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REVIEW

Epigallocatechin Gallate Influences in Acute Respiratory Distress Syndrome by Regulating Gut Microbiota: Current Research Status and Therapeutic Prospects

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Abstract: Acute respiratory distress syndrome (ARDS) is a life-threatening condition characterized by high mortality, with its pathogenesis involving multiple factors, including inflammatory responses, oxidative stress, and immune dysregulation. However, current clinical interventions remain limited. Recently, the "gut-lung axis"—the interplay between gut microbiota and lung diseases—has gained significant attention, offering new perspectives for ARDS prevention and treatment. Epigallocatechin gallate (EGCG), the primary bioactive compound in green tea, exhibits distinct anti-inflammatory, antioxidant, and microbiota-modulating properties. EGCG shows promise in ARDS therapy by restoring gut homeostasis, enhancing barrier function, modulating immune responses, and influencing microbial metabolites. However, the precise mechanisms underlying its effects and its clinical applicability warrant further exploration. This review examines the molecular mechanisms through which EGCG modulates ARDS by regulating gut microbiota and considers its potential as a novel therapeutic approach, offering valuable theoretical and practical insights for future clinical applications.

Keywords: acute respiratory distress syndrome, epigallocatechin-3-gallate, gut microbiota, gut-lung axis, inflammatory response

Introduction

ARDS is a critical condition characterized by severe hypoxemia, widespread pulmonary inflammation, and pulmonary edema, with a mortality rate approaching 40%. Clinical management remains challenging.[1] Early studies focused on the mechanisms of pulmonary inflammation, but the effects of targeted anti-inflammatory therapy are limited. The academic community has begun to pay attention to the perspective of multi-organ interactive regulation, re-examining the pathogenesis of ARDS.[2,3] The "gut-lung axis" hypothesis, introduced in recent years, offers a novel perspective on ARDS pathogenesis. Evidence suggests that dysbiosis of the gut microbiota influences pulmonary inflammation through immune modulation and metabolites such as short-chain fatty acids (SCFAs), presenting a potential therapeutic target.[4,5] EGCG, the primary catechin in green tea, possesses anti-inflammatory, antioxidant, and microbiota-126 modulating properties.[6] EGCG may alleviate ARDS by modulating gut microbiota composition. Studies indicate that EGCG enhances the host's immune response by altering the gut microbiota, including the enrichment of beneficial genera such as *Akkermansia*, which promotes gut barrier integrity and

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systemic immune regulation.[7] Clinically, preliminary trials suggest that EGCG supplementation alleviates radiotherapy-induced esophagitis in patients with lung cancer, though its impact on survival requires further validation through randomized controlled trials (RCTs).[8] In conclusion, EGCG's ability to modulate the gut microbiota and influence immune responses offers promising therapeutic potential for ARDS. This review systematically examines the mechanisms by which EGCG alleviates ARDS via gut microbiota modulation, laying the groundwork for innovative treatment strategies.

Pathogenesis and Current Treatment Status of ARDS

ARDS, a prevalent inflammatory lung disorder, is characterized by diffuse interstitial and alveolar edema, impairing gas exchange and leading to severe hypoxemia and potential respiratory failure.[9] The pathogenesis of ARDS revolves around the initiation and amplification of the inflammatory response, primarily driven by the release of pro-inflammatory cytokines. A massive cytokine release—including TNF-α, IL-6, and IL-1β—exacerbates lung tissue damage.[8,10] These cytokines directly harm alveolar and epithelial cells, increasing pulmonary vascular permeability, thereby promoting edema and impairing oxygenation.[11] Neutrophil infiltration and activation further amplify inflammation, leading to additional cytokine release, which perpetuates a cycle that results in lung failure and multi-organ dysfunction.[12] Oxidative stress is another critical factor in ARDS, with ROS overproduction mediating lung tissue damage. Oxidative stress damages cellular membranes and triggers an intracellular inflammatory response.[11] Typically, antioxidant defenses such as SOD and GSH counteract oxidative damage. However, in patients with ARDS, these systems are often impaired, disrupting redox balance and exacerbating lung injury and inflammation.[13] iNOS, a key marker of oxidative stress, is significantly upregulated in LPS-induced ARDS models.[14] Thus, targeting oxidative stress, such as through antioxidants, emerges as a promising therapeutic strategy. These pathophysiological mechanisms highlight potential targets for ARDS intervention.

