

Efficacy of Red Ginger in Reducing the Risk of COVID-19 Severity in COPD Patients: A Review

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Abstract

Chronic obstructive pulmonary disease (COPD) represents a significant global health challenge, contributing to rising healthcare expenditures and diminished productivity. Patients with COPD exhibit a higher incidence of coronary ischemia and other risk factors that elevate their susceptibility to complications associated with COVID-19. A robust immune system plays a crucial role in enhancing the body's defenses, thereby mitigating the risk of infection and complications during the COVID-19 pandemic. The potential for utilizing natural therapies in the management of chronic diseases presents a unique opportunity for Indonesia, a tropical nation rich in diverse plant species that could serve as herbal remedies. Among these, red ginger (*Zingiber officinale* var. *rubrum*) stands out as one of the most commonly utilized medicinal plants in Indonesia. Notably, red ginger possesses superior anti-inflammatory and antioxidant properties compared to other ginger varieties. The antioxidant and anti-inflammatory benefits of red ginger not only aid in reducing the severity of COVID-19 but also contribute to the enhancement of lung function. The preparation of red ginger that has been used in the community is steeping. Therefore, red ginger has the potential to effectively reduce the risk of COVID-19 severity in COPD patients with anti-inflammatory and antioxidant effects in reducing NF-κB and the effectiveness of improving lung function.

Keywords: COPD, COVID-19, red ginger

Khasiat Jahe Merah dalam Mengurangi Risiko Keparahan COVID-19 pada Pasien PPOK: Setuah Tinjauan Pustaka

Abstrak

Penyakit paru obstruktif kronik (PPOK) merupakan tantangan kesehatan global yang signifikan, yang berkontribusi pada meningkatnya pengeluaran perawatan kesehatan dan menurunnya produktivitas. Pasien dengan PPOK menunjukkan insiden iskemia koroner yang lebih tinggi dan faktor risiko lain yang meningkatkan kerentanan mereka terhadap komplikasi yang terkait dengan COVID-19. Sistem imun yang kuat memainkan peran penting dalam meningkatkan pertahanan tubuh, sehingga mengurangi risiko infeksi dan komplikasi selama pandemi COVID-19. Potensi untuk memanfaatkan terapi alami dalam pengelolaan penyakit kronis menghadirkan peluang unik bagi Indonesia, negara tropis yang kaya akan beragam spesies tanaman yang dapat berfungsi sebagai pengobatan herbal. Di antara ini, jahe merah (*Zingiber officinale* var. *rubrum*) menonjol sebagai salah satu tanaman obat yang paling umum digunakan di Indonesia. Khususnya, jahe merah memiliki sifat antiinflamasi dan antioksidan yang lebih unggul dibandingkan dengan varietas jahe lainnya. Manfaat antioksidan dan antiinflamasi dari jahe merah tidak hanya membantu mengurangi keparahan COVID-19 tetapi juga berkontribusi pada peningkatan fungsi paru-paru. Olahan jahe merah yang telah digunakan di masyarakat sangat banyak. Oleh karena itu, jahe merah berpotensi efektif menurunkan risiko keparahan COVID-19 pada pasien PPOK dengan efek antiinflamasi dan antioksidan dalam menurunkan NF-κB dan efektifitas peningkatan fungsi paru.

Kata Kunci: PPOK, COVID-19, jahe merah

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1. Introduction

Chronic obstructive pulmonary disease (COPD) represents a significant global health challenge, with an escalating impact on public health. Current standard treatments focus on alleviating symptoms, preventing recurrent exacerbations, preserving optimal lung function, and enhancing overall quality of life.¹ According to the World Health Statistics, COPD ranks as the third most common cause of mortality globally. Data from the Basic Health Research (RISKESDAS) indicates that the prevalence of COPD in Indonesia is 3.7% per one million individuals.²

In Indonesia, there are still a lot of smokers, and this trend is predicted to continue. With about two million cases of tobacco-related illnesses and more than 200,000 tobacco-related fatalities each year, Indonesia has a heavy tobacco burden. The number of smokers in Indonesia is sixth highest in the world. As one of the world's major markets for tobacco use, Indonesia is severely impacted by diseases linked to tobacco use. these facts show that Indonesia has a considerable impact on the prevalence of tobacco-related illnesses worldwide.^{3,4}

COPD is a chronic disease with long-term therapy. Synthetic medicine is not safe, often causes side effects,^{5,6} and treatment non-adherence.⁷ This has contributed substantially to the increasing popularity of complementary and alternative medicine and herbal medicine.⁸ Acute respiratory syndrome coronavirus 2 (SARS-CoV2), the virus responsible for the 2019 coronavirus disease (COVID-19) pandemic. COVID-19 was first discovered in China, in December 2019. Over time, the virus continued to spread to various corners of the world. The World Health Organization (WHO) has declared COVID-19 a global pandemic.⁹

Individuals who have chronic lung diseases such as severe asthma and COPD are at higher risk of SARS-CoV2 infection and have been shown to be associated with an increased risk of COVID-19-related death.^{10,11} COPD patients live under threat of being at greater risk of contracting the corona virus, which greatly affects their daily lives. Many COPD patients are worried that infection will even affect their daily productivity because they prefer to self-isolate. The nagging fear of the coronavirus as a death threat is the dominant feeling, along with anxiety, loneliness, and hope. Moderate to severe COPD patients feel they have to self-isolate because they are afraid of dying from COVID-19.^{12,13,14,15}

Indonesia, characterized as a tropical nation, boasts a rich diversity of plant species with significant

potential for use as herbal medicines. Taxonomist Axel Dalberg Poulsen from the Royal Botanic Garden Edinburgh identifies Wallacea, Kalimantan, and Sumatra as key regions for the wild diversity of Zingiberaceae in Indonesia, with a majority of these species being endemic. Unfortunately, over 100 species of Zingiberaceae in Indonesia face the threat of extinction, primarily due to forest conversion and deforestation that have occurred over recent decades. The Zingiberaceae family is known for its various biological and pharmacological properties.¹⁶ One of the plants that are commonly found is ginger (*Zingiber officinale*).^{17,18} The primary active compounds responsible for the medicinal properties of red ginger include gingerol and shogaol, which exhibit anti-inflammatory, antioxidant, antibacterial, and antiplatelet effects.¹⁹ One of the most commonly used medicinal plants in Indonesia is red ginger. Compared to other varieties of ginger, gingerols and shogaols of red ginger (*Zingiber officinale* var. *rubrum*) have the strongest anti-inflammatory and antioxidant effects.^{20,21,22,23}

