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Therapeutic potential of ginger against COVID-19: Is there enough evidence?



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ABSTRACT

In addition to the respiratory system, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strikes other systems, including the digestive, circulatory, urogenital, and even the central nervous system, as its receptor angiotensin-converting enzyme 2 (ACE2) is expressed in various organs, such as lungs, intestine, heart, esophagus, kidneys, bladder, testis, liver, and brain. Different mechanisms, in particular, massive virus replication, extensive apoptosis and necrosis of the lung-related epithelial and endothelial cells, vascular leakage, hyper-inflammatory responses, overproduction of pro-inflammatory mediators, cytokine storm, oxidative stress, downregulation of ACE2, and impairment of the renin-angiotensin system contribute to the COVID-19 pathogenesis. Currently, COVID-19 is a global pandemic with no specific anti-viral treatment. The favorable capabilities of the 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 anti-oxidative 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, antioxidative, and immunomodulatory impacts in an attempt to consider this plant as an alternative therapeutic agent for COVID-19 treatment.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped virus with single-stranded, positive-sense 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, among them the surface-exposed S protein plays a principal role in the attachment of the virus to its target cells.² The S protein 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, testis, liver, and brain.^{3,4} The brain vascular endothelial cells express ACE2, which provides a direct path for the entry of SARS-CoV-2 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}

The COVID-19 symptoms, including dyspnea, fever, nonproductive cough, pneumonia, fatigue, and myalgia emerge following an incubation stage of 2–14 days.^{7,8} Clinically, the symptomatic types of COVID-19 include the following: the mild form (80.0%), which exhibits non-specific minor signs that do not progress to more severe disease; the moderate form (15.0%), which displays localized lung inflammation and pneumonia with or without hypoxia; and severe infection (5.0%), which exhibits systemic hyper-inflammation and acute respiratory distress syndrome (ARDS) with the risk of fatal outcome in critical cases (1–2%).⁹ Various pathways, in particular, massive virus replication, extensive apoptosis and necrosis of the lung-related epithelial- and endothelial cells, vascular leakage, hyper-inflammatory responses, overproduction of the pro-inflammatory mediators, cytokine storm, oxidative stress, ACE2 downregulation, and impairment of the renin-angiotensin system contribute to the COVID-19 pathogenesis.^{10,11}

Currently, no specific therapy such as relevant anti-viral drugs is available for COVID-19. Herbs can provide valuable sources of components that have immunomodulatory, anti-inflammatory, anti-oxidative and antiviral properties, exerting beneficial effects on the systems that are affected by the virus.¹² Experimentally and clinically, ginger (the rhizome of *Zingiber officinale*) has exhibited numerous therapeutic activities, including anti-inflammatory, antioxidative, immunomodulatory, antimicrobial, anti-fungal, anticancer, neuroprotective, antimigraine, hepatoprotective, hypocholesterolemic, cardiovascular protective, respiratory protective, anti-obesity, antidiabetic, anti-nausea, and anti-emetic effects.¹³ Ginger also displays direct anti-viral effects,^{14–19} and can have a protective role against ARDS,^{20,21} which is the major cause of mortality in patients with severe COVID-19. Thus, ginger can have beneficial impacts on many organs that are affected by SARS-CoV-2 infection. This review provides evidence concerning the potential effects of ginger against SARS-CoV-2 infection and underlines its

antiviral, anti-inflammatory, antioxidative and immunomodulatory impacts in an effort to consider this plant as an alternative therapeutic agent for COVID-19 treatment.

Bioactive constituents of ginger

Ginger contains various 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%–3.0% volatile oil.²² Chemically, ginger contains over 400 different compounds, however, the pharmacological effects of ginger are largely attributed to its terpene and phenolic compounds.^{22,23} Terpene ingredients of ginger include zingiberene, bisabolene, farnesene, sesquiphellandrene, limonene, cineole, linalool, borneol, geranial and curcumene.²² Ginger-derived terpenes have various pharmacologic properties such as anticancer, antioxidant, anti-inflammatory, antiviral, antibacterial, antidiabetic, antihyperalgesic, gastroprotective, and neuroprotective effects.²² The ginger-derived phenolic compounds include gingerols, paradols, shogaols, and zingerone. Ginger also contains other gingerol- or shogaol-related compounds such as 1-dehydrogingerdione, 6-gingerdione and 10-gingerdione as well as gingerdiols and diarylheptanoids.²³ The major pungent ingredients of 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 activity, anti-inflammatory, antioxidant, antiangiogenesis, anti-metastasis, antimicrobial, antifungal, neuroprotective, antiemetic and antihyperlipidemic effects.²²

When ginger is dehydrated by drying or cooking, 6-gingerol is converted to 6-shogaol which is more stable and has more powerful 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 reducing the double bond in shogaol which exhibits anticancer, anti-inflammatory, cardioprotective and neuroprotective effects.

Zingerone is not found in fresh ginger, but it can be synthesized from gingerols via reverse aldolization when ginger is dried, heated or roasted.²⁵ Zingerone exhibits various properties, such as anti-inflammatory, antidiabetic, anti-oxidant, antidiarrheic, antispasmodic, anti-hyperlipidemia, anticancer, antiemetic, anxiolytic, antithrombotic, radiation protective and antimicrobial effects.²⁵

Anti-viral properties of ginger

Fresh ginger exerts potent antiviral effects against human respiratory syncytial virus (HRSV) and rhinovirus, supporting its usefulness for the treatment of airway viral infections.¹⁴ In contrary to dried ginger, the aqueous extract of fresh ginger inhibits the attachment and penetration of HRSV to the human larynx epidermoid carcinoma cells and human lung carcinoma cell lines, when

given 1–2 h before virus inoculation.¹⁴ It has been proposed that fresh ginger can block viral attachment and penetration into host cells via interacting with G and F proteins.^{14,15} Fresh ginger also stimulates the secretion of interferon (IFN)- α and IFN- β from infected-epithelial cells.¹⁴ Therefore, fresh ginger can inhibit viral replication in the lower parts of the respiratory tract.¹⁴

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

Aqueous extract of ginger decreases the infectivity of feline calicivirus in pre-treatment of the virus, in coinfection treatment, in post-infection treatment, but not in pre-treatment of target cells.²⁷ The ginger extract contains a kind of propanediol that has anti-viral properties.²⁷ Moreover, *in vitro* tests using a Vero cell line revealed that aqueous extract of ginger displays powerful anti-chikungunya activity.²⁸

The ginger essential oil (GEO) inactivates caprine alphaherpesvirus-1 (CpHV-1) up to 100% by destroying the virus envelope and related structures needing for virus attachment and entrance into host cells.²⁹ GEO reduces the HSV-2 activity by more than 90.0% when the virus is pre-incubated with ginger oil.³⁰ No inhibitory impact was found when the GEO was added to the target cells prior to infection with HSV-2 and CpHV-1 or after virus attachment. Thus, GEO affects HSV-2 and CpHV-1 mainly prior to viral attachment perhaps by interrupting the virus envelope.^{29,30}

