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Review Article

Ginger: Plant Immuno-booster against COVID-19

Prashant Kumar Sharma, Pankaj Kumar Shankhdhar, Amit Gangwar, Neha Pathak and Suman

BIU College of Pharmacy, Bareilly International University, Bareilly, U.P., India.

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ABSTRACT

The entire world is experiencing the Covid, a worldwide pandemic, which has caught the world's regard for the immune system. As the world scrambles to find a solution for Covid-19, health specialists have recommended supporting the body's immunity. The immune system guard against microbes, infection, and different Microorganisms might assist with limiting the impacts and hurry the recuperation from the illness. Coronavirus has a troublingly high death rate. An individual with a solid Immune system and great body health has the option to recuperate from respiratory syndrome coronavirus 2 (SARS-CoV-2) diseases with practically no inconveniences because the invulnerable framework created antibodies. Invulnerability will be "our friend in need" against the infection. The thought is that if you don't have an intense weapon to battle the adversary, a solid and compelling safeguard is simply the smartest choice to secure. Now also there are lots of people in the world who have the risk of getting containment with the COVID- 19 Virus. Ginger plays a big role in increasing the defense system of the body a potent immunomodulatory agent that can help the population to prevent the covid-19 infection.

Keywords: CoVID-19, Ginger, Coronavirus, Immunity Booster, SARS-COV-2.

INTRODUCTION

The outbreak of the new coronavirus (SARS-CoV-2) infection is spreading to every continent; Hailing from a large family of viruses, Corona viruses can cause respiratory illnesses. As per the statistics, geriatric peoples are more susceptible for the COVID-19 infection because of their low immunity against pathogens & various underlying diseases. [1] Covid19 is newly identified infectious disease. In 2019, December the new Coronavirus was found in Wuhan, China with a number of cases of pneumonia patients. Corona Viruses are big group classified in Nidovirales order; by use of a nested set of mRNAs virus get replicated ("nido-" for "nest") [1]. There are four general of Coronavirus sub family: alpha, beta, gamma, and delta corona viruses. Two genera of the human corona viruses (HCoVs): alpha corona viruses (HCoV-229E and HCoV-NL63) and beta corona viruses (HCoV-HKU1, HCoV-OC43, Middle East respiratory syndrome corona virus [MERS-CoV], and the severe acute respiratory syndrome corona virus [SARS-CoV). [1]

Address for Correspondence: Prashant Kumar Sharma, BIU College of Pharmacy, Bareilly International University, Bareilly, U.P., India; E-mail: prashantsharma7615@gmail.com

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COVID-19 AND IMMUNITY

Transmission of COVID-19 (SARS-COV-2): This virus is transferred from one individual to another by airborne droplets to the nasal mucosa. In cells of the ciliated epithelium virus get replicate and then inflammation, cell damage is caused. [3]

Spread of COVID-19: In the year 2019, the new virus (SARS-CoV-2) has breaked out and infection is spreading to every continent which is monitored by the CDC (The Centers for Disease Control and Prevention) [4].

Structure COVID-19: Corona viruses are enveloped pleomorphic or spherical, medium-sized, non-segmented (single stranded) positive sense RNA-Viruses associated with a nucleo-protein within a capsid comprised of matrix protein in Nidovirales Order. The envelope bears spikes like projection on surface which is made up of glycoprotein which gives the virus a characteristic crown-like appearance. [3]

ROLE OF IMMUNITY IN COVID-19

A report in Lancet shows that acute respiratory distress syndrome (ARDS), a common immunopathological event for SARS-CoV-2, SARS-CoV and MERS-CoV infections is the main death cause of COVID-19, and one of the main mechanisms for ARDS is the cytokine storm. The occurrence and development of SARS-CoV-2 depend on the interaction between the virus and the individual's immune system. Viral factors include virus type, mutation, viral load, viral titre, and viability of the virus in vitro.