Current treatments for ARDS primarily involve mechanical ventilation, supportive care, and pharmacotherapy.[15] As the cornerstone of treatment, mechanical ventilation carries the risk of barotrauma and ventilator-associated lung injury (VILI) due to elevated airway pressures.[16] Supportive therapies like fluid management and prone positioning present challenges: assessing fluid requirements is difficult, and prone positioning is complex and carries risks.[17] From a pharmacological standpoint, glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen can modulate macrophage polarization, demonstrating efficacy in LPS-induced models. However, their clinical use is limited by significant side effects, driving the search for novel therapeutic approaches.[15,16] These limitations underscore the need for innovative treatments and combination strategies in ARDS research.

An In-Depth Exploration of the Linkage Between Gut Microbiota and ARDS

Effects of Gut Microbiota on Pulmonary Inflammatory Responses

The gut microbiota, often referred to as the "second genome" and "second immune organ," plays a pivotal role in maintaining human health when balanced. Emerging evidence implicates gut dysbiosis, or microbial imbalance, in the pathogenesis of ARDS.[18] ICU patients are prone to gut dysregulation shortly after admission, due to factors such as altered intestinal motility, medication effects, and compromised gut barrier integrity. These changes elevate nitrate levels, decrease oxygenation, and promote free radical production, all of which contribute to systemic inflammation.[19,20] In ARDS associated with community-acquired pneumonia (CAP), gut dysbiosis is characterized by significant compositional shifts, particularly an increase in Gram-negative bacteria. These bacteria release LPS and endotoxins, which translocate hematogenously to the lungs, where they activate pulmonary immune cells, leading to cytokine release, systemic inflammation, and exacerbated lung injury.[21,22] Gut dysbiosis in ICU patients has also been linked to hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and multiple organ failure (MOF), suggesting its role as a potential contributor to ARDS development.[23] Modulating the gut microbiota, therefore, emerges as a promising therapeutic strategy for ARDS. Probiotics, synbiotics, and fecal microbiota transplantation (FMT) may restore microbial balance and reduce systemic inflammation.[24] This approach capitalizes on the gut-lung axis, where microbial diversity regulates pulmonary immune cell function, and gut homeostasis prevents excessive inflammation.[25,26] In conclusion, gut dysbiosis exacerbates pulmonary inflammation through bacterial and endotoxin translocation, systemic inflammatory activation, and modulation of pulmonary immune responses. These

mechanisms support the rationale for targeting gut microbiota in lung diseases. Future studies should focus on validating clinical interventions that mitigate inflammation, paving the way for novel ARDS treatment strategies.

Bidirectional Interaction Between Gut Dysbiosis and Oxidative Stress

Gut dysbiosis and oxidative stress interact in a bidirectional manner, contributing to ARDS pathogenesis. Physiologically, the gut microbiota supports intestinal mucosal integrity and antioxidant defenses through the production of microbial metabolites.[27] In ARDS, gut dysbiosis typically manifests as a depletion of beneficial genera such as *Akkermansia* and *Bifidobacterium*, along with an overgrowth of pathobionts like *Escherichia coli* and *Klebsiella pneumoniae*. These shifts impair intestinal mucosal metabolism and function.[28,29] Commensal bacteria stimulate enterocytes to produce antioxidant enzymes, including superoxide dismutase (SOD) and glutathione peroxidase (GPx). Dysbiosis-induced depletion of these enzymes compromises free radical scavenging, thereby promoting oxidative stress.[30] Pathobiont-derived molecules, such as LPS, activate immune system cells to generate excessive reactive oxygen species (ROS) and reactive nitrogen species (RNS). When these oxidants overwhelm endogenous defenses, redox imbalance occurs, further intensifying oxidative stress.[31] Additionally, dysbiosis disrupts bile acid metabolism, with aberrant bile acids inducing ROS production in intestinal and hepatic tissues, creating a feedforward loop that amplifies oxidative stress.[32] Oxidative stress exacerbates dysbiosis. ROS and RNS directly compromise the gut barrier by damaging the mucosal epithelium, facilitating bacterial translocation, and disrupting microbial ecology.[33] Oxidative stress also remodels the intestinal niche, selectively suppressing commensals while promoting the expansion of pathobionts.[34,35] This vicious cycle perpetuates pulmonary injury, worsening ARDS progression (Figure 1).