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

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

In addition to direct anti-viral impacts, ginger can potentiate the anti-viral innate immunity (Fig. 1). IFNs are the first protective line against viral infections and an *in vitro* analysis indicated that gingerols promote the IFN- γ secretion from activated T cells.^{35,36} Moreover, the fresh ginger extract stimulates the secretion of IFN- α and IFN- β from HRSV-infected epithelial cells.¹⁴ The aqueous extract of ginger also suppresses influenza virus replication via induction of tumor necrosis factor α (TNF- α) production by macrophages.³⁷

Evidence of ginger's potentials against COVID-19

SARS-CoV-2-related papain-like protease (PLpro) cleaves polyprotein a/b (PP a/b) at different sites yielding several proteins needing for viral survival and replication.³⁸ SARS-CoV-2-related PLpro also interferes with type I IFN anti-virus response.³⁸ Thus, PLpro can be considered as a proper target of anti-SARS-CoV-2

drugs in order to effectively prevent virus replication and survival.³⁹ Molecular docking approaches indicated that 8-gingerol, 10-gingerol, 6-gingerol and another class of the ginger's ingredients potently inhibit PLpro.⁴⁰ According to the molecular docking analyses, it was also found that 6-gingerol exhibit a high binding affinity with a number of virus proteins (main protease, SARS-CoV-2 like molecule and cathepsin K) which are essential for SARS-CoV-2 replication.⁴¹ 6-gingerol also binds to the S protein and several RNA binding proteins of SARS-CoV-2.⁴² Docking analyses also revealed that gingerol, geraniol, shogaol, zingiberene, zingiberenol, and zingerone interact with key residues in the catalytic domain of the MPro.⁴³ Meanwhile, geraniol, shogaol, zingiberene, zingiberenol and zingerone can interfere with S protein-ACE2 binding.⁴³ Docking studies indicated that 6-gingerol, 8-gingerol, 10-gingerol, 10-shogaol, 8-paradol, and 10-paradol interact with the RBD of the virus S protein as well as human ACE2, thus they can inhibit the spreading of SARS-CoV-2.⁴⁴ The results from a computational analysis indicate that a ginger-derived terpene namely sesquiphellandrene binds to S protein and thus interferes with the S protein-ACE2 interaction.⁴⁵ It is obvious that these docking computational studies must be supported by *in vitro* and *in vivo* observations.

The results from a study in Saudi Arabia indicate the consumption of ginger by COVID-19 patients was increased from 36.2% prior infection to 57.6% after infection. The proportion of patients' hospitalization for COVID 19 treatment was also lower among ginger users (28.0%) than in nonusers (38.0%).⁴⁶ In a study from Bangladesh, a few cases of cured COVID-19 patients were described who consumed home medicines containing ginger in mixes of various herbs with or without the use of additional treatments.⁴⁷ According to the results from a Tunisian study, treatment of a few cases of COVID-19 with home medicines containing ginger in combinations with other herbs reduced disease symptoms.⁴⁸ In some parts of Africa, acclaimed remedies containing ginger in mixes of various herbs were also used for the management of COVID-19.⁴⁹ The results from a clinical trial study from Iran indicate that a combination therapy by ginger and Echinacea in suspected COVID-19 outpatients attenuated some of their clinical symptoms (breath shortness, coughing and muscular pain) in comparison with 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 The results from a randomized-controlled study showed that the patients with ARDS who were fed an enteral diet enriched with ginger extract for 21 days exhibited greater oxygenation, lower serum concentrations of IL-1, IL-6, and TNF- α , and spent shorter time on mechanical ventilation compared to control group. However, organ failure, barotrauma and mortality rate similarly occurred in ginger-treated patients and control group.²⁰ Ginger can have beneficial impacts in patients suffering from pulmonary complications such as ARDS, lung fibrosis, and pneumonia, as well as sepsis, all of which are signs observed in COVID-19.⁵¹ Overall, the aforesaid evidence indicates that more high-quality controlled trials need to confirm the effectiveness and safety of ginger or its compound in COVID-19 patients. A clinical trial is going on in Iran, in which a total of 84 patients with COVID-19 were randomly classified into two groups of each with 42 participants, including intervention and control groups. The intervention group will be administrated standard treatment protocol plus 1000 mg ginger three times daily for seven days, whereas the control group will be received standard treatment plus placebo tablets at the same dose and timing.⁵²

