blood counts of Treg cells decreased [216,217]. Indeed, patients with severe COVID-19 have higher numbers of Th17 cells, lower numbers of Treg cells, and lower Treg/Th17 cell ratios [211,218-220]. An imbalance of Th17/Treg cells, with a shift toward Th17 cells, may play a major role in the development of COVID-19-related complications, such as lung damage and ARDS [221,222]. Powerful Th17 cell activities, as well as deficient Treg cell responses, may contribute to excessive secretion of proinflammatory cytokines and chemokines, reinforcing the cytokine storm, exacerbating disease, and perhaps leading to failure. Multi- organ disease and death in some patients with COVID-19. However, the frequency of Treg and Th2 cells in critically ill COVID-19 patients (n = 3) with a poor prognosis was found to be higher than in those (n = 3) with a favorable prognosis [223]. These findings need to be validated in research with a larger sample size.

In EAE mice, ginger extract enhances the generation of TGF-β (an inducer of Treg cells) [194]. However, the production of IL-6 (an inducer of Th17 cells) was inhibited by ginger and some of its ingredients [79,121]. Therefore, ginger has the ability to correct the Th17/Treg imbalance towards Treg cells that may attenuate the severity of COVID-19. Administration of ginger extract to cardiac allograft mice decreases lymphocyte proliferation, downregulates the expression of IFN-γ, IL-2, and IL-4, and increases the production of Treg-related cytokines such as TGF-β and IL -10 [224].

Conclusion

A complex network of immune system, inflammatory and oxidative reactions of SARS-CoV-2, contribute to the pathogenesis of COVID-19. Ginger has been widely used for thousands of years as a spice or dietary supplement, as well as a traditional medicine for the treatment of various disorders [13]. Here, we have provided clear evidence that ginger can exert direct and indirect inhibitory effects on the viral life cycle, including binding, entry, replication, packaging, and assembly, perhaps through interaction with proteins, and key viral enzymes. Ginger may affect

key fundamental processes involved in the pathogenesis of COVID-19 due to its antiviral, anti-inflammatory, immunomodulatory, and antioxidant properties. This review presents a comprehensive understanding of the potentials of ginger and its compounds for the potential management of COVID-19. It is worth accurately identifying the effects of SARS-CoV-2 infection on all host organs and evaluating the impacts of ginger on virus-infected tissues.

The effect of ginger-derived ingredients during COVID-19 infection using suitable animal models needs to be evaluated in future studies. Engineered mice expressing human ACE2 were recommended as a suitable model to study COVID-19 [225]. No significant side effects (except platelet aggregation) were found in preclinical studies with ginger [13]. In addition, clinical trials are needed to investigate the preventive and therapeutic potential of ginger in patients infected with SARS-CoV-2 using ginger or ginger + antiviral treatments. A combined ginger therapy with a validated drug may be a promising candidate for the treatment of COVID-19.

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