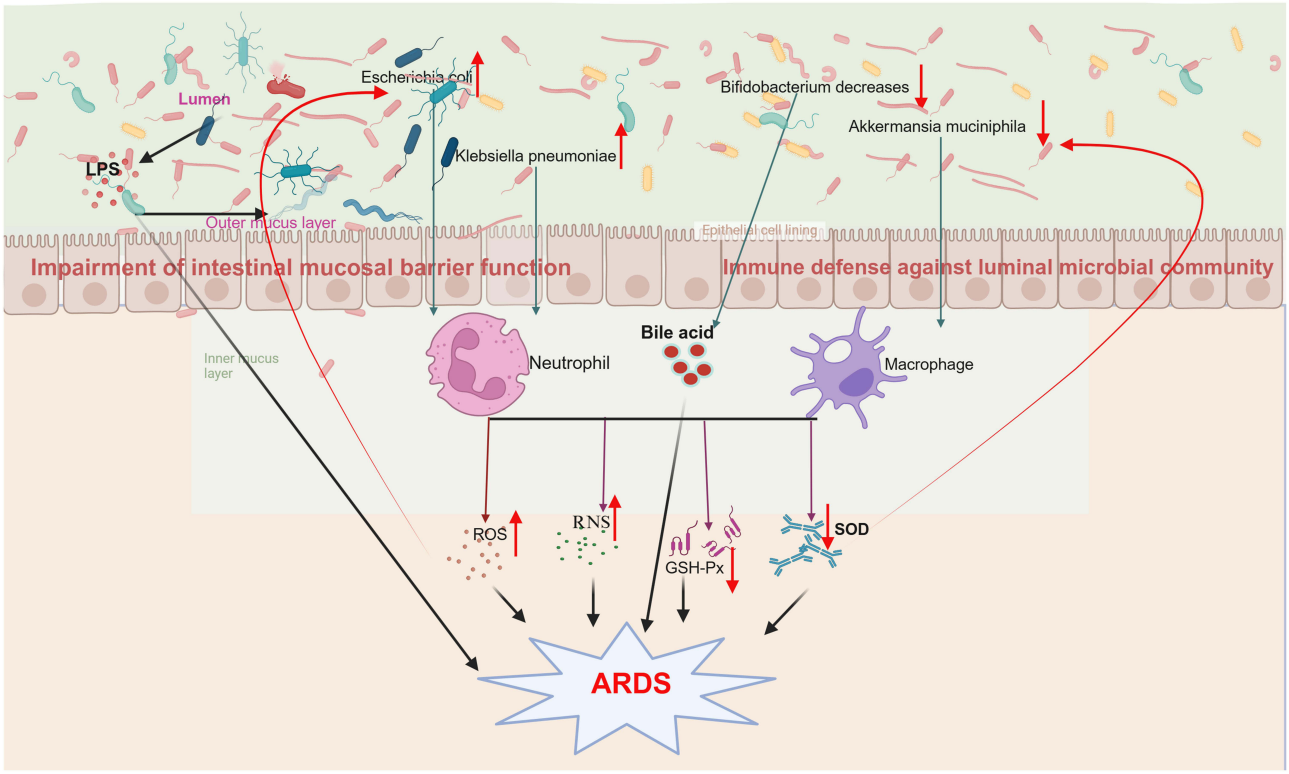

Figure 1 The relationship between gut microbiota dysbiosis and oxidative stress in acute respiratory distress syndrome. When acute respiratory distress syndrome (ARDS) occurs, the number of beneficial bacteria decreases while that of harmful bacteria increases, leading to abnormal bile acid metabolism. Subsequently, the levels of SOD and GSH-Px decrease, while those of LPS, ROS, and RNS increase. These changes in substances damage the function of the intestinal mucosal barrier, promote bacterial translocation, alter the intestinal microenvironment, inhibit the growth of beneficial bacteria, and facilitate the proliferation of harmful bacteria, thus forming a vicious cycle. In the figures of this study, the colors and directions of arrows carry specific meanings. Specifically, black arrows represent a direct causation of ARDS; cyan indicates that gut microbiota and their metabolites can induce changes in the immune system; purple arrows signify that alterations in the immune system can lead to ARDS; curved red arrows show that immune-system changes can affect gut microbiota and their metabolites; upright red arrows pointing upwards suggest an increasing trend of relevant substances, and those pointing downwards indicate a decreasing trend.