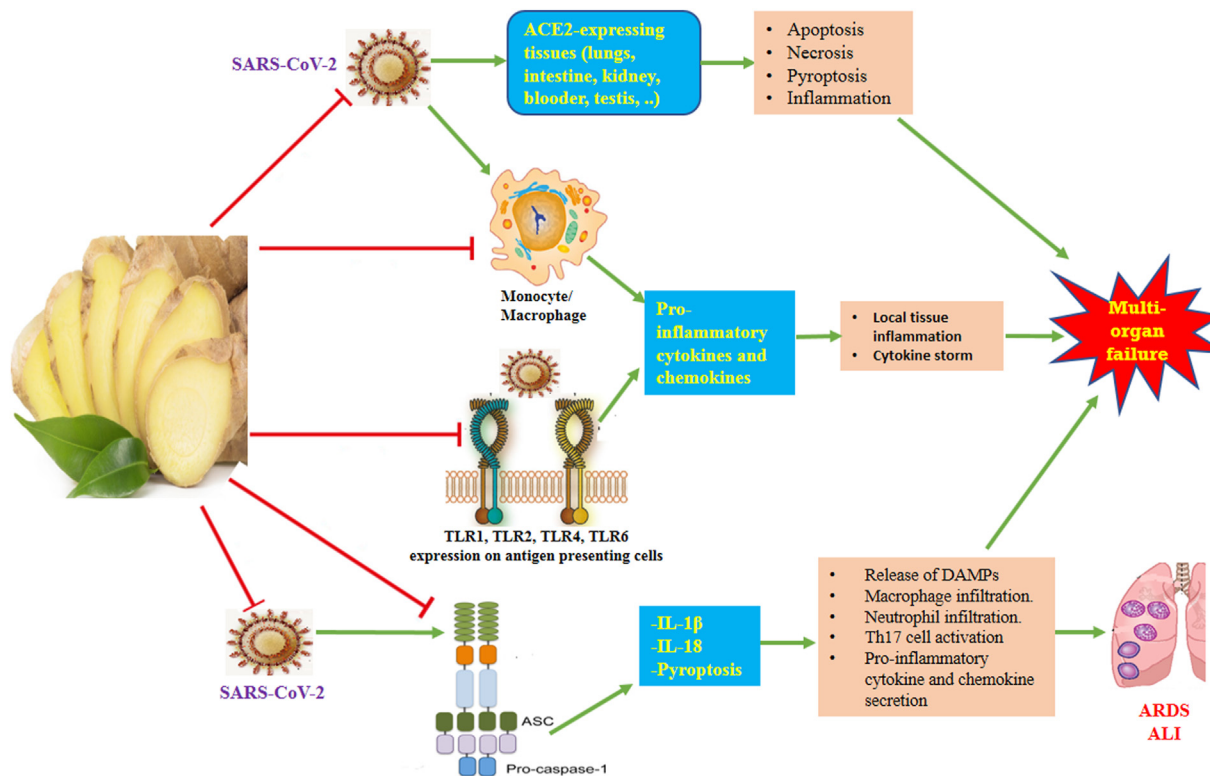


Fig. 1. SARS-CoV-2- and inflammation-mediated impacts on COVID-19 pathogenesis. SARS-CoV-2 infects tissues expressing ACE2 and leads to cell death (via necrosis, apoptosis and pyroptosis) as well as inflammation. SARS-CoV-2-infected macrophages release numerous types of cytokines and chemokines promoting tissue inflammation and cytokine storm. SARS-CoV-2 can also activate some types of TLRs and inflammasomes reinforcing inflammatory responses and tissue damage. Ginger can potentiate anti-viral immune responses and exert direct anti-SARS-CoV-2 effects as well as interfere with macrophage-, TLR- and inflammasome-mediated inflammatory responses. **Abbreviations:** SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ACE2: angiotensin-converting enzyme 2; TLR: toll-like receptor; IL: interleukin; ARDS: acute respiratory distress syndrome; ALI: acute lung injury.

Anti-inflammatory, immunomodulatory, and anti-oxidative potentials of ginger

Ginger potentials to modulate the neutrophil responses

The neutrophils from COVID-19 display an activation status. Neutrophil activation and degranulation can promote inflammation and hemorrhagic lesions in the pulmonary system of COVID-19 patients.⁵³ Lymphopenia and a higher neutrophil-lymphocyte ratio also happen in patients with severe COVID-19.⁵⁴ Patients with COVID-19 exhibited high circulating levels of calprotectin (a neutrophil activation marker) and its quantities were higher in patients who had progressed to the severe form of the disease.⁵⁵ During viral respiratory infections, the quantities of C-X-C motif chemokine ligand (CXCL) 8, which is a neutrophil-recruitment chemokine, in the secretions of airways were positively related to the count of neutrophils, amount of neutrophil-derived elastase, and clinical scores.^{56,57} Activated neutrophils displayed NETosis, autophagy, and reactive oxygen species (ROS) generation leading to lung injury, which promotes ARDS.⁵⁶ The interaction of viral proteins with TLR4 triggers NETosis which consists of large extracellular, web-like structures.^{56,58}

In an experimental inflammatory model, ginger aqueous extract dose-dependently attenuates the neutrophil infiltration and activation that assessed by myeloperoxidase (MPO) production.⁵⁹ Ginger aqueous extract also reduces leukocyte infiltration in an animal model of allergic asthma.⁶⁰ GEO potently suppresses the ROS production by phorbol myristate acetate (PMA)-stimulated human neutrophils.⁶¹ In a mouse model of acute lung injury (ALI),

pretreatment with zingerone decreases lung histopathologic alterations, alveolar hemorrhage as well as neutrophil accumulation and MPO activity.²¹ Ginger extract inhibits the CXCL8 production by fibroblast-like synovial cells collected from patients with rheumatoid arthritis (RA) and osteoarthritis.⁶²

Ginger potentials to modulates the macrophage responses

SARS-CoV-infected human macrophages express C–C chemokine ligand (CCL2), CCL3 (macrophage inflammatory protein 1 α , MIP1 α), CCL8 (MCP2), CCL7 (MCP3), and CXCL10.^{63,64} Treatment of the human monocytes with the purified S protein of SARS-CoV promotes CCL15, CCL16, CCL19, CXCL10, and CXCL11 expression.^{65,66} Similarly, Middle East respiratory syndrome coronavirus (MERS-CoV)-infected human macrophages express CCL2, CCL3, CCL5, interleukin (IL-2), and IL-3.⁶⁷ SARS-CoV-2 can infect several monocyte and macrophage subsets via ACE2-related and/or ACE2-unrelated paths.⁶⁸ SARS-CoV-2-infected monocytes/macrophages secrete great concentrations of pro-inflammatory mediators causing local organ inflammation and cytokine storms. Raised quantities of IFN- γ , TNF- α , granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), CXCL8, CXCL10, IL-1 β , IL-2, IL-7, IL-9, IL-10, IL-17, MCP1, MIP1A, and MIP1B were observed in COVID-19 patients, especially in those who required ICU services.⁶⁹ Both localized organ inflammation and cytokine storm have critical roles in the exacerbation of 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 CXCL11 and CXCL6) were detected in the bronchoalveolar lavage fluid (BALF) specimens collected from COVID-19 patients.⁹ Chemokines recruit leukocytes into the lungs, thus performing an essential role in the occurrence of pulmonary abnormalities.⁹ Patients suffering from severe and moderate COVID-19 display greater frequencies of M1-like macrophages in BALF and greater CXCL9, CXCL10, and CXCL11 quantities in circulation than healthy individuals.⁷⁰

Two major subsets of macrophages, including M1-and M2 macrophages generate large amounts of pro-inflammatory 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} Greater proportions of FCN1⁺- and FCN1⁰ SPP1⁺ macrophages (M1-like type) were detected in the BALF samples collected from patients with severe COVID-19, while BALF specimens that collected from patients with COVID-19 and healthy individuals had greater numbers of FABP4⁺ macrophages (M2-like type).⁷⁰ In animal models of respiratory syncytial virus (RSV) infection, the differentiation of lung macrophage to an M1-like phenotype limits the virus replication.⁷² The sharp depletion of M1-like macrophages occurs during SARS and influenza A infections, which supports the viral expansion.⁷² The improper activation of M2 macrophages leads to lung fibrosis, while hyper-activation of M1 macrophages exacerbates harmful inflammatory responses.^{73,74} However, mitigation of the RSV-linked immunopathologic consequences needs a balanced induction of the 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-Dehydrogingerdione⁸³ repress the production of TNF- α , IL-1 β , IL-6, IL-12, MCP-1, RANTES, cyclooxygenase (COX)-2, inducible nitric oxide synthase (iNOS), and NO in lipopolysaccharides (LPS)-induced mouse macrophages. Ginger extract, 6-gingerol as well as 6-shogaol downregulate IL-6, IL-8, PGE2, and iNOS in a human colonic epithelial cell line stimulated with LPS via nuclear factor kappa B (NF- κ B) downregulation.⁸⁴ Zerumbone prevents the NF- κ B activation and downregulates COX-2, IL-6, TLR2, TLR4, and MyD88 in LPS-activated human macrophages.⁸⁵

