A Molecular Insight into the Pharmacological Activities of *Zingiber officinale* (Ginger) in Acute Lung Injury

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Abstract. Background: Acute Lung Injury (ALI) is a severe pulmonary condition characterized by inflammation, oxidative stress, and epithelial-endothelial barrier dysfunction, often progressing to acute respiratory distress syndrome (ARDS). Current treatments remain largely supportive, with limited therapeutic options targeting the underlying pathophysiology. **Objective:** This study aims to explore the pharmacological potential of *Zingiber officinale* (ginger) in mitigating ALI, focusing on its anti-inflammatory and antioxidant activities mediated by its bioactive compounds. **Methods:** A comprehensive literature review was conducted using PubMed and Scopus through April 15, 2025, to identify preclinical and clinical studies on *the* pharmacological effects of ginger in ALI. Key bioactive constituents, such as 6-gingerol, 6-shogaol, and zingerone, were examined for their mechanisms of action using *in vitro, in vivo*, and *in silico* studies. **Results:** Ginger demonstrated significant anti-inflammatory effects by inhibiting NF-κB and MAPK pathways, reducing the expression of *pro-inflammatory* cytokines (TNF-α, IL-1β, IL-6), and suppressing neutrophil infiltration and alveolar edema. Its antioxidant action was mediated through activation of the Nrf2 pathway, which enhanced endogenous antioxidant enzymes (SOD, CAT, and GSH) and reduced oxidative markers (ROS and MDA). Histopathological improvements in lung tissue, preservation of alveolar structure, and enhanced surfactant production were also observed. Safety assessments confirmed low toxicity at therapeutic doses. **Conclusion:** *Zingiber officinale* holds promise as a natural adjunctive therapy for ALI by targeting key inflammatory and oxidative mechanisms. Its bioactive constituents provide molecular protection for lung tissue and support the future development of ginger-based nutraceutical interventions.

Keywords: Anti-inflammatory, Antioxidant, Cytokines, *Zingiber officinale*.

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1 Introduction

Pulmonary diseases are disorders affecting the respiratory system, particularly the lungs, which are crucial for gas exchange. These conditions can be acute or chronic and can be caused by infections, exposure to harmful substances, genetic factors, or autoimmune responses. Common pulmonary diseases include chronic obstructive pulmonary disease (COPD), asthma, tuberculosis, pneumonia, and lung cancer. Risk factors such as smoking, air pollution, chemical exposure, and microbial infections contribute significantly to their development. Diagnosis typically involves physical examination, imaging (e.g., X-rays or CT scans), and pulmonary function tests. Treatment strategies vary depending on the severity and type, ranging from lifestyle modifications and pharmacotherapy to oxygen therapy and surgery. Preventive measures, such as avoiding toxic exposures, maintaining hygiene, and vaccination, are essential for reducing the disease burden [1-3].

Acute Lung Injury (ALI) and acute respiratory distress syndrome (ARDS) are life-threatening pulmonary conditions associated with severe inflammation and high mortality rates. Despite decades of clinical research, current therapeutic strategies remain largely supportive, focusing on mechanical ventilation, prophylactic or therapeutic antibiotics, fluid management, and treatment of underlying causes [4-6]. These approaches often fail to significantly reduce mortality, which remains as high as 38–46% in hospitalized patients. Survivors may experience long-term physical, psychological, and cognitive impairments. Thus, effective therapeutic interventions targeting the pulmonary inflammatory cascade are urgently needed to improve outcomes [7-9].

Indonesia, rich in biodiversity, offers numerous medicinal plants that have traditionally been used to treat diseases. Advances in pharmacology and bioinformatics have enabled the identification of active plant compounds and their interactions with disease-related targets using network pharmacology methods. Among these plants, *Zingiber officinale* (ginger) has gained attention for its potential as a natural treatment for acute and chronic lung injury, owing to its anti-inflammatory, antioxidant, and tissue-protective properties [10].