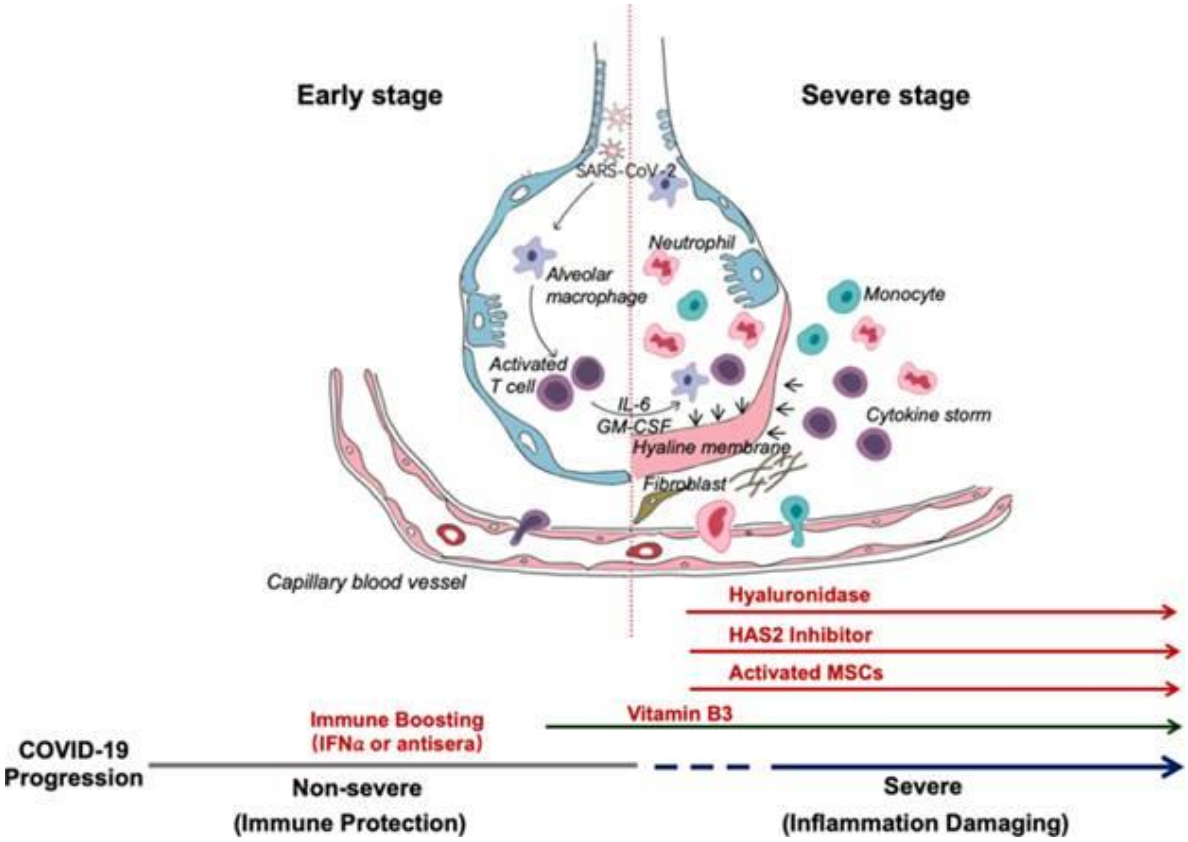

Fig: 1. COVID-19 infection: the perspectives on immune responses in Cell

Genetics (such as HLA genes), age, gender, dietary condition, neuro endocrine-immune modulation, and physical status are all influences in an individual's immune system. All of these factors play a role in whether or not a person becomes infected with the virus, as well as the length and severity of the illness, as well as the risk of reinfection. Accurate diagnosis aids in the control of the disease's transmission in the early phases of the epidemic. [5]

Treatment: As yet, effective treatment is unavailable**,** social distancing &boosting the body's immune system may prevent the disease from spreading.

Immune System: Our immune system is a complex system of cells, processes, and chemicals that protects our bodies from invading pathogens such as viruses, toxins, and bacteria. [6][7]

The invading COVID-19 virus causes non-severe symptoms and elicits protective immune responses after an incubation period. The health status of the infected person, as well as his or her HLA haplotype, have a role in the infection's effective eradication. During this time, immune-boosting techniques can be implemented. If the virus is not eliminated by the infected person's general health status and HLA haplotype, the patient progresses to the severe stage, which is marked by a high harmful inflammatory response, particularly in the lungs. [8]

When the body is unable to mount a sufficient adaptive response to the virus, prolonged innate-induced inflammation appears to trigger a cytokine storm, ARDS, and widespread organ involvement. The population of naive T-cells decreases with age, whereas antigen-experienced, memory T-cells make up a significant component of the T-cell population. [9]

WHO INFECTED MORE?