In a fibromyalgia mouse model, feeding with powdered ginger improves the disorder symptoms and decreases the production of IL-1 β , NO, Thromboxane B2, and PGE2 by macrophages.⁸⁶ In an animal periodontitis model, treatment with 6-shogaol reduces the macrophage numbers, avoids bone destruction, inhibits the osteoclast maturation and activation, and downregulates IL-1 β , 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 the renal functions and declines the generation of TNF- α , IL-1 β , IL-6 and ROS in animal models of nephropathy.^{89,90} In addition, zerumbone downregulates TNF- α , IL-1 β , and IL-6 in an animal neuropathic pain model.⁹¹ Further, gingerols decline the serum quantities of TNF- α , IL-1 β , and IL-6 in rats with ulcerative colitis.⁹² Aforesaid 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 an allergic dermatitis model.⁹⁴ CCL22 and its receptor CCR4 are downregulated by ginger extract in experimental autoimmune encephalomyelitis (EAE) mice.⁹⁵ The ginger extract also dampens the CCL2 and CCL5 production, thus diminishes the monocyte/macrophage migration.^{59,96} In addition to chemokines, the cellular adhesion molecules perform a principal role in the leukocyte migration into the inflamed organs. Zerumbone and

gingerone inhibit the ICAM-1 and VCAM-1 expression.^{97,98}

IL-6 and TNF- α are two powerful players among COVID-19-associated cytokine storm.⁹⁹ Ginger consumption reduces the circulatory TNF- α , IL-1, and IL-6 quantities and in osteoarthritis patients,¹⁰⁰ and in endurance runners.¹⁰¹ Moreover, oral ginger administration in subjects with type 2 diabetes lowers serum TNF- α , IL-6, and C-reactive protein concentrations.¹⁰² Collectively, ginger and its bioactive ingredients effectively modulate macrophage activation and attenuate the generation of the pro-inflammatory mediators leading to the mitigation of inflammatory responses. As a result, they can alleviate the COVID-19-related inflammation (Fig. 1).

Ginger potentials to modulate the TLR-mediated responses

TLRs are innate immunity components that recognize microbial-derived ligands called pathogen-associated molecular patterns (PAMPs) and endogenous-originated ligands named 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 cellular damage.¹⁰⁴

Each TLR molecule has an extracellular area recognizing PAMP/DAMP and an intracellular part that consists of the Toll/IL-1 receptor (TIR) domain, which initiates the signaling.^{103,104} Following TLR ligation, MyD88 connects 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 transitory complex of MyD88-IRAKs-TRAF-6.¹⁰⁶ 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 a NF- κ B inhibitor called I κ B.¹⁰⁶ NF- κ B is then activated and migrates into the nucleus of the cell, where it initiates gene expression of various pro-inflammatory parameters, such as TNF- α , IL-1 β , IL-6, IL-8, IL-12, IL-17, IFN- γ , and iNOS.¹⁰⁸ TAK1-induced MAPK and AP-1 activation also boosts cytokine gene expression.¹⁰⁹ In plasmacytoid dendritic cells (DCs), a myeloid differentiation factor 88 (MyD88)-related pathway upregulates type I IFNs through the IRAK1-stimulated IRF7 activation.¹⁰⁹

All TLRs, except TLR3, require MyD88 to launch signaling.¹¹⁰ TIR-domain-containing adapter-inducing interferon- β (TRIF) is used by TLR3 and TLR4 to initiate signaling and recruits TRAF6 and TRAF3. TRAF6 then triggers RIP kinase-1 and NF- κ B activation, while TRAF3 triggers the production of type I IFNs by inducing TBK-1-related IRF3 activation.^{106,109}

IL-6 and TNF- α as the most effective players in COVID-19-associated cytokine storm are produced via the TLR signaling.¹¹¹ The S molecule of SARS-CoV utilizes TLR2 to promote IL-8 production in monocytes via NF- κ B activation.⁵⁶ The SARS-CoV-2-TLR interaction causes the release of pro-IL-1 β which is eventually converted into active IL-1 β and contributes to lung inflammation.¹¹² According to molecular docking, the S molecule of SARS-CoV-2 can interact with TLR1, TLR4, and TLR6; however, TLR4-S protein interaction displays the strongest affinity compared with TLR6 and TLR1.¹¹³ TLR4 may be important in recognizing SARSCoV2 molecular patterns and inducing inflammatory responses in COVID-19.¹¹³ Thus, targeting the S protein-TLR4 interaction can provide new approaches for COVID-19 treatment. TLR5 can bind to a vaccine candidate of COVID-19.¹¹⁴

Ginger derivatives like 6-shogaol suppresses TRIF-, MyD88- and IKK-linked signaling in murine macrophages, thus downregulates TBK1, IRF3, and NF- κ B activities.^{81,82} Moreover, 6-shogaol inactivates ERK1/2 and prevents MyD88, NOS2 and matrix metalloproteinase 2 (MMP2) and MMP9 expression in LPS-treated chondrocytes.⁹⁶ 6-shogaol protects the microglia against LPS-induced toxicity by inhibiting the MAPK, NF- κ B, NOS, and COX-2 expression.¹¹⁵ The dimerization of TLR4, induction of NF- κ B and expression of COX-2 are likewise prevented by 6-shogaol.¹¹⁶ In animals with oral carcinoma, treatment with 6-shogaol confers anti-carcinogenic impacts via mitigating AP-1 and NF- κ B activity as well as downregulating IL-1, TNF- α , IL-6, and COX-2.¹¹⁷

Moreover, it was found that zingerone inhibits various elements contributing to TLR-related signaling such as TRIF, MyD88, MAPK, IRF-3, and NF- κ B in several animal models.^{118,119} Zingerone declines the HMGB1 release from stimulated and damaged cells, and downregulates TLR2, TLR4 and RAGE that act as HMGB1 receptors.¹²⁰ Zingerone diminishes HMGB1-induced NF- κ B and ERK1/2 activation and downregulates HMGB1-induced adhesion molecule as well as decreases neutrophil migration.¹²⁰

1-dehydro-10-gingerdione suppresses LPS connection to a TLR4-related co-receptor calling MD2, downregulates IL-6, iNOS, and COX-2 and prevents the NF- κ B activation in LPS-induced macrophages.^{121,122} NF- κ B induction and translocation to the cellular nucleus are likewise prevented by 6-dehydrogingerdione.⁸³ Galangin, a ginger-derived flavonoid, has antioxidant, anti-inflammatory as well as anti-apoptosis activities.¹²³ In a nephrotoxicity model, galangin improves kidney function and downregulates NF- κ B, p38 MAPK, ERK1/2, and JNK.¹²³

Altogether, ginger and its bioactive ingredients can mitigate inflammation by decreasing DAMPs released from injured cells, preventing TLR ligation, inhibiting TLR-mediated signals and eventually downregulating inflammation-promoting parameters (Fig. 1).