Ginger contains several bioactive compounds, including 6-gingerol, 8-gingerol, and 6-shogaol, which exhibit significant pharmacological activities [11]. Bioinformatics and molecular docking studies have shown that these compounds interact with key molecular targets involved in ALI pathophysiology, including CASP3 (apoptosis), JUN (inflammation via MAPK pathway), and ESR1 (inflammatory gene regulation). These interactions suggest that ginger's potential lies in its ability to modulate multiple biological pathways implicated in ALI progression [12].

As a widely cultivated tropical herb in the Zingiberaceae family, *Zingiber officinale* has been used for centuries both as a culinary spice and in traditional medicine [16]. Its rhizomes are rich in phenolic compounds—gingerols, shogaols, flavonoids, and oleoresins—that contribute to its anti-inflammatory, antioxidant, antitumor, and immunomodulatory effects [17]. *Ginger's* mechanism of action involves inhibiting COX-2 and LOX, thereby reducing arachidonic acid metabolism and producing effects comparable to those of NSAIDs but without gastrointestinal side effects [19-20].

Although numerous pharmacological agents have been investigated for the prevention and treatment of acute lung injury (ALI), the efficacy of currently available therapies remains limited, and supportive care remains the mainstay of management. This has prompted growing interest in natural products with multifaceted pharmacological properties, particularly those that can modulate both inflammatory and oxidative pathways involved in ALI pathogenesis. Among these candidates, *Zingiber officinale* (ginger) has received considerable attention due to its long history of medicinal use and demonstrated pharmacological activity in respiratory disorders.

Zingiber officinale (ginger) contains major phenolic constituents, including 6-gingerol, 6-shogaol, zingerone, and paradol, which have been shown to exert anti-inflammatory and antioxidant activities in various respiratory disease models. In vivo studies in hyperoxia-exposed newborn models reported that ginger extract protected lung tissue from severe hyperoxia- and inflammation-induced damage, with histopathological improvement and reductions in edema and neutrophil infiltration, indicating its potential to mitigate lung injury under high oxidative stress conditions [21]. In lipopolysaccharide (LPS)-induced lung injury and asthma models, compounds such as 6-shogaol and 6-gingerol suppressed NF-κB and MAPK activation, reduced pro-inflammatory cytokine release (TNF-α, IL-1β, IL-6), and decreased neutrophil infiltration—effects that were also evident in lung histological examination [22-23]. Mechanistic evidence further shows that 6-gingerol can activate the Nrf2 pathway and inhibit NLRP3 inflammasome activation, thereby reducing oxidative stress and apoptosis in sepsis-induced ALI models [24]. Comprehensive reviews and cellular studies also support the role of 6-shogaol as a key bioactive constituent that inhibits endothelial cell dysfunction and pro-inflammatory/angiogenic pathways, suggesting it may preserve pulmonary endothelial integrity and limit capillary leakage contributing to lung edema [25].

Collectively, preclinical research provides strong evidence that ginger and its constituents influence NF-κB, MAPK, Nrf2, and inflammasome pathways—key targets in ALI/ARDS pathophysiology—thus offering a solid basis for considering ginger as an adjunct in ALI treatment. Due to these properties, *Zingiber officinale* emerges as a promising natural agent for addressing ALI by affecting inflammatory and oxidative pathways, deserving further investigation in pharmacological studies.

2 Methods

2.1 Design

This review used a systematic, literature-based approach to examine the pharmacological effects of *Zingiber officinale* on Acute Lung Injury (ALI). Data sources included peer-reviewed research articles from PubMed (https://pubmed.ncbi.nlm.nih.gov) and Scopus (https://www.scopus.com). The included literature focused on the anti-inflammatory and antioxidant activities of ginger and its main bioactive compounds, such as 6-gingerol, 6-shogaol, zingerone, and gingerdione.