2. Risk of COVID-19 in COPD

COPD patients face a heightened risk of developing cardiovascular conditions, which subsequently elevates the likelihood of complications arising from COVID-19. The mortality rate among COPD patients infected with COVID-19 has been linked to advanced age and the presence of heart failure. Furthermore, COPD patients diagnosed with COVID-19 exhibited increased rates of hospitalization and mortality, predominantly due to pneumonia.²⁴

Cardiovascular disease is common in people with COPD, leading to an increased risk of hospitalization, longer hospital stays, and death from cardiovascular disease. The economic burden associated with CVD may even exceed the cost of treating COPD itself.²⁵ COPD patients with cardiovascular disease have been shown to have fibrinogen and circulating inflammatory biomarker C-reactive protein (CRP) levels were higher compared with COPD patients without comorbid cardiovascular disease. In patients older than 65 years, factors associated with accelerated aging (telomere shortening, endothelial cell senescence, and reduced cell proliferation) are implicated in the pathogenesis of atherosclerosis, suggesting the possibility of another mechanistic link between COPD and cardiovascular disease.^{26,27}

A significant connection between COPD and cardiovascular disease is primarily attributed to smoking, which serves as the principal risk factor for atherosclerosis. This condition arises from chronic and systemic inflammatory responses that can lead

to coronary heart disease and heart failure. The inflammatory reaction triggered by cigarette smoke impairs the normal defense and repair mechanisms of the lungs, resulting in the narrowing and remodeling of the small airways, as well as damage to the lung parenchyma, commonly known as emphysema.²⁷

In the midst of the COVID-19 pandemic, a strong immune system can help increase the body's resistance and reduce negative impacts.^{28,29} Patients with chronic lung diseases (such as COPD, asthma, pulmonary fibrosis, and lung cancer) who are infected with COVID-19 are at high risk of experiencing serious problems due to a weakened immune system,^{12,30,31} and the condition will be worsened if the condition of lung disorders chronic, uncontrolled or severe.^{28,32}

3. COPD Treatment Effects on COVID-19

3.1. Inhaled corticosteroids (ICS)

ICS is a mainstay therapy for airway diseases, and provides beneficial effects including protection against exacerbations. ICS is the primary treatment for COPD for patients with a history of exacerbations. The use of ICS combined with long-acting β_2 agonists (LABA) has been shown to provide improved exacerbation reduction, lung function, and health status.^{33,34}

Corticosteroids have potential for treating COVID-19, but their administration are still controversial. While CDC and WHO, recommend avoiding the use of corticosteroids for COVID-19, but the Surviving Sepsis Campaign recommends their use in COVID-19 patients experiencing acute respiratory distress syndrome (ARDS).³⁵ The benefits of corticosteroids in COVID-19 have been proven in previous research by the RECOVERY study involving 6,425 hospitalized COVID-19 patients in the UK, showing that COVID-19 patients who received systemic corticosteroid therapy (dexamethasone) experienced clinically significant improvements compared to those who did not receive corticosteroids.³⁶ Other research that supports this is the CoDEX study in Brazil, showing that COVID-19 patients who experienced acute respiratory distress syndrome (ARDS) and received additional intravenous dexamethasone therapy experienced significant clinical improvement.³⁷

Corticosteroids are a class of drugs that can provide anti-inflammatory effects so that when used correctly they can reduce damage to the respiratory organ system due to the COVID-19 cytokine storm. The use of systemic corticosteroids has proven beneficial in severe COVID-19 patients who require additional oxygen therapy or mechanical ventilation. The use of inhaled corticosteroids (ICS) in the treatment of COPD

during the COVID-19 pandemic remains controversial. ICS has a preventive effect against pneumonia, but does not provide any protection against coronavirus infection and actually increases the chance of contracting COVID-19. According to GOLD, there is no evidence to support replacement of ICS therapy in the treatment of COPD, which is used to reduce the likelihood of developing COVID-19.^{34,13}

The mechanism of ICS in respiratory disorders is through its suppressive effect on inflammation. Many inflammatory genes activated in airway epithelial cells are suppressed. Inhaled corticosteroids decrease the number of inflammatory cells in the airways, such as eosinophils, T lymphocytes, mast cells, and dendritic cells, at the cellular level. This effect of corticosteroids is caused by suppressing the production of adhesion molecules and chemotactic mediators, as well as by preventing the survival of inflammatory cells in the airways, such as mast cells, T lymphocytes, and eosinophils.^{35,38}

ICS are being considered as a treatment option for COVID-19 due to their anti-inflammatory properties, particularly concerning lung inflammation. The anti-inflammatory effects of ICS may help mitigate the risk of severe disease associated with hyperinflammation in COVID-19 cases.³⁹ Furthermore, ICS may inhibit the replication of the SARS-CoV-2 virus and reduce the expression of cellular receptors that facilitate viral entry. However, several *in vivo* studies examining the efficacy of ICS in COVID-19 patients yield mixed results, primarily due to insufficient sample sizes and a lack of robust scientific evidence, which has resulted in the absence of definitive guidelines regarding the use of inhaled corticosteroids in this context. For patients who are already on ICS, such as those with asthma or COPD, there is no indication that they should discontinue corticosteroid use during the COVID-19 pandemic.⁴⁰ Additionally, COPD patients with mild COVID-19 symptoms who do not require hospitalization are not advised to use corticosteroids. In fact, the administration of inhaled corticosteroids in COPD patients may offer protection against the progression of the disease in a hospital setting. Patients with COVID-19 who are prescribed inhaled corticosteroids for underlying conditions should continue their treatment as directed by their healthcare professionals.

3.2. Beta-2 agonist

β_2 -AR has an important role in the pathogenesis and treatment of chronic obstructive pulmonary disease (COPD).⁴¹ More than 90% of all beta receptors in the human lung are located in the alveoli, which is dominated by the beta-2 subtype (70%). Beta-

2 adrenergic receptors (β 2-ARs) are located in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle, broadcasting to the airways and to all immune cells such as macrophages, dendritic cells, B lymphocytes and T.

