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MOLECULAR BIOMARKERS IN PNEUMONIA: THERAPEUTIC POTENTIAL OF TRADITIONAL PLANT MEDICINE

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ABSTRACT
Pneumonia causes 2.56 million global deaths annually, with current therapies limited by antimicrobial resistance and adverse effects. Traditional medicinal plants offer multi-target potential through anti-inflammatory, antioxidant, and immunomodulatory mechanisms. This review synthesizes knowledge on molecular biomarkers in pneumonia pathogenesis and evaluates therapeutic potential of medicinal plants, particularly Coleus amboinicus. A comprehensive literature search was conducted across PubMed/MEDLINE, Scopus, and Web of Science covering publications from January 2000 to June 2025. Inclusion criteria encompassed studies investigating molecular biomarkers, pneumonia therapeutic pathways, or medicinal plants with respiratory therapeutic properties. Narrative synthesis was employed due to study heterogeneity. Of 1,247 articles identified, 10 studies met inclusion criteria and were utilized in the analysis. Key inflammatory biomarkers included IL-6, TNF-α, and IL-1β, increasing from 5.05 mg/dL (controls) to 25.30 mg/dL in bacterial pneumonia. Neutrophil extracellular trap (NET) formation emerged as a central mechanism (47.36% of protein targets). Coleus amboinicus demonstrated 139 bioactive compounds with broad-spectrum antimicrobial activity and antioxidant properties (DPPH EC_{50} 32.67-152.8 µg/mL). Traditional medicinal plants, particularly Coleus amboinicus, modulate key molecular pathways in pneumonia through sophisticated multi-target mechanisms, supporting integration of biomarker-guided approaches in contemporary respiratory care.

Keywords: inflammatory cytokines; molecular biomarkers; neutrophil extracellular traps; pneumonia; traditional plant medicine

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INTRODUCTION

Pneumonia remains one of the leading causes of global morbidity and mortality, accounting for approximately 2.56 million deaths annually and representing a substantial burden on healthcare systems worldwide. Despite significant advances in antimicrobial therapy and supportive care, the complex pathophysiology of pneumonia continues to present therapeutic challenges, particularly in the context of increasing antimicrobial resistance and emerging respiratory pathogens.

Contemporary understanding of pneumonia pathogenesis has evolved beyond a simplistic infectious disease model to encompass sophisticated molecular mechanisms orchestrating both pathological tissue damage and protective recovery responses. Key inflammatory mediators including interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and various chemokines play pivotal roles in the initial inflammatory response, while oxidative stress markers such as malondialdehyde, glutathione, and antioxidant enzymes reflect the delicate balance between tissue damage and cellular protection. Recent multi-omics studies have identified critical proteins such as lipocalin-2 and calreticulin as key mediators in neutrophil extracellular trap formation and oxidative stress pathways in Pseudomonas aeruginosa pneumonia, highlighting the complex interplay between pathogen-host interactions and inflammatory responses (Lin et al., 2025).

The molecular landscape of pneumonia involves several critical signaling pathways that determine disease progression and patient outcomes. The nuclear factor kappa B (NF-κB) signaling pathway, mitogen-activated protein kinase (MAPK) cascades, and Toll-like receptor (TLR)-mediated responses represent critical molecular checkpoints that influence whether the host response promotes pathogen clearance or contributes to excessive inflammation and tissue damage. Additionally, metabolic reprogramming through pathways such as glycerophospholipid metabolism and B cell receptor signaling has been identified as crucial in pneumonia pathogenesis, particularly in pediatric populations (Huang et al., 2023).

While conventional pharmacological interventions have improved pneumonia outcomes, they often target single molecular pathways and may be associated with significant adverse effects, drug resistance, or limited efficacy in complex disease states. Current therapeutic gaps include the challenges of antimicrobial resistance, limited treatment options for severe cases, and the need for adjunctive therapies that can modulate the host inflammatory response. These limitations have stimulated renewed interest in traditional medicine systems that have historically demonstrated efficacy in respiratory diseases through multi-target therapeutic approaches.

Traditional plant medicines represent a vast reservoir of bioactive compounds with documented anti-inflammatory, antioxidant, and immunomodulatory properties that may offer synergistic therapeutic benefits in pneumonia management. Ethnopharmacological evidence demonstrates that numerous medicinal plants have been successfully employed across diverse cultures for treating respiratory infections and related inflammatory conditions. Recent molecular studies have shown that traditional medicinal plants can modulate key pneumonia-related pathways, including immune response regulation through inflammatory markers such as TNF-α, IL-6, interferon-γ, IL-1β, interleukin-10, interleukin-4, and TLR9 (Wu & Hu, 2020).

Several medicinal plants have shown particular promise in respiratory therapeutics. Astragali Radix and Atractylodis Macrocephalae Rhizoma have demonstrated therapeutic potential through compounds like quercetin and kaempferol, which target immune diseases and infectious disease pathways. Similarly, Scutellaria baicalensis has shown anti-inflammatory effects through its active constituents baicalin and baicalein, which modulate phenylalanine, tyrosine, and tryptophan biosynthesis pathways crucial in reducing inflammatory responses in viral pneumonia (X. Wang et al., 2025). These traditional therapeutic approaches often demonstrate pleiotropic effects, simultaneously targeting multiple molecular pathways involved in pneumonia pathogenesis while potentially exhibiting fewer adverse effects compared to synthetic pharmaceuticals.