2.2 Literature Search Strategy

A systematic search was performed in PubMed and Scopus databases through April 15, 2025. Keywords and MeSH terms related to "*Zingiber officinale*," "gingerol," "acute lung injury," "oxidative stress," "NF-κB," "Nrf2," and "inflammation" were used. A comprehensive search strategy was employed across the selected databases. After applying specific inclusion and exclusion criteria, a total of 75 relevant articles were selected for final review.

2.3 Eligibility Criteria

Included studies were experimental (*in silico, in vitro, in vivo,* or clinical) and specifically examined the biological effects of ginger on lung injury and inflammation. Review articles were excluded. Safety-related findings about *Zingiber officinale* encountered during the search were also documented.

2.4 Data extraction and analysis

Data were organized and analyzed to assess the impact of *Zingiber officinale* on key pathophysiological mechanisms of ALI. These included: (1) immunomodulatory effects; (2) anti-inflammatory effects, (3) antioxidants, (3) endothelial dysfunction and increased capillary permeability; (4) epithelial damage and gas exchange impairment. In addition, we also examined the safety of *Zingiber officinale* extracts or their bioactive compounds from the included studies.

3 Results

Zingiber officinale (ginger) is widely used in traditional medicine and is renowned for its diverse array of bioactive compounds. These include, but are not limited to, 6-gingerol, 6-shogaol, 10-gingerol, gingerdiones, gingerdiols, paradols, 6-dehydrogingerols, 5-acetoxy-6-gingerol, 3,5-diacetoxy-6-gingerdiol, and 12-gingerol, all of which contribute to its extensive biological activities. In traditional and modern applications, ginger is frequently employed for its antioxidant, anti-inflammatory, antimicrobial, anticancer, antiobesity, and antiemetic properties, as well as its protective effects on the cardiovascular and respiratory systems [25].

Ginger is composed of a complex mixture of bioactive compounds, which collectively

contribute to its recognized biological activities. These include phenolic compounds, terpenes, lipids, and carbohydrates. Consequently, a significant portion of its pharmacological effects is attributed to its phenolic compounds and terpenes. Among the over 400 identified compounds in ginger, four primary phenolic compounds: gingerol, shogaol, paradol, and zingerone, are primarily responsible for its prominent biological effects. Extensive *in vitro* and *in vivo* research has consistently demonstrated their potent anti-inflammatory and antioxidant activities [26].

Our search for the mechanisms of action of *Zingiber officinale* on key pathophysiological mechanisms of ALI yielded 75 manuscripts (Supplementary Material S1). Some specific mechanisms of action are discussed below.

3.1 Immunomodulatory Effects of *Zingiber officinale*

The overproduction of reactive oxygen and nitrogen species (RONS) plays a critical role in the pathogenesis of various diseases and is a key driver of inflammation. Several studies have demonstrated ginger's potential as an immunomodulator, acting through its antioxidant and anti-inflammatory properties and by modulating other immune components. This multifaceted action enables ginger to prevent oxidative stress and inflammation effectively [27]. Notably, ginger has been shown to possess significant antioxidant capacity, with an IC50 value of 4.25 g/mL. This value indicates excellent antioxidant efficacy (IC50 < 5 mg/mL). Consequently, ginger rhizome is widely recognized and utilized in traditional and complementary medicine as a valuable herbal remedy. *Zingiber officinale* (ginger) exhibits immunomodulatory activity by inhibiting the production of both Th1-type (IL-12, IFN-γ, TNF-α) and Th2-type (IL-4, IL-13) pro-inflammatory cytokines, and by suppressing T lymphocyte activation and proliferation. The active compounds in ginger also reduce the expression of IgE, IL-6, and IL-8, and inhibit the NF-kB and JNK signaling pathways, both of which are crucial in inflammatory processes. Through these effects, ginger can balance immune responses and mitigate immunopathological reactions. This makes it a potential natural agent for regulating the immune system, particularly in chronic inflammatory conditions and lung diseases such as Acute Lung Injury [28].

3.2 Ginger as an Anti-Inflammatory Agent

Inflammation is a defense mechanism involving complex interactions between immune cells, mediators, and signaling pathways. It is closely linked with oxidative stress, sharing regulatory pathways through anti-inflammatory and antioxidant mechanisms.