Beta-2 agonist mechanisms in COPD, namely the role of adrenergic signals in regulating immune and pro-inflammatory responses. The inflammatory reaction is characterized by secreting IL-6 and increasing Th17 responses. Blocking of β 2-AR results in reduced T helper type 17 (Th-17) responses. Th17 cells are believed to be important proinflammatory cells in the pathogenesis of chronic obstructive pulmonary disease (COPD).⁴² In addition, Th17 cells play an important role in the pathogenesis of COVID-19, not only by activating the cytokine cascade but also by inducing Th2 responses, inhibiting Th1 differentiation, and suppressing Treg cells.⁴³ Patients with severe COVID-19 show high levels of IL-17 and GM-CSF. Lung tissue damage may also be caused by Th17 cell-mediated recruitment of neutrophils.⁴³

However, there is also evidence to the contrary, suggesting that administration of β 2-AR agonists induces mitochondria-dependent generation of reactive oxygen species (ROS) that produces cAMP response element binding protein (CREB) resulting in IL-6 activation. This influences the Th1/Th2 balance towards greater Th2 polarization. Beta2-adrenergic signaling inhibits IL-12 production, thereby promoting Th2 differentiation and inhibiting Th1 development associated with antitumor immunity. Catecholamines are also known to impact the immune response through downregulation of IFN- γ production.⁴⁴

Severe COVID-19 patients experience multiple disorders resulting from immune system imbalances and malfunctions that can lead to pro-inflammatory reactions and immunopathological conditions, characterized by deadly inflammation in the lungs and leaky blood vessels. Blockade of β 2-AR can reduce IL-6 and other inflammatory cytokines in patient serum contributing to rebalancing the immune system. Additionally, stress-induced inflammation, which may occur in patients diagnosed with COVID-19, may worsen clinical symptoms.⁴³

4. Potential Herbal Plants For COPD Treatment

Various plant extracts have potential therapeutic effectiveness against inflammatory lung disorders including COPD. Additionally, many different classes of plant constituents were found to inhibit inflammatory responses in the lung, including coumarins, flavonoids, phenolics, iridoids, monoterpenes, diterpenes and triterpenoids.⁴⁵ Although the pathophysiology of

COVID-19 is well understood, it remains unclear how the inflammatory response that causes pain in some patients is controlled. NF- κ B is continuously present during this inflammatory process and has the ability to cause the formation of proinflammatory cytokines. NF- κ B activation and its potential to influence the generation of cytokine storms are now better understood thanks to new information. According to research, SARS-CoV-2 can constantly activate NF- κ B through the RAAS component system and the Toll-like receptor (TLR) system.⁴⁶

4.1. The Role of Red Ginger in Respiratory Medicine

Ginger (*Zingiber officinale* Rosc) is widely recognized as a prominent culinary spice, known for its unique spicy flavor, and is esteemed in traditional Chinese herbal medicine. To date, researchers have extracted and identified over 160 compounds from ginger, which include essential oils, gingerol derivatives, diarylheptanoids, phenylalkanoids, sulfonates, steroids, and monoterpenoid glycosides. A growing body of research indicates that ginger possesses numerous biological properties, particularly in terms of safeguarding the digestive system, combating cancer, and aiding in weight reduction.⁴⁷

Ginger has three varieties namely elephant ginger, red ginger, and empirrit ginger. Studies reported that red ginger (*Zingiber officinale* var. *rubrum*) has greater anti-inflammatory and antioxidant content than the other 2 types.^{15,18,20,48} Red ginger is a rhizome type medicinal plant which is a source of raw material for herbal medicinal plants, which are most widely consumed in Indonesia. Biopharmaceutical demand for red ginger is the highest compared to other rhizome plants, so it has great potential for development. The chemical compounds contained in ginger are essential oils which contain monoterpene and sesquiterpene hydrocarbons which have antibacterial properties. The main active ingredient in fresh rhizomes is gingerol. In fresh ginger, the most phenolic compounds are found in the gingerol type, consisting of 6-gingerol, 8-gingerol, and 10-gingerol. Meanwhile, the main active ingredient in dried rhizomes is shogaol, a derivative of dried gingerol. Ginger essential oil is very useful as an antibacterial agent in dealing with food contamination, extending the shelf life of food.⁴⁹

Heating dried ginger will produce stir-fried ginger and carbonated ginger, so that its antioxidant activity decreases, because this processing can convert gingerol into shogaol. In addition, the 6-gingerol-rich fraction from ginger can reduce H_2O_2 and malondialdehyde levels, increase antioxidant enzyme activity, and increase glutathione by oxidative damage caused by chlorpyrifos. In addition, in previous

research, found that the 6-gingerol-rich fraction prevented the increase in inflammatory markers such as myeloperoxidase, NO, and TNF- α in the brain, ovaries, and uterus of mice treated with chlorpyrifos. Ginger induced significant and rapid relaxation in isolated human airway smooth muscle. Based on the results of guinea pig and human tracheal models, 6-gingerol, 8-gingerol, and 6-shogaol can cause rapid relaxation of previously contracted airway smooth muscle. Nebulized 8-gingerol attenuates airway resistance through reducing Ca^{2+} influx in rats. In another study, 6-gingerol, 8-gingerol, and 6-shogaol increased β -agonist-induced relaxation in human airway smooth muscle through suppression of 4D phosphodiesterase.¹⁹

Ginger has an important role in therapy in the respiratory tract, by inducing bronchodilation by modulating intracellular calcium ($[\text{Ca}^{2+}]_i$) in airway smooth muscle (ASM) thereby causing relaxation. The ginger components 6-gingerol, 8-gingerol, and 6-shogaol, calm ASM, and 8-gingerol attenuates airway hyperresponsiveness, by inhibiting the acetylcholine-induced increase in intracellular calcium ($[\text{Ca}^{2+}]_i$) in airway smooth muscle cells. The most effective constituents in providing a relaxing effect on smooth muscle are 6-shogaol and 8-gingerol, with the mechanism of reducing the influx of $[\text{Ca}^{2+}]_i$ through L-type calcium channels, 8-gingerol and 6-shogaol also reduce the calcium response to Gq-coupled receptor agonists bradykinin and acetylcholine.⁵⁰

4.2. Benefits of Red Ginger for COPD Treatment

Red ginger contains gingerol and shogaol which have the property of inducing bronchodilation by modulating $[\text{Ca}^{2+}]_i$ in airway smooth muscle, thereby causing significant and rapid relaxation.⁵⁰ The effectiveness of 10-gingerol shows the greatest anti-inflammatory and antioxidant effects compared to other gingerols. Pharmacokinetic studies on red ginger are still very lacking compared to other ginger items.²¹

Many studies support the effectiveness of red ginger in COPD. Previous research by Sutyarso et al.,²³ that in preclinical trials, ethanol extract of red ginger can reduce the number of goblet cells and increase the height of cilia in the respiratory tract of white mice exposed to cigarette smoke. Previous research by Lorensia et al.,⁵¹ in stable COPD patients in Mojokerto City, Indonesia, who received red ginger infusion therapy at a dose of 250 grams for 4 months. The results showed that 66.67% of respondents experienced a significant increase in CAT scores after red ginger therapy compared to before therapy. Therefore, red ginger therapy needs attention because it might be developed as a new agent to help treat COPD. Apart

from that, the effectiveness of red ginger infusion can also improve lung function in outpatient COPD patients, which is assessed by the ratio of forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). Red ginger infusion for 4 months was proven to be effective in increasing lung function from FEV1/FVC parameter values significantly.¹⁸