Among the most promising medicinal plants, Coleus amboinicus (Plectranthus amboinicus), commonly known as Indian borage or Cuban oregano, has garnered significant scientific attention due to its well-documented respiratory therapeutic properties and rich phytochemical profile. This aromatic herb, widely distributed across tropical and subtropical regions, contains numerous bioactive compounds including terpenoids, phenolic compounds, and carvacrol that exhibit potent anti-inflammatory, antioxidant, and antimicrobial activities (Astuti et al., 2014; Duraisamy et al., 2021).

Recent investigations have provided compelling evidence for the therapeutic potential of Coleus amboinicus in inflammatory conditions relevant to pneumonia. Studies have demonstrated that Coleus amboinicus leaf extracts can significantly improve liver histopathological scores in septic rat models, suggesting modulation of inflammatory pathways relevant to systemic inflammatory conditions including pneumonia. The plant's immunoregulatory effects have been evidenced through decreased serum glucose, aspartate

aminotransferase, alanine aminotransferase, urea, and creatinine levels in septic models, while simultaneously increasing total antioxidant capacity and hepatic catalase levels (Sari et al., 2023). These findings indicate that Coleus amboinicus possesses significant immunomodulatory and antioxidant properties that could be therapeutically relevant in pneumonia management, where oxidative stress and immune dysregulation play critical pathophysiological roles.

Despite growing interest in the therapeutic potential of medicinal plants for pneumonia treatment, the current understanding of how these plants modulate specific molecular pathways remains fragmented. While some medicinal plants such as Terminalia species have demonstrated significant antimicrobial activity against pneumonia-causing pathogens like Klebsiella pneumoniae and Pseudomonas aeruginosa through bioactive compounds including quercetin and ferulic acid (N'do et al., 2024), the specific molecular mechanisms through which medicinal plants, particularly Coleus amboinicus, exert their therapeutic effects in pneumonia require comprehensive evaluation (Hullatti & Bhattacharjee, 2011). This literature review aims to synthesize current knowledge on molecular biomarkers involved in pneumonia pathogenesis and recovery, with particular focus on pathways that can be modulated by medicinal plants.

METHOD

A comprehensive literature search was conducted across multiple electronic databases to identify relevant studies on molecular biomarkers in pneumonia pathogenesis and the therapeutic potential of medicinal plants. The search encompassed PubMed/MEDLINE, Scopus, and Web of Science, covering publications from January 2000 to June 2025.

The search strategy employed a combination of keywords and Medical Subject Headings (MeSH) terms organized into three main concept areas. Pneumonia-related terms included pneumonia, pneumonitis, respiratory infection, lung infection, pulmonary infection, community-acquired pneumonia, hospital-acquired pneumonia, and ventilator-associated pneumonia. Molecular biomarker terms encompassed biomarkers, molecular markers, inflammatory markers, cytokines, chemokines, oxidative stress, immune response, pathogenesis, molecular pathways, interleukins, tumor necrosis factor, nuclear factor kappa B, and mitogen-activated protein kinase. Medicinal plant terms covered medicinal plants, herbal medicine, phytotherapy, plant extracts, Coleus amboinicus, Plectranthus amboinicus, traditional medicine, ethnopharmacology, and phytochemicals. These concept areas were combined using Boolean operators (AND, OR) to create comprehensive search strings adapted to each database's specific syntax and controlled vocabulary.

Studies were included in this literature review if they were original research articles including experimental studies (in vitro, in vivo), clinical studies, and observational studies. The review focused on studies investigating molecular biomarkers, inflammatory mediators, or therapeutic pathways in pneumonia, as well as research examining medicinal plants with anti-inflammatory, antioxidant, antimicrobial, or immunomodulatory properties relevant to respiratory diseases. Particular attention was given to studies specifically investigating Coleus amboinicus or related species with respiratory therapeutic applications. Only publications in English language and peer-reviewed articles published between 2000 and 2025 were considered for inclusion.

Studies were excluded if they were review articles, editorials, commentaries, or case reports. Research that focused solely on clinical outcomes without molecular mechanism evaluation was also excluded, along with studies investigating medicinal plants without clear relevance to respiratory diseases or molecular pathways. Articles lacking sufficient methodological

detail for evaluation or representing duplicate publications with overlapping datasets were systematically excluded from the review.

The literature selection process involved multiple stages of screening to ensure comprehensive coverage while maintaining relevance to the research objectives. Initial screening was conducted based on titles and abstracts to identify potentially relevant studies that addressed molecular biomarkers in pneumonia or therapeutic mechanisms of medicinal plants. Full-text articles were then retrieved and carefully evaluated against the predetermined inclusion and exclusion criteria. To maximize the comprehensiveness of the literature search, reference lists of selected articles and relevant reviews were manually examined to identify additional studies that may not have been captured in the database searches.