Ginger potentials to downregulate inflammasome-induced responses

Inflammasomes are inflammation amplifiers consisting of a sensor molecule recognizing a stimulator, an adaptor element (called ASC), and an effector component named pro-caspase-1.¹²⁴ Various types of DAMPs and PAMPs activate inflammasomes, which result in the cleavage of pro-IL-1 β and pro-IL-18 into their active forms as well as pyroptosis which enables IL-1 β and IL-18 to be released.^{124,125}

The NOD-like receptor 3 (NLRP3) inflammasome is induced during some lung viral infections, such as RSV and influenza A virus infections.^{126,127} The sustained induction of NLRP3 inflammasome causes the massive discharge of DAMPs (such as HMGB1), infiltration and stimulation of macrophages and neutrophils, massive generation of cytokines (such as IFN- γ , IL-1 β , 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 was indicated between HMGB1 quantities and pneumonia severity as well as ALL-related death, which can be blocked with a specific antibody against HMGB1.^{128,130} NLRP3 inflammasome-deficient mice displayed lower lung injuries and a higher survival rate following influenza infection, suggesting that this inflammasome and IL-1 β contribute to lung inflammation and ARDS.¹³¹

In a mouse model of respiratory viral infection, suppressing the NLRP3 inflammasome at the initial stage of illness increased fatality, while its inhibition during the peak of the infection protected mice.¹³² Thus, inflammasomes may have protective and deleterious impacts during various phases of a virus infection.

The SARS-CoV-derived viroporin 3a directly stimulates the

NLRP3 inflammasome.¹³³ The gene viroporin 3a has been found in the genome of SARS-CoV-2, suggesting that SARS-CoV-2 can similarly trigger NLRP3 inflammasome.¹³⁴ SARS-CoV-related E, ORF3a, and ORF8b proteins induce NLRP3 inflammasome^{135–137} and their sequences were also mapped on the SARS-CoV-2 genome, thus they may perform a role in the COVID-19 pathogenesis.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-1 β secreted by alveolar macrophages cause cell death and the release of DAMPs, which lead to excessive activation of the NLRP3 inflammasome, resulting in a positive inflammatory feedback loop.¹³⁸ Damage to ACE2-expressing type II alveolar epithelial cells also triggers the NLRP3 inflammasome.¹³⁸ Elevation of angiotensin II can be caused by SARS-CoV-2-mediated ACE2 downregulation, which can lead to the activation of NLRP3 inflammasome.^{68,139} NLRP3 inflammasome activation mediated by angiotensin II can promote vascular smooth muscle cell expansion, vascular remodeling, hypertension, and pulmonary fibrosis.^{138,140,141} Irregular stimulation of the NLRP3 inflammasome reinforces cytokine storm, which exacerbates the COVID-19 severity.¹³⁴

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

Suppressing the NLRP3 inflammasome's 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 proper therapeutic candidates for the treatment of inflammatory abnormalities. Some ginger-derived phytochemicals suppress the NLRP3 inflammasome and IL-1 β expression. The pretreatment of a stimulated human macrophage cell line with shogaols prevents the pro-caspase-1 conversion into active caspase-1.¹⁴² Gingerols and shogaols also downregulate the NLRP3 inflammasome and IL-1 β in LPS-induced human macrophages.¹⁴² *In vitro* experiments have revealed that high concentrations of glucose initiate the calcification in human vascular smooth muscle cells via upregulating the NLRP3 inflammasome-IL-1 β axis.¹⁴³ 6-shogaol reduces the calcification through attenuating the ROS production and downregulating the NLRP3 inflammasome.¹⁴³ The ginger-derived exosome-like nanoparticles (ELNs) also inhibit the NLRP3 inflammasome assembling, IL-1 β , and IL-18 production as well as pyroptosis in the mouse macrophages.¹⁴⁴ The ELN-related suppressive activity was largely attributed to its lipid fraction.¹⁴⁴

Ginger potentials to down-regulate the oxidative stress

Oxidative stress (OS) is a prooxidant-antioxidant imbalance that results from excessive production of reactive intermediates such as ROS, reactive nitrogen species (RNS), and free radicals. It damages the DNA, proteins, lipids and polysaccharides, which interrupts the cellular physiologic functions and eventually leads to cell death.¹⁴⁵ OS also contributes to the inflammatory responses via NF- κ B activation.¹⁴⁶ Furthermore, NO elicits COX-2 expression promoting the generation of prostaglandin E2 (PGE2).¹⁴⁶

The nuclear factor erythroid 2-related factor 2 (Nrf2) possesses cell protective mechanisms against OS. Nrf2 maintains cellular homeostasis by triggering the production of various antioxidant factors such as NADPH-quinone oxidoreductase, glutathione synthetase (GSH-S), heme oxygenases and thioredoxin enzyme.¹⁴⁵

Viral infections generally reduce antioxidant reserves and enhance the production of oxidants.¹⁴⁵ A number of pulmonary

viral infections promote ROS generation as a result of leukocyte recruitment into the infection site. The overproduction of ROS along with antioxidant depletion increases viral replication and viral-associated complications.¹⁴⁷ The respiratory viral infections were related to the repression of Nrf2 pathways and/or activation of NF- κ B-related signaling, which cause inflammation and oxidative injury.^{147,148}

Similar to other RNA viruses, SARS-CoV2 can trigger OS.¹⁴⁹ The severity and fatality risks of COVID-19 are enhanced in old ages when the degradation of antioxidants together with the accumulation of prooxidants occurs.^{150,151} In the elderly COVID-19 patients, a reverse association was postulated between the 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 TNF- α , IL-1 β , and IL-6 concentrations, total oxidant status, reduces malondialdehyde (MDA) levels, and MPO levels. It also prevents DNA oxidation and enhances endogenous antioxidants.^{153,154} In various animal models of neurotoxicity and brain damage, treatment with ginger enhances the levels of antioxidant elements such as glutathione S-transferase (GST), catalase (CAT), GSH, SOD, glutathione peroxidase (GPx), glutathione reductase (GR), and quinone reductase (QR), halts lipid peroxidation, prevents NO generation, obliterates the hydroxyl radical, and reduces iNOS expression, caspase-3 expression, and apoptosis.^{155–157} These ginger-related antioxidative properties are due to shogaols, gingerols, and other ketone-phenolic derivatives that attenuate OS.¹⁵⁵