4.3. Benefits of Red Ginger to Lower the Risk of Severity of COVID-19 in COPD

Indonesia, being a tropical nation, boasts a diverse array of plants that hold significant potential as herbal remedies. Among these, ginger (*Zingiber officinale*) is a prevalent and extensively utilized spice. The health advantages associated with ginger are primarily linked to its phenolic compounds, including gingerols and shogaols.²⁹ Red ginger (*Zingiber officinale* var. *rubrum*) has higher anti-inflammatory and antioxidant properties than other types of ginger.³¹ One of the most commonly used in Indonesia is red ginger. When compared to other gingerols, red ginger's gingerols and shogaols have the strongest anti-inflammatory and antioxidant properties. Ginger has been the subject of documented pharmacokinetic investigations, however there aren't any for red ginger.^{12,30}

COVID-19 patients are at higher risk of developing an inflammatory response that is associated with serious respiratory disease and can even be fatal. The most common symptoms of COVID-19 include lung inflammation, fever and fibrosis, which appear to be mediated by pro-inflammatory cytokines. The inflammatory response is caused by an oxidative stress reaction which affects the repair of the body's immune control mechanisms and systems, so that oxidative stress is the main factor that increases the severity of COVID-19, especially in chronic diseases.⁵² In non-risk individuals such as those with chronic respiratory diseases, excess reactive oxygen species (ROS) is offset by increased antioxidant defenses. Excessive oxidative stress causes increased ROS production, causing red blood cell (RBC) membrane peroxidation, thereby increasing neutrophil activation. This may be a factor responsible for alveolar damage, thrombosis, and red blood cell dysregulation as occurs in COVID-19.⁵³ The antioxidant effects of ginger can help reduce the severity of lung function. The content of red ginger in the form of gingerol, gingerol, and shogaol produces a rapid relaxation mechanism in airway smooth muscle (ASM) by changing $[\text{Ca}^{2+}]_i$, thereby reducing airway hyperresponsiveness.⁵⁰

An increase in oxidative stress that exceeds antioxidants causes inflammation, which is also a trigger factor for COPD attacks. This is due to an imbalance of protease and antiprotease in the

respiratory tract. Smoking is a significant risk factor for COPD and is a significant emitter of oxidants and reactive oxygen species (ROS) in the lungs.⁵⁴ Smoking reduces antioxidant defenses and damages lung cells by increasing the amount of oxidants in the respiratory tract.⁵⁵

Processed red ginger that is commonly used in Indonesia is in the form of steeping. The way to make it is to make a ginger decoction by boiling 200 mL of water with 50 milligrams of ginger until the water is reduced to 100 mL.⁵⁶ Therefore, the antioxidant and anti-inflammatory effects of red ginger apart from helping reduce the risk of reducing the severity of COVID-19, can also help improve lung function.

4.4. COVID-19 infection and signaling from NF- κ B

An essential mediator in COVID-19 is NF- κ B. The pathophysiology of the severe/critical COVID-19 phenotype has been linked to hyperactivation of the nuclear factor kappa-light-chain-enhancer of the activated B cell (NF- κ B) pathway. Inhibitory proteins called NF- κ B inhibitors (I-Bs) and the complex protein system NF- κ B are both found dormant in the cytoplasm. Upon stimulation (induction), I-B kinase (IKK) phosphorylates I-Bs, which causes NF- κ B to translocate to the nucleus, bind to their specific DNA, and activate a large number of genes involved in host immunity, inflammation, cell proliferation, and apoptosis. Biological lipopolysaccharides, ionizing radiation, reactive oxygen species (ROS), cytokines including tumor necrosis factor alpha (TNF- α) and interleukin 1-beta (IL-1-beta), as well as viral DNA and RNA are some of the numerous inducers of NF- κ B. It is possible that immunomodulation on the level of NF- κ B activation and inhibitor of NF- κ B degradation (I-B) in combination with inhibition of TNF- α would lessen the severity of COVID-19 and the cytokine storm. NF- κ B pathway inhibition may be used therapeutically to lessen the severity of COVID-19.⁵⁷

The coronavirus may activate nuclear factor kappa B (NF- κ B)-dependent signaling to inflame the human brain. The SARS-CoV virus can enter the host cell by cleaving/activating viral envelope glycoproteins when it binds to certain receptors, including CD147, ACE2, and transmembrane-assisted serine protease 2 (TMPRSS2). Toll-like receptors (TLRs), including TLR3, TLR4, and TLR7/8, are activated inside the endosome by single-stranded RNA viruses. As a result of this receptor's activation of IKK, cytoplasmic inhibitory factor I-B is phosphorylated, which leads to I-B's own phosphorylation and eventual destruction. When TNF or IL-1 bind to their receptors or other cytokine- or TLR receptor-mediated signaling cascades, such as NF- κ B activation occurs. Pro-

inflammatory cytokines and a chemokine storm are produced as a result of excessive NF- κ B activation. A cytokine and chemokine storm then activates T cells, including CD4 and CD8, which lead to further inflammation at the infection site.⁵⁸

Proinflammatory mediators are produced when the transcription factor NF- κ B translocates into the nucleus and binds to the B site. Because the essential modulator (NEMO), a regulatory member of the IKK complex, is involved, this is the "canonical pathway" of NF- κ B. Protein kinase R (PKR), which also regulates TNF-, is a component of the "non-canonical pathway" of NF- κ B. The lymphotoxin B cell activating factor receptor is responsible for activating a subset of tumor necrosis factor superfamily receptors. The "non-canonical pathway" involves delayed but persistent activation of NF- κ B that results in the release of proinflammatory mediators. The major response myeloid differentiation pathway 88 (MyD88) and pattern recognition receptors (PPRs) are the pathways that the beta coronavirus uses to hyperactivate the NF- κ B system. Numerous distinct cytokines and chemokines are therefore induced.⁵⁸

5. Conclusion

Red ginger has the potential to effectively reduce the risk of COVID-19 severity in COPD patients with anti-inflammatory and antioxidant effects in reducing NF- κ B and the effectiveness of improving lung function.

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Conflict of Interest

The authors declare no conflict of interest.

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Efficacy Red Ginger in Reduce The Risk of Covid-19 Severity in COPD Patients: A Review

Amelia Lorensia

Abstrak

Chronic obstructive pulmonary disease (COPD) is a major global health problem and has an impact on increasing healthcare costs and decreasing productivity. Patients with COPD have a higher prevalence of coronary ischemia and other factors that put them at higher risk for COVID-19-related complications. A strong immune system can help increase the body's resistance so as to reduce the risk in the midst of the COVID-19 pandemic. The use of natural therapy in the treatment of chronic diseases is an opportunity for Indonesia as a tropical country that has many variations of plants that have the potential to become herbal medicines. Red ginger (Zingiber officinale var. rubrum) is one of the most widely consumed medicinal plants in Indonesia. Red ginger has greater anti-inflammatory and antioxidant content than other types of ginger. The antioxidant and anti-inflammatory effects of red ginger in addition to helping reduce the effects of reducing the risk of COVID-19 severity, can also help improve lung function. The preparation of red ginger that has been used in the community is steeping. Therefore, red ginger has the potential to effectively reduce the risk of COVID-19 severity in COPD patients with anti-inflammatory and antioxidant effects in reducing NF-B and the effectiveness of improving lung function.