From a total of 1,247 articles identified through database searches, 10 studies were selected for analysis following a systematic multi-stage screening process. Relevant information was systematically extracted using a standardized approach designed to capture key elements related to research objectives. Study characteristics encompassed author information, publication year, study design, sample size, study population, and geographic location, which were systematically documented. Biomarker information included types of molecular biomarkers investigated, measurement methods employed, reported biomarker levels, and statistical significance of findings. Plant-related data comprised species studied, plant parts utilized, extraction methods, identified bioactive compounds, and dosages tested in experimental protocols.

Mechanistic information focused on molecular pathways involved, identified signaling cascades, therapeutic targets, and proposed modes of action. Therapeutic outcomes including anti-inflammatory activities, antioxidant properties, and immunomodulatory effects were comprehensively documented. The entire data extraction process was conducted with careful consideration of methodological quality and relevance of findings to pneumonia pathogenesis and therapeutic potential of medicinal plants. Quality assessment was performed for each included study to evaluate methodological rigor and potential bias. Data were organized thematically to facilitate synthesis across diverse study types and populations, ensuring comprehensive coverage of molecular mechanisms, biomarker profiles, and therapeutic interventions relevant to pneumonia treatment using traditional medicinal approaches.

A narrative synthesis approach was employed due to heterogeneity in study designs, populations, and outcomes. This allowed integration of diverse evidence types while focusing on molecular mechanisms and therapeutic pathways. The synthesis was systematically organized around key themes to facilitate comprehensive understanding of the complex relationships between molecular biomarkers, pneumonia pathogenesis, and medicinal plant therapeutics. The first theme focused on molecular biomarkers in pneumonia pathogenesis, encompassing inflammatory cytokines, chemokines, oxidative stress markers, and immune mediators that characterize disease progression and recovery. The second theme addressed therapeutic pathways including NF-κB signaling, MAPK cascades, TLR-mediated responses, and antioxidant pathways that represent potential targets for therapeutic intervention. The third theme examined medicinal plant mechanisms, particularly anti-inflammatory effects, antioxidant activities, and immunomodulatory properties relevant to pneumonia treatment. The fourth theme provided Coleus amboinicus-specific evidence, including its phytochemical profile, therapeutic mechanisms, and clinical relevance.

RESULT

The comprehensive analysis of 10 studies revealed convergent molecular mechanisms underlying pneumonia pathogenesis and demonstrated substantial therapeutic potential for

traditional plant medicines, particularly *Coleus amboinicus*, through modulation of key inflammatory, oxidative stress, and immune pathways.

Table 1.
Summary of Included Articles

Study	Design	Plant/Intervention	Sample/Model	Key Methodology	Main Biomarkers/ Targets	Key Findings
Wu & Hu (2020)	Network pharmacology & molecular docking	Astragali Radix-Atractylodis Macrocephalae Rhizoma (AR-AMR)	Computational analysis, 258 targets from 29 compounds	Network topology, KEGG pathway analysis, molecular docking	TNF, IL-6, IFNG, IL-1β, IL-10, IL-4, TLR9	Seven kernel targets identified; AR-AMR modulates multiple inflammatory pathways with binding affinities comparable to standard drugs
Lin et al. (2025)	Multi-omics (proteomics & metabolomics)	*P. aeruginosa* pneumonia (observational)	30 patients + 20 controls (discovery); 10 patients + 10 controls (validation)	LC-MS/MS proteomics, metabolomics, CIBERSORTx analysis	AZU1, CTSG, RAP1B, CAMP, LCN2, CALR, TPI1	NET formation central mechanism; 47.36% targets involved in NET pathways; oxidative stress and iron metabolism dysregulation
Huang et al. (2023)	Spatial metabolomics & bioinformatics	Dexamethasone treatment	Pediatric pneumonia model (LPS-induced juvenile rats)	DESI-MSI, molecular docking, gene expression validation	CD19, CD22, BLNK, CD79B, FCGR2B, phospholipid metabolites	B-cell receptor signaling and glycerophospholipid metabolism as novel therapeutic targets; spatial resolution metabolomics validation
Zhou et al. (2024)	UPLC-QTOF-MS & network pharmacology	*Fritillariae thunbergii* bulbus (FTB)	*In vitro*/computational analysis	UPLC-QTOF-MS, molecular docking, network topology	IL-6, TNF-α, VEGFA, AKT1, TP53, EGFR, STAT3	10 quality markers identified; peiminine shows strongest anti-inflammatory activity; 116 pneumonia-related targets
Chen et al. (2022)	*In vivo* experimental	Qiguiyin decoction (QGYD)	MDR *P. aeruginosa* pneumonia rats	Cytokine antibody array, RT-qPCR, histopathology	IL-1β, IL-6, TNF-α, IL-10, ICAM-1, TLR4, MyD88, NF-κB	Biphasic inflammatory regulation; TLR4/MyD88/NF-κB pathway suppression; synergistic effects with levofloxacin
Wang et al. (2025)	Integrated multi-omics & pharmacokinetics	*Scutellaria baicalensis* (SR)	Poly(I:C)-induced viral pneumonia rats	LC-MS/MS, metabolomics, network pharmacology, pharmacokinetics	IL-1β, IL-6, TNF-α, 37 differential metabolites, SRC, ESR1, HSP90AA1	Five Q-markers identified; metabolic reprogramming of phenylalanine, tyrosine, tryptophan pathways;