T cells, especially Th1 and Th2 subsets, play critical roles in regulating immune responses. Th1 cells, induced by IFN-γ and IL-12, are essential for combating intracellular pathogens but can contribute to chronic inflammation when dysregulated. Ginger can suppress Th1 activity by inhibiting IL-12 synthesis and reducing IFN-γ production, thereby modulating T cell activation and cytokine secretion.

Conversely, Th2 differentiation is driven by IL-4 and leads to anti-inflammatory effects by producing cytokines, including IL-4, IL-5, and IL-13. Ginger also modulates Th2 responses and inhibits IgE production. By affecting both Th1- and Th2-type cytokines, ginger reduces T lymphocyte activation and proliferation, and interferes with IL-2 signaling [29,30].

Several studies suggest that ginger can reduce the levels of IL-1, IL-6, and TNF-α, as well as various inflammatory markers, including C-reactive protein. Ginger also inhibits NF-kB activation, reduces the expression of TNF-α, IL-6, and IL-1β, and suppresses the production of reactive oxygen species (ROS). Additionally, ginger can decrease the expression of iNOS, IL-6, and IL-8 by inhibiting NF-κB [30].

According to a researcher on 8-shogaol, this compound exhibits potent anti-inflammatory effects by suppressing the production of pro-inflammatory cytokines, including COX-2, TNF-α, IL-6, and IL-1β in a lipopolysaccharide (LPS)-induced murine inflammation model. This effect is accompanied by the inhibition of the PERK-CHOP signaling pathway and endoplasmic reticulum stress-mediated apoptosis [31].

Several studies have elucidated the anti-inflammatory mechanisms of specific bioactive compounds found in ginger, which include zingerone, shogaols, and ginger extracts

3.2.1 Zingerone

A study on zingerone revealed that it effectively inhibits NF-κB activity and reduces IL-1β levels in a mouse model of inflammation. These findings support zingerone's potential as an anti-inflammatory agent by modulating molecular signaling pathways [32].

3.2.2 Shogaols (e.g., 6-Shogaol, 8-Shogaol)

Oral administration of 6-shogaol markedly reduced NF-κB and AP-1 activity in DMBA-induced carcinogenic hamster models. Given that NF-κB and AP-1 are key transcription factors involved in inflammatory responses and cellular proliferation, these findings indicate that 6-shogaol provides protective effects against inflammation-associated tumorigenesis [33].

In mast cell–based experimental models, 6-shogaol inhibited the production of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-8, while simultaneously

suppressing NF-κB activation and JNK phosphorylation, supporting its role as a potent anti-inflammatory compound. Inhibition of these signaling pathways suggests that 6-shogaol modulates inflammatory signaling at the molecular level in innate immune cells, which is relevant for the management of allergic and chronic inflammatory conditions [34].

Further evidence indicates that 8-shogaol possesses strong anti-inflammatory properties by reducing the production of pro-inflammatory mediators, including COX-2, TNF-α, IL-6, and IL-1β, in lipopolysaccharide-induced murine inflammation models. These anti-inflammatory effects are associated with suppression of the PERK–CHOP signaling pathway and a reduction in endoplasmic reticulum stress–mediated apoptosis [32].

Additional findings demonstrate that 6-shogaol (6-SHO) exhibits significant anticancer effects against human prostate cancer cell lines, including LNCaP, DU145, and PC-3. Treatment with 6-SHO markedly inhibited both constitutive and IL-6–induced STAT3 activation and attenuated TNF-α–induced NF-κB activation. Beyond inhibiting these key signaling pathways, 6-SHO reduced the protein levels of several downstream STAT3 and NF-κB target genes, including cyclin D1, survivin, and c-Myc, which are known to regulate cancer cell proliferation and survival. In addition, 6-SHO altered the mRNA expression of genes involved in chemokine and cytokine signaling, cell-cycle regulation, and apoptosis, including IL-7, CCL5, BAX, BCL2, p21, and p27 [35].