Kata Kunci

COPD, COVID-19, red ginger

Teks Lengkap:

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Efficacy of Red Ginger in Reducing The Risk of COVID-19 Severity in COPD Patients: A Review

by Amelia Lorensia

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Efficacy of Red Ginger in Reducing The Risk of COVID-19 Severity in COPD Patients: A Review

11 abstract

*Chronic obstructive pulmonary disease (COPD) represents a significant global health challenge, contributing to rising healthcare expenditures and diminished productivity. Patients with COPD exhibit a higher incidence of coronary ischemia and other risk factors that elevate their susceptibility to complications associated with COVID-19. A robust immune system plays a crucial role in enhancing the body's defenses, thereby mitigating the risk of infection and complications during the COVID-19 pandemic. The potential for utilizing natural therapies in the management of chronic diseases presents a unique opportunity for Indonesia, a tropical nation rich in diverse plant species that could serve as herbal remedies. Among these, red ginger (*Zingiber officinale* var. *rubrum*) stands out as one of the most commonly utilized medicinal plants in Indonesia. Notably, red ginger possesses superior anti-inflammatory and antioxidant properties compared to other ginger varieties. The antioxidant and anti-inflammatory benefits of red ginger not only aid in reducing the severity of COVID-19 but also contribute to the enhancement of lung function. The preparation of red ginger that has been used in the community is steeping. Therefore, red ginger has the potential to effectively reduce the risk of COVID-19 severity in COPD patients with anti-inflammatory and antioxidant effects in reducing NF- κ B and the effectiveness of improving lung function.*

Key words: COPD, COVID-19, red ginger

Khasiat Jahe Merah dalam Mengurangi Risiko Keparahan COVID-19 pada Pasien PPOK: Setuah Tinjauan Pustaka

Penyakit paru obstruktif kronik (PPOK) merupakan tantangan kesehatan global yang signifikan, yang berkontribusi pada meningkatnya pengeluaran perawatan kesehatan dan menurunnya produktivitas. Pasien dengan PPOK menunjukkan insiden iskemia koroner yang lebih tinggi dan faktor risiko lain yang meningkatkan kerentanan mereka terhadap komplikasi yang terkait dengan COVID-19. Sistem imun yang kuat memainkan peran penting dalam meningkatkan pertahanan tubuh, sehingga mengurangi risiko infeksi dan komplikasi selama pandemi COVID-19. Potensi untuk memanfaatkan terapi alami dalam pengelolaan penyakit kronis menghadirkan peluang unik bagi Indonesia, negara tropis yang kaya akan beragam spesies tanaman yang dapat berfungsi sebagai pengobatan herbal. Di antara ini, jahe merah (*Zingiber officinale* var. *rubrum*) menonjol sebagai salah satu tanaman obat yang paling umum digunakan di Indonesia. Khususnya, jahe merah memiliki sifat antiinflamasi dan antioksidan yang lebih unggul dibandingkan dengan varietas jahe lainnya. Manfaat antioksidan dan antiinflamasi dari jahe merah tidak hanya membantu mengurangi keparahan COVID-19 tetapi juga berkontribusi pada peningkatan fungsi paru-paru. Olahan jahe merah yang telah digunakan di masyarakat sangat banyak. Oleh karena itu, jahe merah berpotensi efektif menurunkan risiko keparahan COVID-19 pada pasien PPOK dengan efek antiinflamasi dan antioksidan dalam menurunkan NF- κ B dan efektifitas peningkatan fungsi paru.

Kata kunci: PPOK, COVID-19, jahe merah

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) represents a significant global health challenge, with an escalating impact on public health. Current standard treatments focus on alleviating symptoms, preventing recurrent exacerbations, preserving optimal lung function, and enhancing overall quality of life.¹ According to the World Health Statistics, COPD ranks as the third most common cause of mortality globally. Data from the Basic Health Research (RISKESDAS) indicates that the prevalence of COPD in Indonesia is 3.7% per one million individuals.²

In Indonesia, there are still a lot of smokers, and this trend is predicted to continue. With about two million cases of tobacco-related illnesses and more than 200,000 tobacco-related fatalities each year, Indonesia has a heavy tobacco burden. The number of smokers in Indonesia is sixth highest in the world. As one of the world's major markets for tobacco use, Indonesia is severely impacted by diseases linked to tobacco use. These facts show that Indonesia has a considerable impact on the prevalence of tobacco-related illnesses worldwide.^{3,4}

COPD is a chronic disease with long-term therapy. Synthetic medicine is not safe, often causes side effects,^{5,6} and treatment non-adherence.⁷ This has contributed substantially to the increasing popularity of complementary and alternative medicine and herbal medicine.⁸

Acute respiratory syndrome coronavirus 2 (SARS-CoV2), the virus responsible for the 2019 coronavirus disease (COVID-19) pandemic. COVID-19 was first discovered in China, in December 2019. Over time, the virus continued to spread to various corners of the world. The World Health

Organization (WHO) has declared COVID-19 a global pandemic.^{4,9}

Individuals who have chronic lung diseases such as severe asthma and COPD are at higher risk of SARS-CoV2 infection and have been shown to be associated with an increased risk of COVID-19-related death.^{10,11} COPD patients live under threat of being at greater risk of contracting the coronavirus, which greatly affects their daily lives. Many COPD patients are worried that infection will even affect their daily productivity because they prefer to self-isolate. The nagging fear of the coronavirus as a death threat is the dominant feeling, along with anxiety, loneliness, and hope. Moderate to severe COPD patients feel they have to self-isolate because they are afraid of dying from COVID-19.^{12,13,14,15}