In a model of chlorpyrifos-induced toxicity, administration of a 6-gingerol rich fraction declines attenuates H₂O₂, MPO, NO, and MDA levels, as well as caspase-3 expression in several organs (such as the brain, uterus and ovary), while enhancing the quantities of antioxidant factors such as SOD, GPx, GST, CAT, and GSH.¹⁵⁸ The 6-gingerol also shows protective influences against the 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 anti-oxidative activities were also attributed to 6-shogaol, such as the suppression of ROS, iNOS, COX-2 production, and the upregulation of anti-oxidant molecules such as Nrf2, GSH, quinone-1 and hemoxygenase-1.^{94,160,161} Similarly, zingerone reinforces the activity of GPx, SOD, and CAT, and promotes GSH production, while diminishing NF- κ B, IL-1 β , IL-6, TNF- α , COX-2, and iNOS expression in a model of cisplatin-mediated toxicity.¹⁶² Zingerone also attenuates OS and age-associated inflammation via the repression of the MAPK/NF- κ B signaling.¹⁶³ Similar to shogaols, paradols exhibit anti-oxidative impacts.^{164,165}

Altogether, ginger and its compounds are able to decrease the oxidative elements and act as potent stimulators for the OS-attenuating proteins. Therefore, the antioxidant activity of ginger can have beneficial effects in COVID-19 patients (Fig. 2).

Ginger potentials to downregulate the prostaglandins and leukotrienes (LTs)

PGs are pro-inflammatory mediators generated through the COX pathway from arachidonic acid (AA).¹⁶⁶ Some subsets of leukocytes constitutively express COX-1, while COX-2 is expressed during inflammation, which promotes 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 B2 virus infections by influencing viral replication.¹⁶⁷ In lung microvascular endothelial cells, PGE2 promotes inflammation via the upregulation of COX-2 expression and also increases CXCL8 production.¹⁶⁸ SARS-CoV increases PGE2

production by binding to COX-2.¹⁶⁹ It was postulated that PGE2 plays a major role in the COVID-19 pathogenesis.¹⁶⁷ During acute inflammation, COX-2 expression and PGE2 production are more increased in men compared with women, thus the increased PGE2 production in men causes more severe COVID-19.¹⁶⁷ The higher severity of COVID-19 in old ages and obese individuals was also attributed to the higher PGE2 levels.^{170,171} PGE2 also contributes to intravascular thrombosis which is a crucial complication in COVID-19 patients.¹⁷²

During SARS-CoV-2, AA is released by several types of leukocytes. AA, as an antiviral component, can inactivate enveloped viruses, such as SARS-CoV-2.¹⁷³ Hence, AA deficiency promotes the human susceptibility to SARS-CoV-2.^{171,173} The suppression of mPGES-1 reduces the PGE2 generation and can promote the immune response against SARS-CoV-2.^{171,173} Selective suppression of mPGES-1 stimulates antiviral immunity and enhances the 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 the expansion of the influenza virus.¹⁷⁵ LTB₄-exposed neutrophils 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 via various cell types such as microglia and colonic epithelial cells stimulated with LPS *in vitro*.^{84,115,178} The COX-2 expression was also repressed in the stimulated macrophages using gingerols, 8-paradol and dehydrogingerdione.^{179,180} In patients with rheumatoid arthritis (RA) and osteoarthritis, ginger supplementation prevents PG and LT production.¹⁸¹ Ginger prevents PG and LT synthesis via inactivating the COX-1/2 and 5-LOX enzymes, respectively.¹⁷⁷ The dual repression of PGs and LTs generation by ginger might mitigate hyperinflammation in COVID-19 patients (Fig. 2).

Ginger potentials to modulate T cell-mediated responses

Ginger potentials to modulate Th1 cell-mediated responses

The effector CD4⁺ Th1 cells secrete several cytokines, in particular IFN- γ , IL-2, and TNF- α , which provide help for CD8⁺ T lymphocytes as well as natural killer (NK) cells to eliminate the virally infected cells and reduce the viral load.^{182–184} SARS-CoV-2 eradication appears to need timely and proper Th1 cell activation. However, Th1 cells may perform various roles during different periods of COVID-19. During SARS, Th1- and Th2 cell responses appear to be linked with resistance and disease progression, respectively.¹⁸⁵ All virus-specific CD4⁺ T cells in individuals who recovered from mild COVID-19 were Th1 cell subsets.¹⁸⁶ The CD4⁺ Th cells were decreased in COVID-19 patients who were unresponsiveness to antigenic stimulation with SARS-CoV-2 major proteins.¹⁸⁷ Older age and higher comorbidity index were also associated with a smaller number of IFN- γ -producing cells.¹⁸⁷

The immunopathological reactions may be provoked by unbalanced and excessive Th1 cell-mediated responses.^{188,189} In COVID-19 patients who suffered from ARDS, virus-specific T cells mostly generated Th1 cell-related cytokines, while Th17- and Th2 cell-related cytokines were also produced.¹⁹⁰ Patients with severe COVID-19 displayed greater proportions of Th1 cells in their secondary lymphoid organs, which were related to reduced Tfh cell numbers.¹⁹¹ In transgenic mice that express human ACE2, the SARS-CoV-2 infection results in macrophage and lymphocyte accumulation in the lungs with predominant Th1 cell activity as well as large amounts of pro-inflammatory cytokines/chemokines.¹⁹² Importantly, elevated quantities of TNF- α , IFN- γ , IFN- γ