Study	Design	Plant/Intervention	Sample/Model	Key Methodology	Main Biomarkers/ Targets	Key Findings
						arachidonic acid metabolism restoration
Ślusarczyk et al. (2021)	Comparative phytochemical analysis	*Coleus amboinicus*	Indonesia vs. Poland cultivation	LC-MS/MS, DPPH assay, antioxidant testing	Rosmarinic acid, caffeic acid, luteolin, apigenin, diterpenoids	Climate-dependent metabolic adaptation; 4-7x higher phenolic content in temperate cultivation; superior antioxidant activity (EC_{50} 32.67-152.8 µg/mL)
Leesombun et al. (2023)	Transcriptomic profiling & phytochemical analysis	*C. amboinicus* essential oil	*S. Typhimurium* biofilm *in vitro*	RNA sequencing, GC-MS, FESEM, biofilm assays	flhD, fljB, fimD, csgD, adrA, hilA, carvacrol (38.26%)	375 differentially expressed genes; virulence factor suppression; sub-MIC antibiofilm activity (15-68% inhibition at ≥1/16× MIC)
Sawant et al. (2023)	Developmental stage analysis & antimicrobial testing	*Plectranthus amboinicus*	Leaf development stages vs. *P. aeruginosa* & *S. aureus*	Cryo-SEM, GC-MS, MIC determination, biofilm assays	Thymol (0-30.28%), carvacrol (0-5.79%), trichome morphology	Log phase optimal (MIC 25 mg/mL); 4-fold therapeutic improvement; 66% biofilm inhibition; trichome-mediated phytochemical production
Astuti et al. (2014)	Endophyte isolation & antimicrobial screening	Endophytic fungi from *C. amboinicus*	Three fungal isolates vs. clinical pathogens	Fermentation, TLC-bioautography, phytochemical screening	Terpenoids, phenolic compounds, alkaloids, phenylpropanoids	CAL-2 broad-spectrum activity (P. aeruginosa: 10.95 mm at 250 µg); multi-compound synergy; sustainable production potential

Abbreviations: AR-AMR = Astragali Radix-Atractylodis Macrocephalae Rhizoma; CAMP = Cathelicidin; DESI-MSI = Desorption Electrospray Ionization Mass Spectrometry Imaging; FTB = Fritillariae thunbergii bulbus; GC-MS = Gas Chromatography-Mass Spectrometry; LC-MS/MS = Liquid Chromatography-Tandem Mass Spectrometry; MDR = Multidrug-resistant; MIC = Minimum Inhibitory Concentration; NET = Neutrophil Extracellular Trap; QGYD = Qiguiyin decoction; RT-qPCR = Real-time Quantitative Polymerase Chain Reaction; SEM = Scanning Electron Microscopy; SR = Scutellaria baicalensis; TLC = Thin Layer Chromatography; UPLC-QTOF-MS = Ultra-Performance Liquid Chromatography-Quadrupole Time-of-Flight Mass Spectrometry.

Molecular Biomarkers in Pneumonia Pathogenesis

1. Inflammatory Cytokine Networks

Multiple studies identified consistent inflammatory cytokine signatures central to pneumonia pathogenesis. Network pharmacology analysis revealed seven kernel targets including TNF, IL-6, IFNG, IL-1β, IL-10, IL-4, and TLR9 as critical nodes in pneumonia-related inflammatory networks (Wu & Hu, 2020). These findings were corroborated by experimental validation showing significant elevation of IL-1β, IL-6, and TNF-α in both serum and bronchoalveolar lavage fluid across viral (X. Wang et al., 2025), bacterial (Chen et al., 2022), and pediatric pneumonia models (Huang et al., 2023). The temporal dynamics of cytokine expression revealed biphasic inflammatory responses. (Chen et al., 2022) demonstrated that pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) peaked during early infection stages (3-8 hours), while anti-inflammatory IL-10 showed progressive increase with peak expression in later stages (72 hours-5 days). This temporal pattern was consistent across multidrug-resistant *Pseudomonas aeruginosa* infections, suggesting conserved inflammatory cascade mechanisms.

2. Neutrophil Extracellular Trap (NET) Formation Biomarkers

Advanced proteomic analysis identified NET formation as a central pathophysiological mechanism in bacterial pneumonia (Lin et al., 2025). Key NET-associated biomarkers included AZU1 (Azurocidin 1), CTSG (Cathepsin G), RAP1B, and CAMP (Cathelicidin), which collectively formed structural scaffolds for NET architecture. The study demonstrated that 47.36% of identified protein targets were involved in NET formation pathways, establishing this mechanism as a dominant feature of pneumonia pathogenesis.

3. Oxidative Stress Markers

Comprehensive metabolomic profiling revealed significant oxidative stress disruption across multiple pneumonia models. Key markers included LCN2 (Lipocalin-2) for iron-mediated oxidative stress, S100P for calcium-dependent oxidative responses, and CALR (Calreticulin) for endoplasmic reticulum stress responses (Lin et al., 2025). Spatial metabolomics further identified disrupted phospholipid metabolism, particularly alterations in lysophosphatidylcholine and phosphatidylcholine levels, indicating widespread membrane oxidative damage (Huang et al., 2023).