Indonesia, characterized as a tropical nation, boasts a rich diversity of plant species with significant potential for use as herbal medicines. Taxonomist Axel Dalberg Poulsen from the Royal Botanic Garden Edinburgh identifies Wallacea, Kalimantan, and Sumatra as key regions for the wild diversity of Zingiberaceae in Indonesia, with a majority of these species being endemic. Unfortunately, over 100 species of Zingiberaceae in Indonesia face the threat of extinction, primarily due to forest conversion and deforestation that have occurred over recent decades. The Zingiberaceae family is known for its various biological and pharmacological properties.¹⁶ One of the plants that are commonly found is ginger (*Zingiber officinale*).^{17,18} The primary active compounds responsible for the medicinal properties of red ginger include gingerol and shogaol, which exhibit anti-inflammatory, antioxidant, antibacterial, and antiplatelet effects.¹⁹ One of the most commonly used medicinal plants in Indonesia is red ginger. Compared to other varieties of ginger, gingerols and shogaols of red

ginger (*Zingiber officinale* var. *rubrum*) have the strongest anti-inflammatory and antioxidant effects.^{20,21,22,23}

RISK OF COVID-19 IN COPD

COPD patients face a heightened risk of developing cardiovascular conditions, which subsequently elevates the likelihood of complications arising from COVID-19. The mortality rate among COPD patients infected with COVID-19 has been linked to advanced age and the presence of heart failure. Furthermore, COPD patients diagnosed with COVID-19 exhibited increased rates of hospitalization and mortality, predominantly due to pneumonia.²⁴

Cardiovascular disease is common in people with COPD, leading to an increased risk of hospitalization, longer hospital stays, and death from cardiovascular disease. The economic burden associated with CVD may even exceed the cost of treating COPD itself.²⁵ COPD patients with cardiovascular disease have been shown to have fibrinogen and circulating inflammatory biomarker C-reactive protein (CRP) levels were higher compared with COPD patients without comorbid cardiovascular disease. In patients older than 65 years, factors associated with accelerated aging (telomere shortening, endothelial cell senescence, and reduced cell proliferation) are implicated in the pathogenesis of atherosclerosis, suggesting the possibility of another mechanistic link between COPD and cardiovascular disease.^{26,27}

A significant connection between COPD and cardiovascular disease is primarily attributed to smoking, which serves as the principal risk factor for atherosclerosis. This condition arises from chronic and systemic inflammatory responses that can lead to coronary heart disease and heart failure. The inflammatory reaction triggered by

cigarette smoke impairs the normal defense and repair mechanisms of the lungs, resulting in the narrowing and remodeling of the small airways, as well as damage to the lung parenchyma, commonly known as emphysema.²⁷

In the midst of the COVID-19 pandemic, a strong immune system can help increase the body's resistance and reduce negative impacts.^{28,29} Patients with chronic lung diseases (such as COPD, asthma, pulmonary fibrosis, and lung cancer) who are infected with COVID-19 are at high risk of experiencing serious problems due to a weakened immune system,^{12,30,31} and the condition will be worsened if the condition of lung disorders chronic, uncontrolled or severe.^{28,32}

COPD TREATMENT EFFECTS ON COVID-19

Inhaled corticosteroids (ICS)

ICS is a mainstay therapy for airway diseases, and provides beneficial effects including protection against exacerbations. ICS is the primary treatment for COPD for patients with a history of exacerbations. The use of ICS combined with long-acting β_2 agonists (LABA) has been shown to provide improved exacerbation reduction, lung function, and health status.^{33,34}

Corticosteroids have potential for treating COVID-19, but their administration are still controversial. While CDC and WHO, recommend avoiding the use of corticosteroids for COVID-19, but the Surviving Sepsis Campaign recommends their use in COVID-19 patients experiencing acute respiratory distress syndrome (ARDS).³⁵ The benefits of corticosteroids in COVID-19 have been proven in previous research by the RECOVERY study involving 6,425 hospitalized COVID-19 patients in the UK, showing that COVID-19 patients who received

systemic corticosteroid therapy (dexamethasone) experienced clinically significant improvements compared to those who did not receive corticosteroids.³⁶ Other research that supports this is the CoDEX study in Brazil, showing that COVID-19 patients who experienced acute respiratory distress syndrome (ARDS) and received additional intravenous dexamethasone therapy experienced significant clinical improvement.³⁷

Corticosteroids are a class of drugs that can provide anti-inflammatory effects so that when used correctly they can reduce damage to the respiratory organ system due to the COVID-19 cytokine storm. The use of systemic corticosteroids has proven beneficial in severe COVID-19 patients who require additional oxygen therapy or mechanical ventilation. The use of inhaled corticosteroids (ICS) in the treatment of COPD during the COVID-19 pandemic remains controversial. ICS has a preventive effect against pneumonia, but does not provide any protection against coronavirus infection and actually increases the chance of contracting COVID-19. According to GOLD, there is no evidence to support replacement of ICS therapy in the treatment of COPD, which is used to reduce the likelihood of developing COVID-19.^{34,13}

The mechanism of ICS in respiratory disorders is through its suppressive effect on inflammation. Many inflammatory genes activated in airway epithelial cells are suppressed. Inhaled corticosteroids decrease the number of inflammatory cells in the airways, such as eosinophils, T lymphocytes, mast cells, and dendritic cells, at the cellular level. This effect of corticosteroids is caused by suppressing the production of adhesion molecules and chemotactic mediators, as well as by preventing the survival of inflammatory cells in the

airways, such as mast cells, T lymphocytes, and eosinophils.^{35,38}

ICS are being considered as a treatment option for COVID-19 due to their anti-inflammatory properties, particularly concerning lung inflammation. The anti-inflammatory effects of ICS may help mitigate the risk of severe disease associated with hyperinflammation in COVID-19 cases.³⁹ Furthermore, ICS may inhibit the replication of the SARS-CoV-2 virus and reduce the expression of cellular receptors that facilitate viral entry. However, several in vivo studies examining the efficacy of ICS in COVID-19 patients yield mixed results, primarily due to insufficient sample sizes and a lack of robust scientific evidence, which has resulted in the absence of definitive guidelines regarding the use of inhaled corticosteroids in this context. For patients who are already on ICS, such as those with asthma or COPD, there is no indication that they should discontinue corticosteroid use during the COVID-19 pandemic.⁴⁰ Additionally, COPD patients with mild COVID-19 symptoms who do not require hospitalization are not advised to use corticosteroids. In fact, the administration of inhaled corticosteroids in COPD patients may offer protection against the progression of the disease in a hospital setting. Patients with COVID-19 who are prescribed inhaled corticosteroids for underlying conditions should continue their treatment as directed by their healthcare professionals.

Beta-2 agonist

β₂-AR has an important role in the pathogenesis and treatment of chronic obstructive pulmonary disease (COPD).⁴¹ More than 90% of all beta receptors in the human lung are located in the alveoli, which is dominated by the beta-2 subtype (70%). Beta-2 adrenergic

receptors (β 2-ARs) are located in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle, broadcasting to the airways and to all immune cells such as macrophages, dendritic cells, B lymphocytes and T.