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Gut Microbiota Metabolites in ARDS Pathogenesis

Gut microbiota metabolites play a pivotal role in modulating ARDS progression and immune responses through various mechanisms.[36] SCFAs, as key microbial metabolites, energize intestinal epithelial cells, maintain gut homeostasis, exert systemic effects via circulation, and mediate anti-inflammatory actions.[37] SCFAs activate G protein-coupled receptors (GPCRs), suppressing inflammatory cascades and mitigating pulmonary hyperinflammation.[38] Butyrate and propionate exhibit anti-inflammatory effects through GPCR activation (eg, GPR41/43) and histone deacetylase (HDAC) inhibition, the latter enhancing histone acetylation to upregulate anti-inflammatory genes.[39] Additionally, butyrate activates FFAR2, promoting regulatory T cell (Treg) expansion, which helps maintain immune tolerance and curtail pulmonary inflammation.[40] SCFAs also strengthen alveolar epithelial integrity, reinforce the pulmonary barrier, and limit the translocation of bacteria and toxins.[41] Dysbiosis associated with ARDS depletes SCFAs, impairing their pulmonary anti-inflammatory effects. The concurrent accumulation of harmful metabolites, such as hydrogen sulfide, exacerbates this depletion, inducing oxidative stress and epithelial damage.[42] Preclinical studies show that probiotic and synbiotic supplementation restores SCFA levels, enhances gut barrier integrity, and alleviates systemic inflammation in ARDS models.[43] Tryptophan metabolites, particularly indole derivatives, also play a role in regulating pulmonary immunity. These compounds activate the aryl hydrocarbon receptor (AhR), a key regulator of immune balance. Through AhR signaling, indole derivatives promote anti-inflammatory immune responses by upregulating IL-10 and suppressing TNF-α and IL-6.[44] AhR activation also directs T-cell differentiation, favoring Treg over Th17 cells, which helps prevent immunopathology.[45] In summary, gut microbiota metabolites modulate ARDS-related immune responses through diverse mechanisms, presenting novel therapeutic targets. Precision modulation of microbial communities to enhance SCFA and indole production offers a promising strategy for ARDS treatment.

Advances in Research on EGCG's Biological Activities, Gut Effects, and Application in ARDS

The Progress of Research on the Biological Activities of EGCG and Its Relevance to ARDS

EGCG, the predominant polyphenol in green tea, has become a focal point in medical and nutritional research due to its antioxidant, anti-inflammatory, and immunomodulatory properties, all attributed to its unique chemical structure.[46] The structure of EGCG includes a benzopyran core with multiple hydroxyl groups, with the 3-galloyl moiety playing a critical role in its pharmacological activity. Its hydroxyl groups facilitate two key actions: metal ion chelation and inhibition of oxidative stress. Additionally, EGCG scavenges free radicals through the activation of the Nrf2/HO-1 pathway, thereby mitigating cellular damage.[47] EGCG also directly interacts with proteins, notably inhibiting matrix metalloproteinase (MMP-9), while upregulating antioxidant enzymes (SOD, GPx) through epigenetic modulation. These combined actions suppress lipid peroxidation and preserve membrane integrity.[48] In terms of anti-inflammatory effects, in vitro studies show that EGCG significantly reduces the release of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β in alveolar epithelial cells and macrophages. It further inhibits the activation of signaling pathways like NF-κB, MAPK, NLRP3, and JAK/STAT, reducing the production of pro-inflammatory cytokines.[49–51] EGCG also enhances cellular antioxidant capacity and alleviates inflammation by activating the Nrf2 signaling pathway. Its anti-inflammatory effects are dose-dependent, with higher concentrations potentially inducing pro-apoptotic effects, while lower concentrations are more effective in exerting protective anti-inflammatory actions.[52] Furthermore, EGCG plays a critical role in immune regulation by inhibiting excessive neutrophil activation and infiltration, thereby reducing ROS and proteolytic enzyme release.[53] It also regulates macrophage polarization, promoting anti-inflammatory M2 macrophages and inhibiting pro-inflammatory M1 macrophages,[54] while modulating T-cell differentiation (eg, Th1, Th17) to decrease pro-inflammatory cytokine production and enhance the immunosuppressive function of Tregs, collectively promoting pulmonary inflammation resolution and tissue repair.[55]