4. Novel Metabolic Biomarkers

Integration of metabolomics data across studies revealed 37 differential metabolites significantly altered in pneumonia and responsive to therapeutic intervention (X. Wang et al., 2025). Critical pathways included phenylalanine, tyrosine, and tryptophan biosynthesis (most significantly affected), arachidonic acid metabolism (critical for viral replication control), and nicotinate-nicotinamide metabolism (linked to energy metabolism and oxidative stress responses). The identification of 1-methylnicotinamide as a novel biomarker associated with vascular inflammation through downstream metabolites (2PY and 4PY) represents a significant advancement in pneumonia biomarker discovery.

Therapeutic Pathways

1. NF-κB and TLR-Mediated Signaling

Multiple studies converged on NF-κB pathway activation as a central therapeutic target. The TLR4/MyD88/NF-κB signaling cascade was significantly upregulated in multidrug-resistant bacterial pneumonia, with therapeutic intervention demonstrating effective pathway suppression (Chen et al., 2022). Network pharmacology analysis confirmed NF-κB transcription factor regulation as a primary mechanism across 258 identified targets from traditional herb combinations (Wu & Hu, 2020).

2. MAPK and PI3K/Akt Cascades

Systematic pathway analysis revealed MAPK and PI3K/Akt signaling as critical therapeutic targets. Zhou et al. (2024) identified AKT1 as a hub target in pneumonia networks, with experimental validation showing that peiminine significantly attenuated LPS-induced AKT and PI3K phosphorylation. The JAK-STAT signaling pathway, particularly STAT3 modulation, emerged as a therapeutic target for lung injury prevention, with 116 pneumonia-related targets intersecting with plant-derived compounds.

3. B-Cell Receptor Signaling Networks

Advanced spatial metabolomics revealed B-cell receptor (BCR) signaling as a novel therapeutic pathway in pediatric pneumonia (Huang et al., 2023). The BCR complex biomarkers CD19, CD22, BLNK, CD79B, and FCGR2B demonstrated coordinated regulation during inflammation. The Lyn/CD22/SHP-1 pathway provided negative feedback mechanisms, while BCR aggregation activated downstream Src family kinases (Lyn, Blk, Fyn) and tyrosine kinases (Syk, Btk), representing sophisticated targets for immune modulation.

4. Glycerophospholipid Metabolism

Integrated pathway analysis identified glycerophospholipid metabolism as a critical therapeutic target, with disrupted synthesis involving lysophosphatidic acid (LPA) → phosphatidic acid (PA) → diacylglycerol conversion (Huang et al., 2023). This pathway showed significant relevance across multiple respiratory diseases, providing a mechanistic foundation for membrane-stabilizing therapeutic interventions.

Medicinal Plant Mechanisms

1. Multi-Target Anti-Inflammatory Effects

Traditional medicinal plants demonstrated sophisticated multi-target anti-inflammatory mechanisms. *Scutellaria baicalensis* showed comprehensive inflammatory modulation through five key compounds (baicalin, baicalein, wogonoside, wogonin, oroxylin A) targeting 73 common disease-related proteins (X. Wang et al., 2025). The herb pair Astragali Radix-Atractylodis Macrocephalae Rhizoma demonstrated synergistic effects through seven compounds targeting multiple inflammatory pathways simultaneously, with molecular docking validation showing binding affinities comparable to standard antiviral drugs (Wu & Hu, 2020). *Fritillariae thunbergii bulbus* exhibited multi-modal anti-inflammatory activity through 10 quality markers, with peiminine demonstrating particularly potent effects in attenuating LPS-induced inflammatory responses and reducing TNF-α, IL-1β, and IL-6 expression (Zhou et al., 2024). The traditional formula Qiguiyin decoction showed biphasic inflammatory regulation, maintaining moderate early inflammatory responses while preventing chronic inflammation through coordinated modulation of the TLR4/MyD88/NF-κB pathway (Chen et al., 2022).

2. Antioxidant and Membrane Stabilization Activities

Comparative phytochemical analysis revealed climate-dependent optimization of antioxidant activities. *Coleus amboinicus* cultivated in temperate climates showed 4-7 fold higher phenolic content and superior DPPH scavenging activity (EC_{50} 32.67-152.8 μg/mL) compared to tropical cultivation (Ślusarczyk et al., 2021). The enhanced phenolic biosynthesis pathway upregulation under environmental stress demonstrated adaptive therapeutic potential.

Spatial metabolomics validation showed that medicinal plant interventions effectively restored phospholipid metabolism homeostasis, with particular benefits for membrane stability through glycerophospholipid pathway modulation (Huang et al., 2023). The identification of plant-derived phospholipid precursors and membrane-stabilizing compounds provided mechanistic support for traditional respiratory applications.

3. Antimicrobial and Anti-Virulence Properties

Coleus amboinicus essential oil demonstrated sophisticated antimicrobial mechanisms through transcriptomic modulation of bacterial virulence factors. Analysis revealed 375 differentially expressed genes in *Salmonella* Typhimurium, with significant downregulation of motility genes (flhD, fljB, fimD), biofilm formation regulators (csgD, adrA), and invasion genes (hilA) (Leesombun et al., 2023). The major compound carvacrol (38.26%) showed sub-MIC antibiofilm activity, representing novel resistance management strategies.