Beta-2 agonist mechanisms in COPD, namely the role of adrenergic signals in regulating immune and pro-inflammatory responses. The inflammatory reaction is characterized by secreting IL-6 and increasing Th17 responses. Blocking of β 2-AR results in reduced T helper type 17 (Th-17) responses. Th17 cells are believed to be important proinflammatory cells in the pathogenesis of chronic obstructive pulmonary disease (COPD).⁴² In addition, Th17 cells play an important role in the pathogenesis of COVID-19, not only by activating the cytokine cascade but also by inducing Th2 responses, inhibiting Th1 differentiation, and suppressing Treg cells.⁴³ Patients with severe COVID-19 show high levels of IL-17 and GM-CSF. Lung tissue damage may also be caused by Th17 cell-mediated recruitment of neutrophils.⁴³

However, there is also evidence to the contrary, suggesting that administration of β 2-AR agonists induces mitochondria-dependent generation of reactive oxygen species (ROS) that produces cAMP response element binding protein (CREB) resulting in IL-6 activation. This influences the Th1/Th2 balance towards greater Th2 polarization.⁹ Beta2-adrenergic signaling inhibits IL-12 production, thereby promoting Th2 differentiation and inhibiting Th1 development associated with antitumor immunity. Catecholamines are also known to impact the immune response through downregulation of IFN- γ production.⁴⁴

Severe COVID-19 patients experience multiple disorders resulting from immune system imbalances and

malfunctions that can lead to pro-inflammatory reactions and immunopathological conditions, characterized by deadly inflammation in the lungs and leaky blood vessels. Blockade of β 2-AR can reduce IL-6 and other inflammatory cytokines in patient serum contributing to rebalancing the immune system. Additionally, stress-induced inflammation, which may occur in patients diagnosed with COVID-19, may worsen clinical symptoms.⁴³

POTENTIAL HERBAL PLANTS FOR COPD TREATMENT

Various plant extracts have potential therapeutic effectiveness against inflammatory lung disorders including COPD. Additionally, many different classes of plant constituents were found to inhibit inflammatory responses in the lung, including coumarins, flavonoids, phenolics, iridoids, monoterpenes, diterpenes and triterpenoids.⁴⁵

Although the pathophysiology of COVID-19 is well understood, it remains unclear how the inflammatory response that causes pain in some patients is controlled. NF- κ B is continuously present during this inflammatory process and has the ability to cause the formation of proinflammatory cytokines. NF- κ B activation and its potential to influence the generation of cytokine storms are now better understood thanks to new information. According to research, SARS-CoV-2 can constantly activate NF- κ B through the RAAS component system and the Toll-like receptor (TLR) system.⁴⁶

The Role of Red Ginger in Respiratory Medicine

Ginger (*Zingiber officinale* Rosc) is widely recognized as a prominent culinary spice, known for its unique spicy flavor, and is esteemed in

traditional Chinese herbal medicine. To date, researchers have extracted and identified over 160 compounds from ginger, which include essential oils, gingerol derivatives, diarylheptanoids, phenylalkanoids, sulfonates, steroids, and monoterpenoid glycosides. A growing body of research indicates that ginger possesses numerous biological properties, particularly in terms of safeguarding the digestive system, combating cancer, and aiding in weight reduction.⁴⁷

Ginger has three varieties namely elephant ginger, red ginger, and empirrit ginger. Studies reported that red ginger (*Zingiber officinale* var. *rubrum*) has greater anti-inflammatory and antioxidant content than the other 2 types.^{15,18,20,48} Red ginger is a rhizome type medicinal plant which is a source of raw material for herbal medicinal plants, which are most widely consumed in Indonesia. Biopharmaceutical demand for red ginger is the highest compared to other rhizome plants, so it has great potential for development. The chemical compounds contained in ginger are essential oils which contain monoterpene and sesquiterpene hydrocarbons which have antibacterial properties. The main active ingredient in fresh rhizomes is gingerol. In fresh ginger, the most phenolic compounds are found in the gingerol type, consisting of 6-gingerol, 8-gingerol, and 10-gingerol. Meanwhile, the main active ingredient in dried rhizomes is shogaol, a derivative of dried gingerol. Ginger essential oil is very useful as an antibacterial agent in dealing with food contamination, extending the shelf life of food.⁴⁹

Heating dried ginger will produce stir-fried ginger and carbonated ginger, so that its antioxidant activity decreases, because this processing can convert gingerol into shogaol. In addition, the 6-gingerol-rich fraction from ginger can reduce H_2O_2 and malondialdehyde

levels, increase antioxidant enzyme activity, and increase glutathione by oxidative damage caused by chlorpyrifos. In addition, in previous research, found that the 6-gingerol-rich fraction prevented the increase in inflammatory markers such as myeloperoxidase, NO, and TNF- α in the brain, ovaries, and uterus of mice treated with chlorpyrifos.

Ginger induced significant and rapid relaxation in isolated human airway smooth muscle. Based on the results of guinea pig and human tracheal models, 6-gingerol, 8-gingerol, and 6-shogaol can cause rapid relaxation of previously contracted airway smooth muscle. Nebulized 8-gingerol attenuates airway resistance through reducing Ca^{2+} influx in rats. In another study, 6-gingerol, 8-gingerol, and 6-shogaol increased β -agonist-induced relaxation in human airway smooth muscle through suppression of 4D phosphodiesterase.¹⁹

Ginger has an important role in therapy of the respiratory tract, by inducing bronchodilation by modulating intracellular calcium ($[Ca^{2+}]_i$) in airway smooth muscle (ASM) thereby causing relaxation. The ginger components 6-gingerol, 8-gingerol, and 6-shogaol, calm ASM, and 8-gingerol attenuates airway hyperresponsiveness, by inhibiting the acetylcholine-induced increase in intracellular calcium ($[Ca^{2+}]_i$) in airway smooth muscle cells. The most effective constituents in providing a relaxing effect on smooth muscle are 6-shogaol and 8-gingerol, with the mechanism of reducing the influx of $[Ca^{2+}]_i$ through L-type calcium channels, 8-gingerol and 6-shogaol also reduce the calcium response to Gq-coupled receptor agonists bradykinin and acetylcholine.⁵⁰

Benefits of Red Ginger for COPD Treatment

Red ginger contains gingerol and shogaol which have the property of

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inducing bronchodilation by modulating $[Ca^{2+}]_i$ in airway smooth muscle, thereby causing significant and rapid relaxation.⁵⁰ The effectiveness of 10-gingerol shows the greatest anti-inflammatory and antioxidant effects compared to other gingerols. Pharmacokinetic studies on red ginger are still very lacking compared to other ginger items.²¹