Preclinical studies on ARDS highlight EGCG's therapeutic potential. In LPS- or ventilator-induced ARDS models, EGCG treatment demonstrates multifaceted therapeutic effects, reducing alveolar septal thickening and protein exudation, and decreasing collagen deposition through suppression of transforming growth factor-β (TGF-β) expression. These structural improvements correlate with significant attenuation of acute inflammation, as evidenced by ≥2-fold

improvement in histological scores. These changes not only alleviate immediate pathological features but also may facilitate long-term lung tissue remodeling.[56] EGCG pretreatment induces macrophage polarization toward the anti-inflammatory M2 phenotype, evidenced by reductions in pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) alongside increases in arginase 1 (Arg1) and Krüppel-like factor 4 (KLF4). This phenotypic shift is associated with a significant reduction in malondialdehyde (MDA) levels, indicating concurrent attenuation of oxidative stress.[57] EGCG also enhances autophagy flux and lung tissue regeneration, as demonstrated by increased proliferating cell nuclear antigen (PCNA) and nuclear antigen Ki67, correlating with improved lung function.[57] Moreover, EGCG expands Treg populations, which suppress effector T-cell activity and reduce inflammatory cytokine production.[56,58] EGCG helps restore Th1/Th2 balance in ARDS, primarily by suppressing Th2 cytokines (IL-4 and IL-13).[56,59] In conclusion, EGCG's structural properties enable multimodal actions—antioxidant, anti-inflammatory, and immunomodulatory—that collectively ameliorate ARDS pathology, supporting its translational potential as an adjunctive therapy.

Effects of EGCG on Gut Microbiota Composition and Microbial Metabolites

EGCG modulates gut microbiota composition and microbial metabolite production, offering therapeutic potential for gut-immune axis disorders. It reshapes the gut microbiota structure through multiple mechanisms. On one hand, it significantly enhances the abundance of beneficial bacteria such as *Bifidobacterium*, *Akkermansia*, and *Lactobacillus*, while reducing the Firmicutes-to-Bacteroidetes ratio.[60] On the other hand, EGCG effectively inhibits the over-proliferation of opportunistic pathogens like *Escherichia coli* and Clostridium difficile, thereby maintaining the balance of the gut microecosystem.[61] The selective regulatory effects of EGCG on the gut microbiota vary; its polyphenol structure directly targets pathogenic bacteria, disrupting their cell membranes and inhibiting growth.[62] Acting as a prebiotic, EGCG promotes the fermentation of beneficial bacteria, leading to the production of key metabolites such as SCFAs, indole, and its derivatives. Additionally, EGCG regulates the gut's redox state, creating an optimal environment for the colonization of symbiotic bacteria.[63,64] Animal model studies provide strong evidence for the efficacy of EGCG. In mouse models of antibiotic-induced gut microbiota dysbiosis or high-fat diet-induced obesity, EGCG administration significantly improves gut microbial composition, increases SCFA levels, optimizes the gut immune environment, reduces inflammation, enhances host immune responses, and effectively resists pathogen invasion.[65] However, the dose-response effect of EGCG is a "double-edged sword." Low doses (10–100 mg/kg) enhance microbiota diversity, while high doses (> 500 mg/kg) may disrupt the gut microbiota's ecological balance.[66] In conclusion, EGCG plays a pivotal role in improving gut health and regulating host immune responses through its precise modulation of gut microbiota and metabolites, offering a potentially effective approach for treating inflammation-related diseases.

The Protective Effect of EGCG on Intestinal Barrier Function

Maintaining intestinal barrier integrity is crucial in ARDS pathology. Recent studies highlight EGCG's significant role in enhancing intestinal barrier function, with current research suggesting that it preserves barrier integrity through a multi-target mechanism. EGCG upregulates the expression of tight-junction proteins, including occludin, claudin-1, and ZO-1, in intestinal epithelial cells. These proteins are essential for the structural and functional stability of the intestinal barrier, preventing harmful substances and pathogens from crossing the intestinal epithelium and reducing intestinal permeability.[67] In vitro studies have demonstrated that EGCG increases tight junction protein expression in intestinal epithelial cells, such as Caco-2 cells, and strengthens intercellular adhesion.[68] In vivo experiments have confirmed that EGCG can mitigate the decline in intestinal barrier function induced by ischemia-reperfusion injury, among other factors. Additionally, EGCG significantly reduces endotoxin translocation (eg, LPS), inhibits the systemic inflammatory response and multi-organ damage triggered by endotoxin translocation, and protects intestinal epithelial cells.[69] EGCG also promotes the secretion of mucin MUC2 by goblet cells, enhancing the protective function of the intestinal mucus layer.[70] In a dextran sulfate sodium (DSS)-induced colitis model, EGCG intervention reduced intestinal permeability by 40% and increased mucus layer thickness by 25%.[71] Moreover, EGCG regulates the intestinal microbiota composition by promoting the growth of beneficial bacteria and inhibiting harmful bacteria, thus restoring microbiota diversity. For example, in cases of intestinal damage induced by Staphylococcal enterotoxin A, EGCG can reconstruct the intestinal barrier and prevent bacterial and endotoxin translocation. Its metabolites activate the AhR pathway, promoting interleukin-22 (IL-22) secretion and accelerating intestinal epithelial repair.[72] Therefore, EGCG

holds substantial promise in regulating intestinal barrier function, improving gut health, and preventing or treating diseases related to intestinal barrier dysfunction. Particularly in the treatment of ARDS, EGCG provides a novel theoretical framework and experimental evidence for future clinical applications, warranting further in-depth exploration and validation of its effects.