The National Institutes of Health (NIH) suggest that several groups of people have the highest risk of developing complications due to COVID-19. These groups include Young children, According to WHO People aged 65 years or older get infected more because of weak immunity & According to CDC due to physiologic and immunologic changes Pregnant Women are more susceptible to viral respiratory infections, including Covid19. [10] The people more infected by Covid19 are who suffers with diseases like Chronic Respiratory disease, diabetes, Cancer, Cardiac problem. [11]

Population is generally susceptible to SARS-CoV-2, the median age was 47.0 years (IQR, 35.0 to 58.0), 87% case patients were 30 to 79 years of age, and 3% were age 80 years or older, and the number of female patients was 41.9%. Most cases were diagnosed in Hubei Province, China (75%). 81% cases were classified as mild, 14% cases were severe, and 5% were critical. The overall case-fatality rate (CFR) was 2.3%, but cases in those aged 70 to 79 years had an 8.0% CFR and cases in those aged 80 years and older had a 14.8%. [12]

Anti-tumor necrosis factor (TNF) antibodies have been identified in disease tissues of patients with COVID-19. Also there is sufficient evidence to support clinical trials of anti-TNF therapy in patients with COVID-19. [13] Except in children and adolescents this virus infects the age group evenly and it is reported in a survey of 1000 patients in Wuhan, china. Near 15% cases progress to severe phase and 65% have big chance to progress to severe phase. [14]

IMMUNITY WORK

Immunity solitary break the chain of transmission by starved pathogen of host infect, breaking chain of transmission help to protect health of humans. [15] The division of two-phase is playing an important role: the first immune defense-based protective phase and the second inflammation-driven damaging phase. Doctors should try to increase immune responses throughout the first phase and put down it in the second phase. [14] To conclude, in populations at risk (elderly, associated co morbidities, immunosuppressed), when activation of the innate immune system fails to produce an adequate adaptive response (i.e., virus-specific CD8+ T-cells), it seems that persistent self-induced inflammation can then cause mortality. Thus, mounting an early adaptive immune response may save lives. [9]

CURCUMIN AND IMMUNITY

Ginger: Ginger (*Zingiber officinale*) is a flowering plant whose rhizome, **ginger root** or ginger, is widely used as a spice and a folk medicine.[17] It is a herbaceous perennial which grows annual pseudostems (false stems made of the rolled bases of leaves) about one meter tall bearing narrow leaf blades. The inflorescences bear flowers having pale yellow petals with purple edges, and arise directly from the rhizome on separate shoots.[16]

(a) (b)

Fig 2- *Zingiber officinale* Roscoe and Ginger

CHEMISTRY

Gingerol: IUPAC name - (5*S*)-5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)decan-3-one

Gingerol, properly as [6]-gingerol, is a phenol phytochemical compound found in fresh ginger that activates spice receptors on the tongue. Molecularly, gingerol is a relative of capsaicin and piperine, the compounds which are alkaloids, though the bioactive pathways are unconnected. It is normally found as a pungent yellow oil in the ginger rhizome, but can also form a low-melting crystalline solid

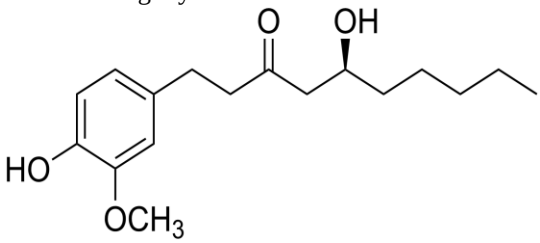

Fig 3- Chemical structure of Gingerol

Zingerone: Zingerone, also called **vanillylacetone**, is a major flavor component of ginger, providing the sweet flavor of cooked ginger. Zingerone is a crystalline solid that is sparingly soluble in water and soluble in ether. Zingerone is similar in chemical structure to other flavor chemicals such as vanillin and eugenol. It is used as a flavor additive in spice oils and in perfumery to introduce spicy aromas. Fresh ginger does not contain zingerone, but it is produced by cooking or drying of the ginger root, which causes a reverse aldol reaction on gingerol.