Many studies support the effectiveness of red ginger in COPD. Previous research by Sutyarso et al.,²³ that in preclinical trials, ethanol extract of red ginger can reduce the number of goblet cells and increase the height of cilia in the respiratory tract of white mice exposed to cigarette smoke. Previous research by Lorensia et al.,⁵¹ in stable COPD patients in Mojokerto City, Indonesia, who received red ginger infusion therapy at a dose of 250 grams for 4 months. The results showed that 66.67% of respondents experienced a significant increase in CAT scores after red ginger therapy compared to before therapy. Therefore, red ginger therapy needs attention because it might be developed as a new agent to help treat COPD. Apart from that, the effectiveness of red ginger infusion can also improve lung function in outpatient COPD patients, which is assessed by the ratio of forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). Red ginger infusion for 4 months was proven to be effective in increasing lung function from FEV1/FVC parameter values significantly.¹⁸

Benefits of Red Ginger to Lower the Risk of Severity of COVID-19 in COPD

Indonesia, being a tropical nation, boasts a diverse array of plants that hold significant potential as herbal remedies. Among these, ginger (*Zingiber officinale*) is a prevalent and extensively utilized spice. The health advantages associated with ginger are primarily

linked to its phenolic compounds, including gingerols and shogaols.²⁹ Red ginger (*Zingiber officinale* var. *rubrum*) has higher anti-inflammatory and antioxidant properties than other types of ginger.³¹ One of the most commonly used in Indonesia is red ginger. When compared to other gingerols, red ginger's gingerols and shogaols have the strongest anti-inflammatory and antioxidant properties. Ginger has been the subject of documented pharmacokinetic investigations, however there aren't any for red ginger.^{13,12,30}

COVID-19 patients are at higher risk of developing an inflammatory response that is associated with serious respiratory disease and can even be fatal. The most common symptoms of COVID-19 include lung inflammation, fever and fibrosis, which appear to be mediated by pro-inflammatory cytokines. The inflammatory response is caused by an oxidative stress reaction which affects the repair of the body's immune control mechanisms and systems, so that oxidative stress is the main factor that increases the severity of COVID-19, especially in chronic diseases.⁵² In non-risk individuals such as those with chronic respiratory diseases, excess reactive oxygen species (ROS) is offset by increased antioxidant defenses. Excessive oxidative stress causes increased ROS production, causing red blood cell (RBC) membrane peroxidation, thereby increasing neutrophil activation. This may be a factor responsible for alveolar damage, thrombosis, and red blood cell dysregulation as occurs in COVID-19.⁵³ The antioxidant effects of ginger can help reduce the severity of lung function. The content of red ginger in the form of gingerol, gingerol, and shogaol produces a rapid relaxation mechanism in airway smooth muscle (ASM) by changing

[Ca²⁺]_i), thereby reducing airway hyperresponsiveness.⁵⁰

An increase in oxidative stress that exceeds antioxidants causes inflammation, which is also a trigger factor for COPD attacks. This is due to an imbalance of protease and antiprotease in the respiratory tract. Smoking is a significant risk factor for COPD and is a significant emitter of oxidants and reactive oxygen species (ROS) in the lungs.⁵⁴ Smoking reduces antioxidant defenses and damages lung cells by increasing the amount of oxidants in the respiratory tract.⁵⁵

Processed red ginger that is commonly used in Indonesia is in the form of steeping. The way to make it is to make a ginger decoction by boiling 200 mL of water with 50 milligrams of ginger until the water is reduced to 100 mL.⁵⁶ Therefore, the antioxidant and anti-inflammatory effects of red ginger apart from helping reduce the risk of reducing the severity of COVID-19, can also help improve lung function.

COVID-19 infection and signaling from NF-κB

An essential mediator in COVID-19 is NF-κB. The pathophysiology of the severe/critical COVID-19 phenotype has been linked to hyperactivation of the nuclear factor kappa-light-chain-enhancer of the activated B cell (NF-κB) pathway. Inhibitory proteins called NF-κB inhibitors (I-Bs) and the complex protein system NF-κB are both found dormant in the cytoplasm. Upon stimulation (induction), I-B kinase (I-12) phosphorylates I-Bs, which causes NF-κB to translocate to the nucleus, bind to their specific DNA, and activate a large number of genes involved in host immunity, inflammation, cell proliferation, and apoptosis. Biological lipopolysaccharides, ionizing radiation, reactive oxygen species (ROS), cytokines including tumor necrosis

factor alpha (TNF-alpha) and interleukin 1-beta (IL-1-beta), as well as viral DNA and RNA are some of the numerous inducers of NF-κB. It is possible that immunomodulation on the level of NF-κB activation and inhibitor of NF-κB degradation (I-B) in combination with inhibition of TNF- would lessen the severity of COVID-19 and the cytokine storm. NF-κB pathway inhibition may be used therapeutically to lessen the severity of COVID-19.⁵⁷

The coronavirus may activate nuclear factor kappa B (NF-κB)-dependent signaling to inflame the human brain. The SARS-CoV virus can enter the host cell by cleaving/activating viral envelope glycoproteins when it binds to certain receptors, including CD147, ACE2, and transmembrane-assisted serine protease 2 (TMPRSS2). Toll-like receptors (TLRs), including TLR3, TLR4, and TLR7/8, are activated inside the endosome by single-stranded RNA viruses. As a result of this receptor's activation of IKK, cytoplasmic inhibitory factor I-B is phosphorylated, which leads to I-B's own phosphorylation and eventual destruction. When TNF or IL-1 bind to their receptors or other cytokine- or TLR receptor-mediated signaling cascades, such as NF-κB activation occurs. Pro-inflammatory cytokines and a chemokine storm are produced as a result of excessive NF-κB activation. A cytokine and chemokine storm then activates T cells, including CD4 and CD8, which lead to further inflammation at the infection site.⁵⁸

Proinflammatory mediators are produced when the transcription factor NF-κB translocates into the nucleus and binds to the B site. Because the essential modulator (NEMO), a regulatory member of the IKK complex, is involved, this is the "canonical pathway" of NF-κB. Protein kinase R (PKR), which also regulates TNF-, is a

component of the "non-canonical pathway" of NF- κ B. The lymphotoxin B cell activating factor receptor is responsible for activating a subset of tumor necrosis factor superfamily receptors. The "non-canonical pathway" involves delayed but persistent activation of NF- κ B that results in the release of proinflammatory mediators. The major response myeloid differentiation pathway 88 (MyD88) and pattern recognition receptors (PPRs) are the pathways that the beta coronavirus uses to hyperactivate the NF- κ B system. Numerous distinct cytokines and chemokines are therefore induced.⁵⁸

CONCLUSION

Red ginger has the potential to effectively reduce the risk of COVID-19 severity in COPD patients with anti-inflammatory and antioxidant effects in reducing NF- κ B and the effectiveness of improving lung function.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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