EGCG Directly Affects the Pulmonary Microbiota in ARDS

In ARDS research, the direct impact of EGCG on the pulmonary microbiota has garnered significant attention. EGCG exhibits potent antibacterial and anti-inflammatory properties, as in vitro studies demonstrate its ability to inhibit the growth of various pathogenic bacteria, including common pulmonary pathogens such as Enterococcus faecalis and Staphylococcus lugdunensis. This is achieved through mechanisms such as disruption of bacterial cell membranes and inhibition of protein synthesis and DNA replication, showcasing notable antibacterial efficacy.[73] Furthermore, EGCG regulates pulmonary immune cell functions. During ARDS onset, EGCG modulates the chemotaxis and activation of macrophages and neutrophils, thereby mitigating the detrimental effects of excessive inflammation on the pulmonary microbiota.[74,75] Specifically, EGCG promotes the abundance of beneficial bacteria, including *Lactobacillus* and *Bifidobacterium*, while reducing harmful bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa*, thereby restoring the balance of the pulmonary microbiota.[76,77] However, current research is limited, with most studies conducted in animal models and clinical trials involving relatively small sample sizes. Therefore, further in-depth studies are required to elucidate its mechanisms of action and potential clinical applications.

Potential Mechanisms of EGCG in Regulating ARDS Through the "Gut-Lung Axis"

In summary, the treatment of ARDS presents numerous challenges, but EGCG shows considerable therapeutic potential through its unique mechanism of action, closely linked to the "gut-lung axis." EGCG modulates pulmonary immunity indirectly by improving the gut environment. It acts as a "balance master," regulating gut microbiota by inhibiting harmful bacteria (eg, *Escherichia coli*) and promoting beneficial bacteria (eg, *Akkermansia*), thereby correcting ARDS-induced dysbiosis and improving inflammatory responses. More profoundly, EGCG promotes the growth of specific microbial communities by increasing the abundance of SCFA-producing and tryptophan-producing bacteria. This leads to enhanced production of SCFAs (eg, butyrate, propionate), indole, and its derivatives, which serve as powerful anti-inflammatory agents. SCFAs exert their effects on immune cells via GPCRs, while indole and its derivatives activate the AhR pathway, promoting anti-inflammatory cytokine secretion, inhibiting pro-inflammatory factors, and reducing oxidative stress. These metabolites also strengthen the gut barrier, reducing permeability, preventing bacterial and metabolite translocation to the lungs, limiting harmful substance entry into the bloodstream, reducing pulmonary inflammatory cell infiltration, and alleviating ARDS-related inflammation (Figure 2). In conclusion, EGCG provides new insights and strategies for ARDS treatment by regulating gut microbiota balance, reducing pro-inflammatory cytokine release, and promoting anti-inflammatory cytokine production, establishing an important foundation for exploring its role in modulating the gut microbiota-immune axis and its clinical applications.

Future Prospects

Develop Combination Therapy Strategies Based on EGCG

EGCG holds significant promise for ARDS treatment. In antibacterial applications, its combination with antibiotics enhances their efficacy, especially in combating drug-resistant bacterial infections. Studies in mice have demonstrated that EGCG can inhibit pathogenic bacterial growth, enhance the bactericidal effects of antibiotics, boost host defense, and significantly alleviate ARDS.[78] In anti-inflammatory treatments, considering the long-term side effects of glucocorticoids, such as immunosuppression and osteoporosis, EGCG's strong immunomodulatory properties make it a potential adjuvant. Combining EGCG with glucocorticoids can reduce their dosage while maintaining therapeutic efficacy, as EGCG reduces inflammation by regulating immune cell activity, inhibiting pro-inflammatory cytokine production, and promoting anti-inflammatory cytokine expression[79] Moreover, EGCG not only exhibits antioxidant and anti-inflammatory effects but also