In line with these findings, 8-shogaol has been reported to exert potent anti-inflammatory effects by suppressing the production of pro-inflammatory cytokines, including COX-2, TNF-α, IL-6, and IL-1β, in lipopolysaccharide-induced murine models of inflammation. This activity is accompanied by inhibition of the PERK–CHOP signaling pathway and attenuation of endoplasmic reticulum stress–mediated apoptosis [32].

3.2.3 Ginger Extract

Ginger extract, which comprises a synergistic blend of its bioactive compounds, also demonstrates broad anti-inflammatory effects by modulating cytokines and specific inflammatory markers.

Ginger is well-known for its anti-inflammatory properties, primarily by inhibiting the formation of Th1- and Th2-associated cytokines and suppressing IgE production. Ginger effectively modulates both Th1-type cytokines (such as IL-12, IFN-γ, and TNF-α) and Th2-type cytokines (e.g., IL-4 and IL-13), thereby reducing T lymphocyte activation and proliferation. Furthermore, ginger decreases IFN-γ production by T lymphocytes, suppresses IL-2 secretion by stimulated T lymphocytes, and interferes with IL-2 receptor signaling [36].

Numerous studies indicate that ginger can reduce the levels of IL-1, IL-6, and TNF-α, as well as various other inflammatory markers, including C-reactive protein. Ginger also inhibits NF-κB activation, reduces the expression of TNF-α, IL-6, and IL-1β, and suppresses the production of reactive oxygen species (ROS). Additionally, ginger can decrease the expression of iNOS, IL-6, and IL-8 by inhibiting the NF-κB [37].

Evidence indicates that ginger hexane extract (GHE) suppresses the production of nitric oxide, PGE_2, TNF-α, and IL-1β in lipopolysaccharide-stimulated microglial cells by modulating the MAPK and NF-κB signaling pathways, thereby contributing to its neuroprotective and anti-inflammatory effects [38]. *Zingiber officinale* extract has also been shown to downregulate the gene expression of pro-inflammatory cytokines, including TNF-α and IL-6, while attenuating NF-κB activation in high-fat diet–fed mice, supporting its potential role as a nutraceutical intervention for metabolic inflammation [39]. In experimental models of acute inflammation, administration of ginger root capsule extract (GRCE) significantly alleviated pain, enhanced mobility, and reduced serum markers of inflammation and oxidative stress, such as TNF-α and IL-6 [40].

3.3 Ginger as an Antioxidant

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are key contributors to oxidative stress, leading to the damage of essential biomolecules, including lipids, proteins, DNA, and polysaccharides, through peroxidation and nitrosation. This disruption impairs cellular function, disturbs neuronal homeostasis, and induces apoptosis. Oxidative stress also compromises mitochondrial function and ATP transport along axons, potentially resulting in neurodegeneration. Moreover, it amplifies inflammatory responses by activating NF-κB and inducing nitric oxide (NO)-mediated COX-2 expression, thereby elevating prostaglandin E2 synthesis. Cellular defense against oxidative stress is primarily regulated by the transcription factor Nrf2, which controls the expression of antioxidant proteins and detoxification enzymes, including those involved in glutathione (GSH) synthesis, to maintain cellular homeostasis. [41-43].

Ginger is known to possess antioxidant properties, derived from compounds such as shogaol, gingerol, zingerone, and paradol, which help reduce ROS production. Ginger stimulates the recovery of antioxidant enzymes like superoxide dismutase (SOD) and catalase (CAT), enhances glutathione levels, prevents lipid peroxidation, inhibits NO production, and neutralizes hydroxyl radicals. Additionally, ginger significantly suppresses iNOS expression, reduces caspase-3-positive cells, and decreases TNF-α expression, thereby inhibiting ROS production and MAPK-related signaling. Ginger also upregulates the expression of specific antioxidant elements, such as glutathione, heme oxygenase-1, and quinone reductase 1, through Nrf2 activation. Moreover, ginger inhibits the expression of the pro-apoptotic protein Bax, prevents the production of H2O2, malondialdehyde (MDA), and myeloperoxidase (MPO), and activates phosphatidylinositol-3-kinase (PI3K) and protein kinase B (Akt) in activated B cells, providing protective effects against cellular damage caused by oxidative stress and inflammation [44,45].