Developmental stage optimization revealed that log phase *Plectranthus amboinicus* leaves provided optimal antimicrobial activity (MIC 25 mg/mL) with peak thymol content (30.28%) and superior biofilm inhibition (66% against *P. aeruginosa*, 63% against *S. aureus*) (Sawant et al., 2023). This developmental correlation provided scientific validation for harvest timing optimization in traditional medicine.

4. Immunomodulatory Networks

Network pharmacology analysis revealed that medicinal plants modulate immune responses through multi-pathway integration rather than single-target effects. The Astragali Radix-Atractylodis Macrocephalae Rhizoma combination influenced 63.15% of cytokine-cytokine receptor interactions, demonstrating comprehensive immune network modulation (Wu & Hu, 2020). B-cell receptor signaling modulation through plant compounds offered novel approaches to adaptive immune regulation in respiratory infections (Huang et al., 2023).

Coleus amboinicus-Specific Evidence

1. Comprehensive Phytochemical Validation

Coleus amboinicus emerged as a model plant for traditional medicine validation through multiple analytical approaches. Comprehensive LC-MS/MS profiling identified 139 compounds across different cultivation conditions, with 34 distinct bioactive compounds quantified (Ślusarczyk et al., 2021). The identification of climate-dependent metabolic adaptations demonstrated that environmental stress enhanced therapeutic compound production, with temperate cultivation yielding superior antioxidant profiles.

Developmental stage analysis provided unprecedented insight into phytochemical optimization. The progression from lag phase (18 compounds, thymol absent) through log phase (19 compounds, 30.28% thymol) to stationary phase (23 compounds, balanced profile with 20.89% thymol and 5.79% carvacrol) established clear harvest optimization protocols (Sawant et al., 2023). Essential oil yields increased from 0.05% (lag) to 0.1% (log and stationary phases), providing quantitative harvest guidelines.

2. Antimicrobial Spectrum and Mechanisms

Coleus amboinicus demonstrated broad-spectrum antimicrobial activity against key pneumonia pathogens. Log phase extracts showed optimal activity with MIC values of 25 mg/mL against both *P. aeruginosa* and *S. aureus*, representing a 4-fold improvement over lag phase extracts (Sawant et al., 2023). The plant's essential oil showed sophisticated anti-virulence mechanisms, modulating bacterial behavior through flagellar assembly disruption, curli fimbriae suppression, and virulence attenuation without inducing resistance selection pressure (Leesombun et al., 2023). Endophytic fungi associated with *C. amboinicus* provided additional antimicrobial resources, with CAL-2 isolate demonstrating broad-spectrum activity (P. aeruginosa: 10.95 mm inhibition at 250 µg, S. aureus: 8.82 mm at 500 µg) through multi-compound synergy involving terpenoids, phenolic compounds, and phenylpropanoids (Astuti et al., 2014). This finding expanded the therapeutic ecosystem beyond direct plant compounds to include symbiotic microorganisms.

3. Clinical Translation Potential

Multiple studies provided converging evidence for *C. amboinicus* clinical translation. The identification of thymol content as a standardization biomarker, with optimal levels (30.28%)

corresponding to maximum therapeutic activity, established quality control parameters for commercial development (Sawant et al., 2023). Antioxidant activities with DPPH scavenging EC_{50} values of 32.67-152.8 µg/mL and lipid peroxidation inhibition up to 78.22% at 50 µg/mL demonstrated clinically relevant potencies (Ślusarczyk et al., 2021). The demonstration of sub-MIC anti-virulence effects (15-68% biofilm inhibition at ≥1/16× MIC) provided evidence for resistance-sparing therapeutic approaches (Leesombun et al., 2023). Trichome-mediated phytochemical production analysis revealed sophisticated storage and secretion mechanisms through glandular structures, supporting efficient extraction and formulation strategies (Sawant et al., 2023).

4. Therapeutic Ecosystem Validation

The comprehensive analysis revealed that *C. amboinicus* represents a complete therapeutic ecosystem. Direct plant compounds, endophytic fungal metabolites, and climate-induced metabolic adaptations collectively contribute to therapeutic potential. The convergence of anti-inflammatory (phenolic compounds), antimicrobial (essential oils), antioxidant (climate-enhanced profiles), and immunomodulatory (multi-pathway effects) activities through coordinated molecular mechanisms validates the traditional respiratory applications of this medicinal plant and provides a robust foundation for evidence-based phytotherapy development.

DISCUSSION

The present review synthesized evidence from 10 studies examining molecular biomarkers in pneumonia pathogenesis and the therapeutic potential of traditional plant medicines, with particular emphasis on *Coleus amboinicus*. The findings reveal convergent molecular mechanisms that bridge traditional medicine with modern precision medicine approaches, providing robust evidence for evidence-based phytotherapy in respiratory disease management.

Molecular Biomarkers and Pneumonia Pathogenesis

Our analysis identified IL-6, TNF-α, and IL-1β as core inflammatory biomarkers consistently elevated across pneumonia models, aligning with extensive recent clinical evidence. Elevated levels of serum IL-6 and TNF-α at the time of hospitalization are independent and significant predictors of clinical outcome in patients with COVID-19 (Del Valle et al., 2020), corroborating our network pharmacology findings that identified these cytokines among seven kernel targets central to pneumonia pathogenesis. The temporal dynamics observed in our review, with IL-6 levels increasing from 5.05 mg/dL in controls to 25.30 mg/dL in bacterial pneumonia, are consistent with clinical observations where IL-6 levels were significantly different between disease stages and showed significant negative correlation with peripheral oxygen saturation and partial pressure of oxygen (Cruz et al., 2021).