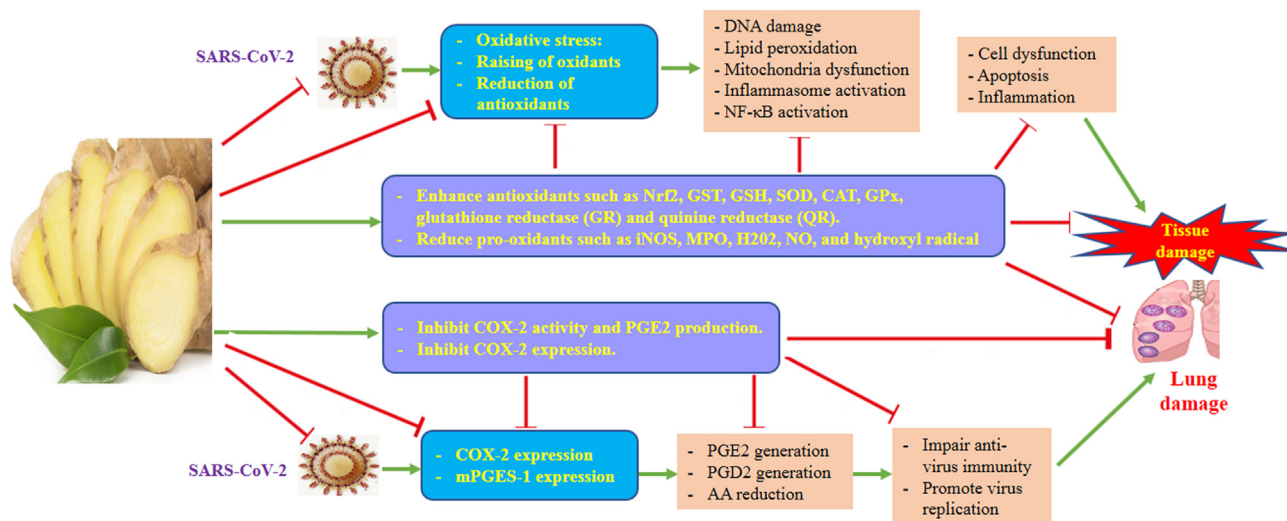


Fig. 2. Oxidative stress and PG-mediated impacts on COVID-19 pathogenesis. SARS-CoV-2 promotes oxidative stress by enhancing pro-oxidant production and reducing anti-oxidants. SARS-CoV-2 can promote PG production and reduce arachidonic acid levels. Ginger has the capability to decrease oxidative elements and promote anti-oxidant factors. Ginger prevents PG production via inactivating COX enzymes and perhaps the mPGES-1 enzyme. These ginger capabilities may be useful to COVID-19 patients. **Abbreviations:** PG: prostaglandin; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; COX: cyclooxygenase; mPGES-1: microsomal PGE synthase-1; AA: arachidonic acid.

inducible protein 10 (IP-10), and MCP-1 were correlated with COVID-19 severity.^{69,193}

Th1 cell-mediated responses can be regulated by ginger as it inhibits the IL-12 (an inducer of Th1 cells) production and downregulates MHC class II molecules as well as costimulatory molecules (such as CD80 and CD86) by antigen-presenting cells (APCs).⁷⁶ Ginger can modulate antigen presentation, CD4⁺ T cell response as well as secretion of IFN- γ and IL-2 by T cells.⁷⁶ The ginger extract also reduces the IL-12 and IFN- γ production 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 the T cell activation and proliferation, as well as the IFN- γ and IL-2 secretion by activated T cells.¹⁹⁶ In a powerful Th1-polarizing medium, 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 count of the splenic IFN- γ - and IL-17- producing CD4⁺ T cells, while reducing the count of the splenic FOXP3⁺ regulatory T (Treg) cells.¹⁹⁸ In immunocompromised mice, treatment with ginger extract enhances the serum quantities of Th1 cytokines, such as IFN- γ and TNF- α .¹⁹⁹ Collectively, ginger and some of its bioactive compounds can modulate the Th1 cell responses (Fig. 3).

Ginger potentials 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 auxiliary signals for B cells to produce antiviral antibodies.^{13,200} Suitable antibody responses to certain parts of the S protein, in particular the RBD, can block the SARS-CoV-2 attachment to ACE2-expressing cells.²⁰¹ Although the exact role of Th1/Th2 cells at different stages of SARS-CoV-2 infection is obscure, balanced Th1/Th2-dependent responses appear to be necessary for successful control of the virus. Th2 cell responses—rather than Th1 responses—are induced against SARS-CoV-2 in patients who need intensive care.²⁰² In fact, great quantities of Th2 cell cytokines were identified in fatal COVID-19 cases when compared with cured patients.²⁰³

In mouse models of airway allergy, ginger extract and 6-gingerol

suppress the expansion and differentiation of both Th1- and Th2 cells, downregulate cytokines related to Th1- and Th2 cells, suppress the IgE generation as well as block mast cell accumulation.^{60,197,204} 6-gingerol also directly inhibits the polarization of Th2 cells in a strong Th2-polarizing medium.¹⁹⁷ A better understanding of the Th2 cell-dependent responses in the COVID-19 needs more studies. If the Th2 cell contribution to the COVID-19 pathogenesis is identified, ginger has a potent capability to regulate these cells (Fig. 3).

Ginger potentials 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-1 β , IL-6, CXCL1, CXCL8 (IL-8), CXCL6, CCL2, GM-CSF, and G-CSF are all generated by different lymphoid and non-lymphoid cell types in response to IL-17A.^{13,205}

The hyper-activation of Th1/Th17 cells results in the generation of many pro-inflammatory cytokines that promote lung dysfunction. Robust Th17 cell-related responses are elicited in SARS-CoV- and MERS-CoV-infected patients.^{206,207} Higher blood concentrations of Th17 cells were indicated in severe COVID-19 patients.²⁰⁸ A number of COVID-19-associated risk factors such as obesity, chronic kidney disease (CKD), hypertension, aging, diabetes, and male gender have been linked to powerful Th17 cell activity.²⁰⁹ Hypoxia and ACE2 downregulation 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 hyper-inflammatory reactions and tissue damage in patients with severe COVID-19. In patients with ARDS, alveolar inflammation, lung damage, organ dysfunction, and poor outcome have all been associated with greater levels of IL-17A in the BALF.²¹⁰ In SARS-CoV-2 and SARS-CoV-infected patients, IL-22 augments the generation of the life-threatening edema filled with fibrin and mucins.²¹¹

Ginger extract declines the generation of IL-23 (full activator of Th17 cells) and IL-17 in EAE mice.²¹² Further, ginger extract declines IL-17, IFN- γ and IL-4 production in mice with arthritis.²¹³ Ginger extract downregulates ROR- γ t, T-bet and GATA-3 (transcription factors of Th17, Th1, and Th2 cells, respectively) in PBMCs collected