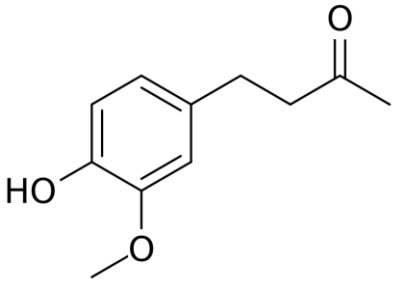

Fig 4- Chemical structure of Zingerone

Ginger as Immunity Boosters

Hot Tea is given with Ginger because it helps respiratory system to stay healthyelp in booting the immune system of our body. [17] **Ginger** has positive/good effects on numerous disease conditions in patients and in animal systems. The terminal stage of viral diseases is often the onset of a cytokine storm, the massive overproduction of cytokines by the body's immune system. The suppression of cytokine release by Curcumin correlates with clinical improvement in experimental models of disease conditions where a cytokine storm plays a significant role in mortality. [18]

Ginger regulates inflammatory cytokines such as IL-17A, IL- 17F, IL-21, IL-22, IL-26, TNF-a, CCL20, and GM-CSF.13,205 TNF-a, IL- 1b, IL-6, CXCL1, CXCL8 (IL-8), CXCL6, CCL2, GM-CSF, and G-CSF. As Curcumin (diferuloylmethane), a component of Ginger (Curcuma longa) can block TNF-α action and production in in-vitro models, in animal models and in humans.[20] Ginger was shown inhibitory properties for SARS- CoV in the range of 3–10μM.[21] A study shown significant decreases in all markers of inflammation (soluble CD40 ligand (sCD40L), interleukin 1 beta (IL-1β), interleukin 6 (IL-6), soluble vascular cell adhesion molecule 1 (sVCAM-1), and erythrocyte sedimentation rate (ESR) comparing baseline to follow-up, while the control group did not.[22]

A molecular docking study with the aim to examine several medicinal plant-derived compounds that may be used to inhibit the COVID-19 infection pathway found the Curcumin molecule have good affinity, and low binding energy with low inhibition constant, this study also conclude that demethoxycurcumin, curcumin's related compound, have stronger affinity than the Curcumin molecule. [23]

Therefore, we suggested that demethoxycurcumin and Curcumin are few of the most recommended compounds found in medicinal plants that may act as potential inhibitors of COVID-19. [23]

Proof of ginger's working 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 PL pro also interferes with type I IFN anti-virus response.[36] Thus, PL pro 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.[38] 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-CoV3C like molecule and cathepsin K) which are essential for SARS-CoV-2 replication.[39] 6-gingerol also binds to the S protein and several RNA binding proteins of SARS-CoV-2.[40] Docking analyses also revealed that gingerol, geraniol, shogaol, zingiberene, zingiberenol, and zingerone interact with key residues in the catalytic domain of the MPro.[41] 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.[42] 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.[43] 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.[45] 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.[46] 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.[47]