Based on numerous studies concerning the antioxidant and anti-inflammatory properties of ginger, ginger extract is known to modulate the expression of Nrf2 target genes, such as heme oxygenase-1 (HO-1), metallothionein 1 (MT1), aldo-keto reductase 1B10 (AKR1B10), ferritin light chain (FTL), and glutamyl transferase-like activity 4 (GGTLA4). This modulation enhances the production of antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), and

increases glutathione (GSH) levels. The augmentation of these endogenous antioxidant defenses can reduce the synthesis of reactive oxygen and nitrogen species (RONS), as well as the levels of malondialdehyde (MDA) and myeloperoxidase (MPO). Ultimately, ginger extract has been proven to decrease oxidative stress, lipid peroxidation, DNA damage, and cell death [46–48].

Furthermore, ginger extract has been shown to exert significant protective effects against IL-1β–induced oxidative stress and mitochondrial apoptosis in C28I2 cells. Specifically, treatment with ginger extract reduced intracellular reactive oxygen species (ROS) generation, which are highly reactive molecules capable of inducing cellular damage. In addition, ginger extract attenuated lipid peroxidation, a process involving free radical–mediated lipid degradation, and decreased the Bax/Bcl-2 ratio and caspase-3 activation, both of which are key indicators of apoptosis and programmed cell death. These protective effects are primarily attributed to the antioxidant properties of ginger extract, which facilitate free radical scavenging and limit oxidative cellular injury. Collectively, these findings suggest that ginger extract holds promise as a therapeutic agent for conditions associated with oxidative stress and apoptosis [49].

3.4 The effect of ginger on Endothelial Dysfunction and Increased Capillary Permeability

Endothelial dysfunction and increased capillary permeability are critical conditions that significantly contribute to the development of various respiratory diseases. *Zingiber officinale* (ginger) has long been recognized for its antioxidant and anti-inflammatory properties, which can help improve endothelial function and reduce capillary permeability. Ginger's antioxidant and anti-inflammatory attributes help protect endothelial cells from damage caused by free radicals and inflammation. In the context of respiratory diseases, ginger's anti-inflammation can reduce the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, which are implicated in pulmonary endothelial damage. Furthermore, ginger can inhibit the NF-κB pathway, thereby suppressing inflammation and maintaining endothelial integrity [50-52].

A previous study investigated the effect of red ginger extract administration on macrophage count and blood vessel formation in clean wounds of male mice. The results indicated that red ginger extract significantly reduced macrophage numbers on day 3. However, no significant difference in the number of blood vessels was observed between the treatment and control groups. This reduction in macrophage count suggests ginger's potential to modulate macrophage inflammatory responses during wound healing, which could improve endothelial function and capillary permeability [53].

Another study explored the anti-inflammatory and senoprotective activities of *Zingiber officinale* Roscoe extract (ZOE) on human endothelial cells. The findings revealed a potential protective role of ZOE in neuroinflammation and endothelial inflammation/activation, suggesting its relevance in delaying the development and progression of ARDS, which is characterized by endothelial dysfunction. ZOE inhibited NF-κB activation in BV2 cells. Among ZOE constituents, this research indicated that the terpenoid-enriched fraction (ZTE) was the component that counteracted NF-kappaB

(p65) phosphorylation. Furthermore, treatment with 10 μg/mL ZOE provided anti-inflammatory activity in LPS-stimulated young human umbilical vein endothelial cells (yHUVEC) and senomorphic activity in replicative senescent HUVEC (sHUVEC), significantly reducing the expression levels of IL-1β, TNF-α, IL-8, MCP-1, and ICAM-1. Additionally, ZTE treatment substantially reduced secreted IL-8 levels in the medium of LPS-stimulated yHUVEC and sHUVEC [55,56].