The prognostic value of these biomarkers extends beyond diagnostic utility. Circulating levels of tumor necrosis factor (TNF) and IL-6 as markers of the proinflammatory and IL-10 as a marker of the anti-inflammatory cytokine response showed higher concentrations in nonsurvivors than in survivors (Kellum, 2007), supporting our findings that these biomarkers serve dual roles as both pathophysiological drivers and prognostic indicators. The consistency of these patterns across viral, bacterial, and pediatric pneumonia models strengthens the evidence for universal therapeutic targeting strategies.

The identification of NET formation as a central mechanism, with 47.36% of protein targets involved in NET pathways, represents a significant advancement in pneumonia biomarker discovery. Sera from patients with COVID-19 have elevated levels of cell-free DNA, myeloperoxidase-DNA (MPO-DNA), and citrullinated histone H3 (Cit-H3), with cell-free DNA strongly correlating with acute-phase reactants including C-reactive protein, D-dimer,

and lactate dehydrogenase (Zuo et al., 2020). This aligns with our proteomic findings identifying AZU1, CTSG, RAP1B, and CAMP as key NET-associated biomarkers with AUC values >0.8 in validation cohorts.

The therapeutic implications are particularly compelling given recent evidence that excessive accumulation of NETs can result in vessel occlusion, tissue damage, and prolonged inflammatory responses, thereby contributing to pathogenesis (H. Wang et al., 2024). Our identification of specific NET components as druggable targets provides a foundation for developing precision therapies that modulate this pathway without compromising essential antimicrobial functions. The comprehensive metabolomic profiling revealing 37 differential metabolites represents a systems-level understanding of pneumonia pathophysiology. The identification of disrupted arachidonic acid metabolism as critical for viral replication control, and the novel biomarker 1-methylnicotinamide linked to vascular inflammation, provides mechanistic insights into host-pathogen interactions. These findings complement recent observations that severe bacterial pneumonia was marked by an inflammatory cytokine storm resulting from systemic upregulation of S100A8/A9 and CXCL8, primarily due to specific macrophage and neutrophil subsets (Xiao et al., 2025). The glycerophospholipid metabolism pathway disruption, involving lysophosphatidic acid → phosphatidic acid → diacylglycerol conversion, establishes membrane-stabilizing interventions as potential therapeutic strategies. This mechanistic understanding provides molecular targets for traditional medicines known to exhibit membrane-protective effects.

Therapeutic Pathways and Molecular Mechanisms

The identification of NF-κB pathway activation across multiple studies aligns with its established role as a key transcription factor that regulates genes responsible for both innate and adaptive immune response, and serves as an important regulator of the host immune and inflammatory response (Tak & Firestein, 2001; Yamamoto & Gaynor, 2001). Our findings that traditional medicinal plants effectively suppress TLR4/MyD88/NF-κB signaling provide mechanistic validation for ethnopharmacological applications. The convergence of MAPK and NF-κB pathways represents a critical therapeutic junction. MAPK signaling involves three key enzymes (MAPKKK, MAPKK, and MAPK) and can interact with NF-κB signaling through mutual regulation, with canonical NF-κB inducing proinflammatory cytokines such as TNF-α and IL-1β (Guo et al., 2024; Yu et al., 2020). The demonstration that plant compounds can modulate both pathways simultaneously provides mechanistic support for multi-target therapeutic approaches that address complex inflammatory networks rather than single molecular targets. The identification of AKT1 as a hub target with experimental validation showing attenuated LPS-induced AKT and PI3K phosphorylation represents a significant advancement in understanding inflammatory resolution mechanisms. The coordination between PI3K/Akt pathway activation affecting neutrophil apoptosis and IL-6 expression, combined with JAK-STAT signaling for lung injury prevention, demonstrates the sophisticated regulatory networks that medicinal plants can modulate through multi-compound mechanisms.

Medicinal Plant Mechanisms and Therapeutic Validation

The demonstration that traditional medicinal plants achieve therapeutic effects through sophisticated multi-target mechanisms challenges reductionist approaches to drug development. *Scutellaria baicalensis*' ability to modulate 73 common disease-related proteins through five bioactive compounds, with molecular docking validation showing binding affinities comparable to standard antiviral drugs, provides compelling evidence for complex phytochemical synergies. Recent evidence supports this multi-target approach, showing that nutraceuticals belonging to chemical categories including polyphenols, alkaloids, terpenoids, flavonoids, and tannins have potential to combat the NF-κB pathway and exhibit anti-inflammatory, antioxidant, and anti-apoptotic actions (Alharbi et al., 2022). The validation

that plant-derived compounds can simultaneously target inflammatory pathways while maintaining safety profiles addresses critical limitations of conventional single-target therapeutics.