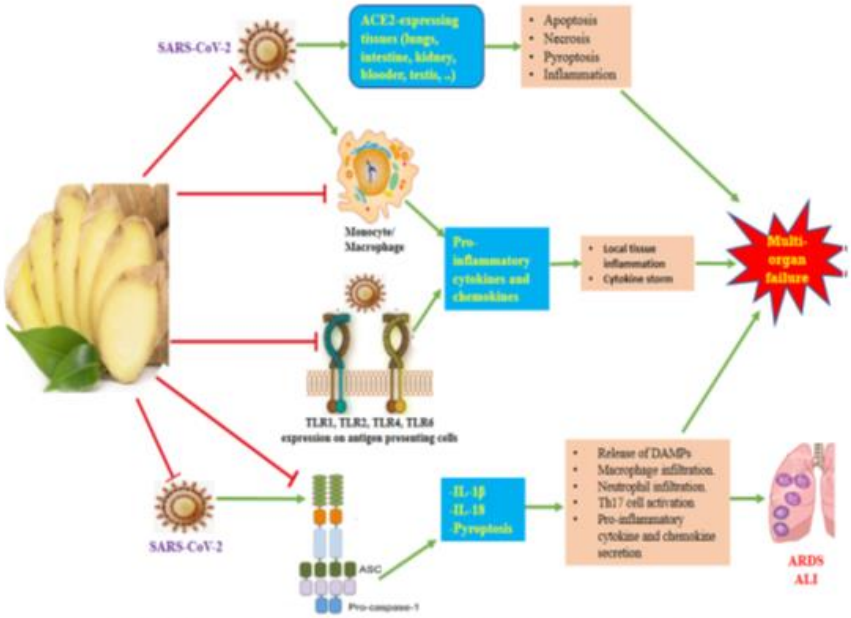

Fig 5- SARS-CoV-2- and inflammation-mediated impacts on COVID-19 pathogenesis. SARS-CoV-2 infects tissues expressing ACE2 and leads to cell death (via necrosis, apoptosis and pyroptosis) as well as inflammation. SARS-CoV-2-infected macrophages release numerous types of cytokines and chemokines promoting 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.

In addition, the hospitalization rate in the intervention group (2.0%) was lower than that in the control group (6.0%). 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-a, 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.[41] 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.

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-a, CCL20, and GM-CSF.13,205 TNF-a, IL- 1b, 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.[42,43] Robust Th17 cell-related responses are elicited in SARS-CoVand MERS-CoV-infected patients. Higher blood concentrations of Th17 cells were indicated in severe COVID-19 patients.[47] 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.[48] Hypoxia and ACE2 downregulation also potentiate Th17 cell activities in COVID-19.[48] 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 levelsof IL-17A in the BALF.[44] In SARS-CoV-2 and SARS-CoV-infected patients, IL-22 augments the generation of the life-threatening edema filled with fibrin and mucins.[50,51] Ginger extract declines the generation of IL-23 (full activator of Th17 cells) and IL-17 in EAE mice.[50] Further, ginger extract declines IL-17, IFN-g and IL-4 production in mice with arthritis.[51] Ginger extract downregulates ROR-gt, T-bet and GATA-3 (transcription factors of Th17, Th1, and Th2 cells, respectively) in PBMCs collectedfrom asthmatic patients.[54] In LPS-exposed microglial cells, 6-shogaol downregulates the expression of IL-1b and TNF-a (as the promoters of Th17 polarization).[49] Collectively, ginger can attenuate deleterious inflammatory reactions in COVID-19 patients by suppressing Th17 cell-related responses (Fig. 3).

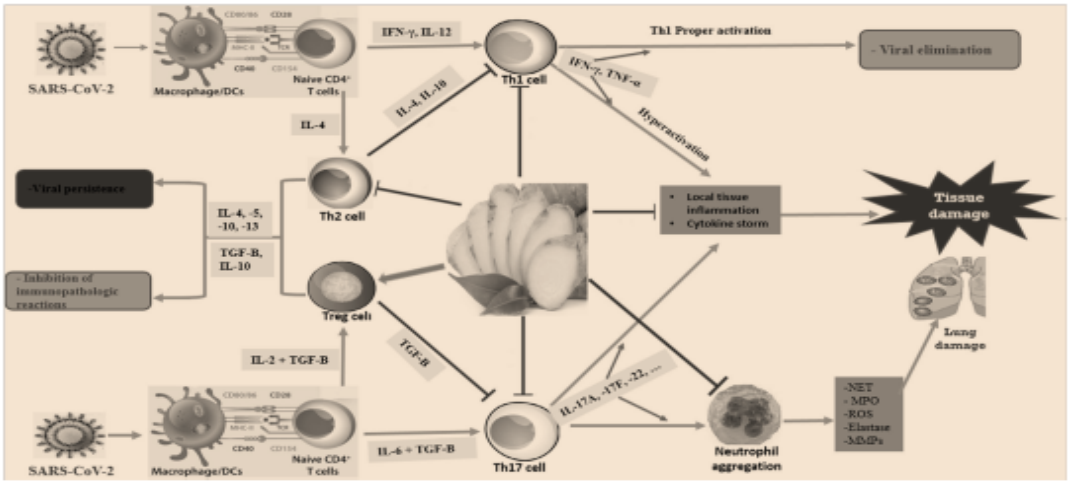

Fig. 3. T cell-mediated responses during COVID-19. The naïve CD4þ T cells recognize SARS-CoV-2-derived antigens presented by antigen-presenting cells (APCs) and then can differentiate into various types of effector T cells, such as Th1-, Th2-, Th17- and Treg cells. It seems that timely and proper CD4þ 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.

CONCLUSION

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, immune-modulatory 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. 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 þ 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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