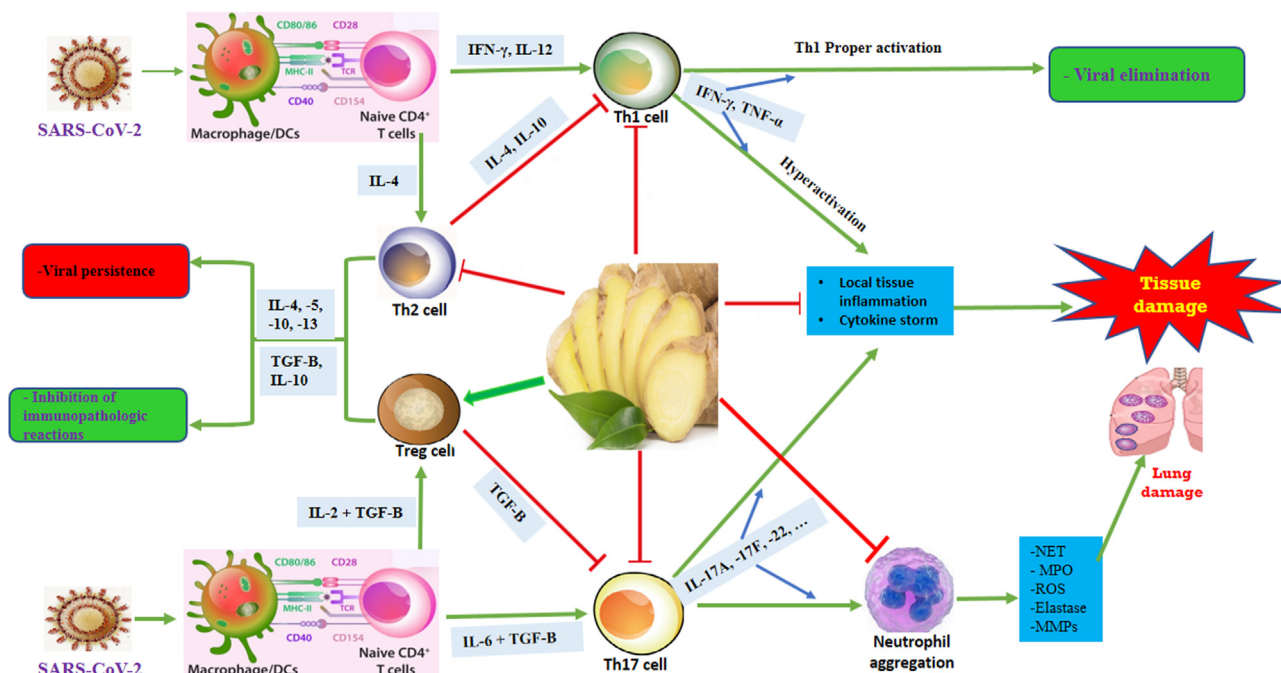


Fig. 3. T cell-mediated responses during COVID-19. The naïve CD4⁺ T cells recognize SARS-CoV-2-derived antigens presented by antigen-presenting cells (APCs) and then can differentiate into various types of effector T cells, such as Th1-, Th2-, Th17- and Treg cells. It seems that timely and proper CD4⁺ Th1 cell responses contribute to the eradication of SARS-CoV-2. However, improper Th1 cell hyper-activation and/or over-exuberant Th17 cell activities contribute to COVID-19 pathogenesis by reinforcing local tissue inflammation, promoting the cytokine storm and recruiting neutrophils. Specific Th2- and Treg cell-mediated responses help virus persistence while balanced Th2- and Treg cell activities can limit immunopathologic reactions. Ginger has the capabilities to modulate inappropriate Th1-, Th2-, Th17- and Treg cell activities.

Abbreviations: SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; APCs: antigen-presenting cells; IFN: interferon; IL: interleukin; TNF: tumor necrosis factor; TGF: transforming growth factor; NET: neutrophil extracellular trap; MPO: myeloperoxidase; ROS: reactive oxygen species; MMP: matrix metalloproteinase.

from asthmatic patients.²¹⁴ In LPS-exposed microglial cells, 6-shogaol downregulates the expression of IL-1β and TNF-α (as the promoters of Th17 polarization).¹¹⁵ Collectively, ginger can attenuate deleterious inflammatory reactions in COVID-19 patients by suppressing Th17 cell-related responses (Fig. 3).

Ginger potentials to modulate Treg cell-mediated responses

Treg cells generate immune-modulating cytokines TGF-β, IL-10, and IL-35, which perform a key role in maintaining tolerance to autoantigens and preventing uncontrolled harmful immune responses during infections.^{13,205} However, hyper-activation of Treg cells can help pathogen persistence.^{205,215} Treg cells can play different roles during the various phases of COVID-19. Hyper-activation of Treg cells in the initial stages of infection may result in SARS-CoV-2 persistence, whereas their activation during the later stages can minimize immunopathologic reactions (Fig. 3).

In patients with severe COVID-19, the blood counts of Treg cells were decreased.^{216,217} Indeed, patients with severe COVID-19 have a higher number of Th17 cells, a lower number of Treg cells, and lower ratios of Treg/Th17 cells.^{211,218–220} An imbalance of Th17/Treg cells, with a shift toward Th17 cells, may play a principal role in the development of COVID-19-related complications such as lung damage and ARDS.^{221,222} Powerful Th17 cell activities, as well as poor Treg cell responses, may contribute to the excessive secretion of pro-inflammatory cytokines and chemokines, which reinforce the cytokine storm, exacerbate the diseases, and perhaps lead to multiorgan failure and death in some COVID-19 patients. However, the frequency of Treg- and Th2 cells in the critical COVID-19 patients (n = 3) with a bad prognosis was found to be higher than those (n = 3) with a favorable prognosis.²²³ These findings should be validated in research with larger sample size.

In EAE mice, ginger extract enhances the generation of TGF-β (an inducer of Treg cells).¹⁹⁴ However, IL-6 (an inducer of Th17 cells)

production was inhibited by ginger and some of its ingredients.^{79,121} Therefore, the ginger has the capacity to correct the Th17/Treg imbalance toward Treg cells which can attenuate COVID-19 severity. Administration of ginger extract to mice with cardiac allograft declines lymphocyte proliferation, downregulates IFN-γ, IL-2, and IL-4 expression and increases the production of Treg-related cytokines such as TGF-β and IL-10.²²⁴

Conclusion

A complex network of SARS-CoV-2-, immune-, inflammatory- and oxidative-mediated reactions contribute to the COVID-19 pathogenesis. Ginger was used widely for thousands of years as a spice or dietary supplement as well as a traditional medicine for treating various disorders.¹³ Here, we have provided clear evidence that ginger can exert direct and indirect inhibitory effects on the viral life cycle, including the binding, entry, replication, packaging and assembling, perhaps via the interacting with viral key proteins and enzymes. Ginger can affect key fundamental processes participating in the COVID-19 pathogenesis due to its anti-viral, anti-inflammatory, immunomodulatory and antioxidant properties. This review presents comprehensive knowledge concerning the potentials of ginger and its compounds for the possible management of COVID-19. It is worthy to exactly identify the effects of SARS-CoV-2 infection on all host organs and to evaluate the impacts of ginger on the 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 the aggregation of platelets) were found in the preclinical studies using ginger.¹³ Moreover, clinical trials need to be conducted to investigate the preventive and

therapeutic potential of ginger in SARS-CoV-2-infected patients using ginger or ginger + anti-virus treatments. A combination therapy using ginger with a validated medication can be a promising candidate for the treatment of COVID-19.

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CRediT authorship contribution statement

Abdollah Jafarzadeh: Conceptualization, project administration, formal analysis, writing – review and editing. **Sara Jafarzadeh:** Data curation and writing – original draft. **Maryam Nemati:** Data curation and writing – original draft.

Declaration of competing interest

The authors have no any conflict of interest.

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