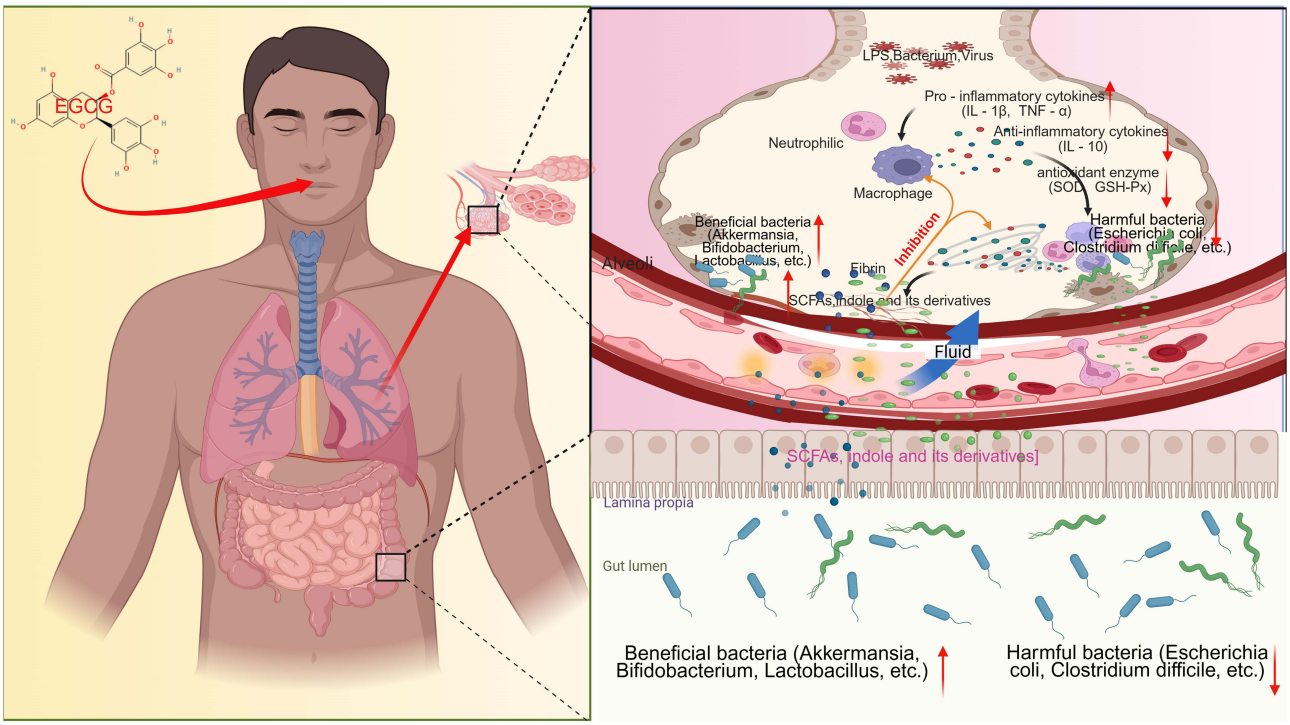

Figure 2 Schematic diagram of the mechanism of EGCG regulating ARDS through the gut-lung axis. The curved and movable arrow is used to indicate that after oral intake of epigallocatechin gallate (EGCG), it improves acute respiratory distress syndrome (ARDS) through gut microbiota and their metabolites. The oblique red arrow represents the magnified image of the lung. The vertical upward red arrow symbolizes an increasing trend of the relevant substances, while the vertical downward red arrow means a decreasing trend of the relevant substances. The blue arrow indicates that gut microbiota metabolites cross the blood vessels to reach the lungs. The light yellow arrow reflects the inhibitory effect of the metabolites on immune cells, inflammatory factors, and enzymes related to oxidative stress. The black arrow represents the counter-effect of inflammatory factors and enzymes related to oxidative stress on immune cells and gut microbiota metabolites.

enhances autophagy by modulating intracellular signaling pathways like MAPK/NLRP3, improving the pathological progression of ARDS.[70] Future research could focus on its combination with other anti-inflammatory or antioxidant drugs for synergistic effects. For example, combining EGCG with nanoparticles coated with platelet-neutrophil hybrid membranes (PNM) could improve drug targeting to inflammatory sites and enhance ROS scavenging.[80] Additionally, combining EGCG with antiviral drugs, such as protease inhibitors targeting SARS-CoV-2, could offer a novel strategy for treating ARDS caused by COVID-19. In conclusion, EGCG presents innovative strategies and approaches for the clinical treatment of ARDS.