3.5 The Effect on Endothelial Cell Damage and Gas Exchange Impairment

Alveolar epithelial damage and impaired gas exchange are hallmark characteristics of various respiratory diseases, including Acute Lung Injury (ALI) and acute respiratory distress syndrome (ARDS). Research indicates that *Zingiber officinale* (ginger) possesses the potential to mitigate such damage through several mechanisms [6].

Inflammation in lung tissue can directly harm the alveolar epithelium, compromising gas exchange. Active compounds in ginger, such as gingerol and shogaol, are known to exert significant anti-inflammatory effects. A study demonstrated that ginger could prevent hyperoxia and inflammation-induced histopathological lung damage, including fibrosis and abnormal alveolar structures [21].

3.6 Safety of ginger

Ginger is widely recognized for its anti-inflammatory, antioxidant, and antiemetic properties. Its bioactive compounds, such as gingerol and shogaol, offer various health benefits. However, like other active substances, excessive consumption or interaction with specific health conditions can lead to toxic effects [57].

An acute toxicity evaluation of *Zingiber officinale* Roscoe rhizome ethanol extract involved oral administration at doses of 300 and 2000 mg/kg/day to both male and female rats. The findings indicated that exposure to the higher dose (2000 mg/kg/day) was associated with histopathological alterations. Observed hepatic changes included mild lymphocytic portal inflammation, nuclear condensation of hepatocytes, eosinophilia, and moderate hepatic steatosis. Renal tissues showed mild lymphocytic infiltration, with polymorphonuclear cells surrounding renal tubules and glomeruli at the same dose. In the brain, a slight increase in astrocyte numbers accompanied by focal glial reactions was noted, while mild inflammatory changes were also detected in gastric and cardiac tissues. In addition, serum biochemical parameters, including cholesterol, triglycerides, AST, ALT, ALP, urea, and creatinine, exhibited statistically significant differences at the 2000 mg/kg/day dose compared with controls [58].

In a separate subacute toxicity study, red ginger extract (*Zingiber officinale* var. *rubrum*) was administered orally to mice (*Mus musculus*) for 28 days. Histopathological examination revealed no significant alterations in liver tissue, suggesting that red ginger extract was well tolerated during the treatment period [59].

Collectively, these preclinical findings indicate that ginger extract, whether administered as a single preparation or as part of a formulation, demonstrates a favorable safety profile in cytotoxicity and toxicity evaluations. This characteristic supports its potential utility in developing herbal-based therapeutic agents with a low risk of adverse effects on normal cells. Nevertheless, further well-designed preclinical and clinical studies are necessary to establish its safety and therapeutic efficacy comprehensively.

Trials in humans have assessed the safety of ginger intake, particularly when consumed as supplements or extracts or as part of dietary interventions. Findings from most of these studies indicate that ginger is generally well tolerated at therapeutic doses and is rarely associated with serious adverse effects. A randomized controlled clinical trial evaluating the use of ginger for nausea and vomiting during pregnancy demonstrated that administration of ginger at a dose of 1 g/day for several days did not result in toxic effects or pregnancy-related complications, indicating that low-dose ginger consumption is safe for pregnant women [60].

In another randomized, double-blind, placebo-controlled clinical trial, the efficacy and safety of steamed ginger extract (GGE03) were evaluated in individuals with mild knee osteoarthritis. A total of 100 participants received either 1.6 g/day of GGE03 or a placebo for 12 weeks. The intervention group showed significant reductions in pain scores and improvements in joint function, without clinically meaningful changes in safety parameters, including liver and kidney function or hematological indices. These results indicate that GGE03 is safe and well-tolerated over the study period [61].

Overall, evidence from clinical studies suggests that ginger consumption at appropriate doses and durations does not induce significant toxic effects in either healthy individuals or patients with specific medical conditions. Accordingly, ginger demonstrates a high safety margin in clinical use, particularly when employed as an adjunctive or complementary therapeutic agent.