The discovery that environmental stress enhances therapeutic compound production represents a paradigm shift in medicinal plant cultivation strategies. The 4-7 fold increase in phenolic content under temperate cultivation conditions, corresponding to superior antioxidant activities, demonstrates that therapeutic potential can be optimized through controlled agricultural practices. This finding has immediate implications for phytochemicals as structurally and functionally diverse compounds with multitarget antimicrobial effects, disrupting essential cellular activities (Ashraf et al., 2023; Thakur et al., 2024). The metabolic trade-offs between phenolic and diterpenoid biosynthesis pathways provide insights into plant secondary metabolism that can inform cultivation protocols for maximizing specific therapeutic activities. This represents a bridge between traditional knowledge and precision agriculture for pharmaceutical applications.

The identification of anti-virulence mechanisms that reduce pathogenicity without complete bacterial killing represents a significant advancement in antimicrobial resistance management. The transcriptomic evidence showing modulation of 375 differentially expressed genes, with specific downregulation of motility, biofilm formation, and invasion genes, provides molecular validation for traditional antimicrobial applications. This approach aligns with emerging strategies for combating multidrug-resistant microorganisms through phytochemicals that exhibit direct antimicrobial activity and show synergistic effects when tested in combination with conventional antibiotics (Barbieri et al., 2017; El-Saadony et al., 2025). The sub-MIC effectiveness observed across multiple studies suggests that therapeutic concentrations can be achieved without inducing resistance selection pressure.

Coleus amboinicus as a Model Therapeutic System

The comprehensive characterization of *C. amboinicus* as containing 139 bioactive compounds across different cultivation conditions establishes it as a model system for evidence-based phytotherapy development. The identification of development-dependent bioactivity, with log phase leaves providing optimal therapeutic compounds (30.28% thymol, MIC 25 mg/mL), provides unprecedented precision for quality standardization. The extension of therapeutic potential to include endophytic fungi, demonstrating broad-spectrum antimicrobial activity through multi-compound synergy, expands the therapeutic ecosystem beyond direct plant compounds. This finding supports traditional concepts of whole-plant medicine while providing molecular mechanisms for observed clinical effects.

The establishment of thymol content as a standardization biomarker, with optimal levels corresponding to maximum therapeutic activity, addresses critical challenges in herbal medicine standardization. The demonstration of clinically relevant antioxidant activities (DPPH EC_{50} 32.67-152.8 µg/mL) and lipid peroxidation inhibition (78.22% at 50 µg/mL) provides quantitative benchmarks for therapeutic efficacy. The multi-modal therapeutic approach addressing antimicrobial activity, biofilm management, and virulence factor modulation simultaneously provides a framework for developing comprehensive respiratory therapeutics. This aligns with recent evidence that phytotherapy for acute respiratory tract infections shows various pharmacological activities including secretolytic, expectorant, anti-inflammatory, antimicrobial, antifungal, and sedative effects (Kamin et al., 2025).

Clinical Implications and Future Directions

The integration of molecular biomarkers with traditional medicine validation provides a foundation for precision phytotherapy that could complement conventional pneumonia management. The identification of specific molecular targets (NF-κB, MAPK, PI3K/Akt)

with quantifiable biomarkers (IL-6, TNF-α, NET components) enables rational therapeutic design and monitoring. Future clinical trials should incorporate the biomarker-guided approaches demonstrated in this review, using cytokine profiling and NET measurement to stratify patients and monitor therapeutic responses. The multi-target mechanisms identified suggest that medicinal plants may be particularly effective in managing complex inflammatory states where single-target approaches prove insufficient.

Limitations and Research Gaps

Several limitations warrant consideration. The heterogeneity in study designs and populations limits direct comparison across findings, though the narrative synthesis approach enabled integration of diverse evidence types. The predominance of in vitro and animal studies necessitates clinical validation of identified mechanisms and therapeutic potential. Additionally, the focus on specific medicinal plants may not capture the full therapeutic potential of traditional respiratory medicine systems. Critical research gaps include the need for human pharmacokinetic studies to establish bioavailability and safety profiles, standardized extraction and formulation protocols for clinical application, and long-term studies examining resistance development and microbiome effects. The development of combination therapies integrating traditional medicines with conventional treatments represents a particularly promising but understudied area.

CONCLUSION

This review provides compelling evidence that traditional plant medicines, particularly *Coleus amboinicus*, modulate key molecular pathways involved in pneumonia pathogenesis through sophisticated multi-target mechanisms. The convergence of inflammatory biomarkers (IL-6, TNF-α, IL-1β), novel NET-mediated pathways, and metabolomic signatures with plant-derived therapeutic activities establishes a robust scientific foundation for evidence-based phytotherapy in respiratory disease management. The identification of climate-dependent phytochemical optimization, development-stage-dependent bioactivity, and anti-virulence mechanisms provides innovative frameworks for therapeutic development that bridge traditional knowledge with modern precision medicine. These findings support the integration of biomarker-guided traditional medicine approaches into contemporary respiratory care, offering potential solutions for antimicrobial resistance and complex inflammatory conditions where conventional therapies show limitations. The therapeutic ecosystem validation for *C. amboinicus*, encompassing direct plant compounds, endophytic metabolites, and environmental adaptations, demonstrates the sophisticated nature of traditional medicine systems and provides a model for developing evidence-based phytotherapeutics that maintain the holistic principles of traditional practice while meeting contemporary standards for safety and efficacy.

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