The Combination of EGCG and Gut Microbiota Modulation Emerges as a Novel Strategy for ARDS Management

Although existing studies have preliminarily confirmed the therapeutic effects of EGCG on ARDS, research remains insufficient regarding the specific mechanisms by which EGCG regulates ARDS progression through gut microbiota interactions. Given the close association between gut microbiota dysbiosis and ARDS pathogenesis, and considering that EGCG's therapeutic efficacy and anti-inflammatory mechanisms may vary with individual microbiome composition, it is crucial to identify EGCG-responsive bacterial populations through microbiome analysis tailored to patients' specific microbiota profiles. Future research should explore whether EGCG indirectly modulates pulmonary inflammation by regulating gut microbiota composition and microbial metabolites, such as SCFAs. Gut microbiota markers could serve as biomarkers for early ARDS diagnosis and prognosis assessment, and when combined with EGCG's regulatory effects, this approach could enable precision ARDS treatment. Clinically, gut microbiome sequencing and bioinformatics analysis could foster the development of individualized treatment models that account for patients' clinical manifestations and therapeutic responses. In antibiotic therapy, EGCG may: (1) ameliorate drug-induced microbiota imbalance, (2) inhibit bacterial biofilm formation to enhance the efficacy of antibiotics, and (3) restore gut microecological balance. These properties position EGCG as a potential adjuvant in treating multidrug-resistant

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infections. Overall, EGCG-mediated modulation of the gut microbiota represents a promising future strategy for ARDS treatment.

Optimization of EGCG Administration Modes to Enhance Bioavailability

EGCG's clinical application in ARDS is primarily limited by its low bioavailability and stability. Despite EGCG's anti-inflammatory and antioxidant effects, rapid metabolism and poor absorption significantly restrict its therapeutic utility for ARDS. To address these limitations, researchers have developed targeted nanocarriers, such as PNM-coated MSN-TK, for site-specific EGCG release at inflammatory sites.[80] Other systems, including gelatin-, poly-γ-glutamic acid-, or gum arabic-based nanoparticles, enhance EGCG's gastric stability, storage performance, and sustained release during digestion, supporting clinical and functional food applications[81] However, EGCG's safety requires further evaluation, as high doses may cause adverse effects. Future work should optimize administration parameters (dose, route, and formulation) and integrate pharmacokinetic studies to facilitate clinical translation. Although small-scale trials have provided preliminary confirmation of EGCG's efficacy and safety in ARDS, large-scale RCTs and combination therapy evaluations are now essential. Clinical translation also faces regulatory hurdles due to the lack of standardized evaluation criteria, necessitating collaboration among agencies to establish guidelines. Advances in precision medicine now allow for ARDS treatment personalization based on individual gut microbiota profiles. Microbiome analysis could guide EGCG dosing, and integrating clinical and pathological data may enhance both efficacy and safety. Future studies should focus on developing individualized strategies to maximize EGCG's clinical impact in ARDS.

Conclusion

EGCG holds significant potential for future research in ARDS treatment, positioning itself as a multi-target therapeutic agent. Through its regulation of the gut microbiota, EGCG modulates the gut-lung axis, exerting anti-inflammatory, antioxidant, and immunomodulatory effects. Specifically, EGCG can alleviate ARDS pathology by suppressing inflammation, maintaining intestinal barrier integrity, and balancing immune responses. This positions EGCG as a promising candidate for adjuvant therapy in ARDS, offering novel clinical intervention strategies. However, several challenges remain in its clinical application, including low bioavailability, unresolved concerns regarding long-term high-dose toxicity, variability in treatment outcomes due to individual differences in gut microbiota, and unclear mechanisms of interaction between EGCG and the gut microbiota in ARDS pathogenesis. These challenges, however, also provide directions for future research. Studies could focus on optimizing administration strategies to enhance EGCG bioavailability, exploring its synergistic effects with anti-inflammatory or anti-infective agents to amplify therapeutic efficacy, conducting large-scale RCTs to provide robust evidence for clinical application, and thoroughly investigating the EGCG-gut microbiota-immune regulatory network to elucidate its mechanisms of action.

Data Sharing Statement

The datasets used and/or analyzed during this study are available from the corresponding author, Xianming Fan, upon reasonable request.

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Author Contributions

All authors have made substantial contributions to the work, whether in the conception, study design, execution, data acquisition, analysis and interpretation, or all these areas. They participated in drafting, revising, or critically reviewing the article, gave final approval of the version to be published, agreed on the journal for submission, and are accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests.

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