4 Discussion

Acute lung injury (ALI) is a severe pathological condition characterized by widespread damage to the alveolar structures and pulmonary capillary endothelium, primarily driven by excessive inflammatory responses and oxidative stress. The underlying pathophysiology involves activation of immune cells, including macrophages and neutrophils; increased release of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6; heightened vascular permeability; injury to type I and II alveolar epithelial cells; and activation of key inflammatory signaling pathways, such as NF-κB and MAPK. These interconnected processes collectively contribute to alveolar dysfunction and impaired gas exchange [4-9].

Zingiber officinale (ginger) contains several bioactive compounds, including 6-gingerol, 6-shogaol, zingerone, paradol, and gingerdione, which exhibit broad therapeutic potential by targeting multiple aspects of ALI pathogenesis [13,16,20,26, 28]. These compounds can modulate inflammatory signaling cascades, particularly NF-κB and MAPK pathways. By inhibiting phosphorylation of key regulatory proteins such as IKK and p65, ginger constituents suppress the expression of inflammatory mediators, including TNF-α, IL-6, IL-1β, iNOS, and COX-2. In addition, suppression of JNK and p38 MAPK activation contributes to reduced pulmonary inflammation and apoptosis [29-39].

Ginger also exerts strong antioxidant effects by activating the Nrf2 signaling pathway. Compounds such as shogaol and zingerone upregulate the expression of antioxidant-related genes, including HO-1, GCLM, GCLC, and NQO1. This activation enhances endogenous antioxidant defenses by increasing levels of glutathione, superoxide dismutase, and glutathione peroxidase, while simultaneously reducing oxidative stress markers, including reactive oxygen species, malondialdehyde, and nitric oxide [41-49].

In addition to its anti-inflammatory and antioxidant actions, ginger provides protective effects on the pulmonary endothelium by enhancing endothelial nitric oxide synthase expression and downregulating adhesion molecules such as VCAM-1 and ICAM-1. These effects reduce inflammatory cytokine production in endothelial cells and help preserve endothelial barrier integrity, thereby limiting capillary leakage and pulmonary edema formation [50-56].

Ginger also contributes to the protection of alveolar epithelial cells by mitigating the damage caused by hyperinflammation and oxidative stress. Its bioactive components support epithelial repair processes and help maintain surfactant production by type II alveolar cells, which is essential for maintaining alveolar stability and optimal lung function [21].

Finally, ginger demonstrates immunomodulatory properties by regulating T-cell–mediated immune responses. It suppresses excessive differentiation of Th1 and Th2 cells by reducing cytokine production, including IL-12, IFN-γ, IL-4, and IL-13. This balanced modulation of immune activity helps prevent exaggerated immune reactions that can exacerbate lung tissue injury in acute lung injury [27-28].

5 Conclusion

In conclusion, *Zingiber officinale* acts as a multi-target agent, operating at various molecular and cellular levels to suppress the inflammatory cascade, reduce oxidative stress, bolster endogenous antioxidant systems, and maintain the structural and functional integrity of lung tissue. With this comprehensive approach, ginger holds significant potential as a natural adjuvant therapy targeting the core mechanisms of ALI pathophysiology, offering a substantial contribution to clinical improvement and mortality reduction in patients with acute respiratory disorders.

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Nomenclature

TNF-α	Tumor necrosis factor-alpha
IL	Interleukin
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
COX-2	Cyclooxygenase-2
CAT	Catalase
eNOS	Endothelial Nitric Oxide Synthase
MAPK	Mitogen-Activated Protein Kinase
MDA	Malondialdehyde

Author Contribution

HH and ML conceptualized and designed the study. HH wrote the initial draft, and all the authors provided critical revisions to the final manuscript.

Conflict of Interest

The authors assert that there is no conflict of interest. The authors bear sole responsibility for the accuracy and integrity of the content of this paper.

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