



Herbal Drugs in the Treatment of Respiratory Disorders

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Abstract

Respiratory disorders, including asthma, chronic obstructive pulmonary disease (COPD), bronchitis, and respiratory tract infections, collectively represent one of the most significant global health burdens, contributing to millions of premature deaths and substantial morbidity annually. Current pharmacological interventions, such as inhaled corticosteroids, bronchodilators, and antimicrobials, provide symptomatic relief but are frequently associated with adverse effects, high treatment costs, growing antimicrobial resistance, and limited efficacy in refractory disease. These limitations have stimulated increasing scientific and clinical interest in herbal drugs as adjunctive or complementary therapeutic strategies. This review critically evaluates the pharmacological basis, therapeutic efficacy, and translational relevance of herbal medicines in the management of respiratory disorders. Key medicinal plants and their bioactive constituents, including glycyrrhizin from *Glycyrrhiza glabra*, thymoquinone from *Nigella sativa*, curcumin from *Curcuma longa*, andrographolide from *Andrographis paniculata*, and boswellic acids from *Boswellia serrata*, are examined for their anti-inflammatory, bronchodilatory, antioxidant, and immunomodulatory properties. Evidence from *in vitro*, preclinical, and clinical studies is synthesized to assess current knowledge and identify gaps. Challenges related to pharmacokinetic variability, lack of standardization, and regulatory ambiguity are discussed. The review concludes that while herbal drugs offer a scientifically compelling and clinically relevant adjunct to conventional respiratory therapy, rigorous randomized controlled trials and harmonized regulatory frameworks are essential for their safe and effective integration into mainstream respiratory medicine.

Keywords: Herbal drugs, Respiratory disorders, Asthma, Chronic obstructive pulmonary disease, Phytotherapy, Anti-inflammatory agents

1. Introduction

Respiratory diseases constitute a major and growing component of the global disease burden. According to the World Health Organization, over 550 million people currently live with chronic obstructive pulmonary disease (COPD), while asthma affects approximately 262 million individuals worldwide ^[1, 2]. Acute lower respiratory tract infections remain a leading cause of mortality, particularly in low- and middle-income countries, with pneumonia accounting for more than 2.5 million deaths annually ^[3]. The clinical and socioeconomic implications of these disorders are profound, including reduced quality of life, impaired occupational productivity, and escalating healthcare expenditures ^[4].

Conventional pharmacotherapy for respiratory disorders encompasses inhaled corticosteroids, long-acting beta-2 agonists, anticholinergic agents, methylxanthines, leukotriene receptor antagonists, and antibiotic regimens for infectious etiologies ^[5]. Despite established clinical utility, these treatments are subject to significant limitations. Prolonged corticosteroid use is associated with adrenal suppression, osteoporosis, and increased susceptibility to infection ^[6]. Antibiotic resistance to

respiratory pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae* represents an escalating therapeutic challenge [7]. Moreover, a substantial proportion of patients with severe asthma or COPD remain inadequately controlled on maximal pharmacological therapy [8]. These unmet clinical needs have prompted the global resurgence of interest in plant-derived therapeutics as adjunctive, complementary, or integrative interventions.

Herbal medicine, which encompasses the use of plant materials including roots, leaves, seeds, and extracts for therapeutic purposes, has been practiced across diverse cultures for millennia [9]. Ethnopharmacological traditions in Ayurveda, Traditional Chinese Medicine (TCM), Unani, and other systems have long employed medicinal plants for the management of respiratory ailments [10]. Advances in phytochemistry, molecular pharmacology, and preclinical research have provided mechanistic insights into the therapeutic actions of numerous herbal compounds, lending scientific credibility to many traditional claims [11]. This review aims to critically synthesize current evidence on the pharmacological mechanisms, therapeutic efficacy, and translational prospects of herbal drugs in the management of respiratory disorders.

2. Pathophysiology of Major Respiratory Disorders

The pathophysiology of chronic respiratory diseases is characterized by a complex interplay of persistent airway inflammation, structural remodeling, oxidative stress, and dysregulated immune responses [12]. In bronchial asthma, allergen exposure activates mast cells and dendritic cells, initiating a Th2-dominant immune cascade. This results in the release of interleukins IL-4, IL-5, and IL-13, which drive eosinophilic infiltration, mucus hypersecretion, and smooth muscle hypertrophy [13]. The resulting bronchospasm and airway hyperresponsiveness underpin the cardinal clinical features of wheezing, dyspnea, and chest tightness. Activation of nuclear factor-kappa B (NF- κ B) and signal transducer and activator of transcription 6 (STAT6) signaling pathways further amplifies the pro-inflammatory milieu [14]. COPD is pathogenically distinct, arising predominantly from chronic exposure to cigarette smoke or environmental pollutants, which activates alveolar macrophages and epithelial cells to release neutrophil chemoattractants including IL-8 and leukotriene B₄ [15]. Sustained neutrophilic and macrophagic infiltration leads to the release of proteases such as matrix metalloproteinase-9 (MMP-9), elastase, and cathepsins, culminating in progressive parenchymal destruction, emphysema, and small airway fibrosis [16]. Oxidative stress, mediated through reactive oxygen species (ROS) generated by activated inflammatory cells and inhaled toxicants, further potentiates tissue injury and impairs endogenous antioxidant defense mechanisms [17]. The Nrf2-Keap1 antioxidant signaling axis, which governs the expression of cytoprotective enzymes such as heme oxygenase-1 (HO-1) and superoxide dismutase (SOD), is notably compromised in COPD airways [18].

Respiratory tract infections impose additional immunopathological burdens. Viral pathogens, including rhinoviruses and influenza viruses, induce innate immune activation through toll-like receptors (TLRs), triggering the production of interferons, tumor necrosis factor-alpha (TNF-alpha), and pro-inflammatory cytokines [19]. Bacterial pathogens trigger complement activation and neutrophil recruitment, contributing to the cytokine storm associated

with severe pneumonia [20]. These overlapping pathological mechanisms collectively represent the molecular targets at which herbal drugs may exert their therapeutic effects.

3. Commonly Used Herbal Drugs and Their Bioactive Constituents

Glycyrrhiza glabra (licorice), a perennial legume native to the Mediterranean and Central Asia, has been extensively utilized in both Ayurvedic and TCM traditions for the management of cough, bronchitis, and sore throat [21]. Its principal bioactive constituent, glycyrrhizin, and its hydrolytic metabolite 18-beta-glycyrrhetic acid, exert potent anti-inflammatory and antiviral effects. Glycyrrhizin has been shown to inhibit NF- κ B activation, downregulate the release of TNF-alpha and IL-6, and inhibit the replication of several respiratory viruses including influenza A and severe acute respiratory syndrome coronavirus [22].

Curcuma longa (turmeric), a rhizomatous plant of the Zingiberaceae family, contains curcumin as its principal pharmacologically active polyphenol. Curcumin exerts pleiotropic effects on airway inflammation through simultaneous inhibition of NF- κ B, activator protein-1 (AP-1), and the cyclooxygenase-2 (COX-2) enzyme pathway [23]. Its capacity to modulate Th1/Th2 cytokine balance and enhance Nrf2-mediated antioxidant responses positions it as a promising candidate for both asthma and COPD management [24].

Nigella sativa (black seed), widely employed in Unani medicine, contains thymoquinone as its most studied bioactive component. Thymoquinone inhibits mast cell degranulation, reduces histamine release, and suppresses the production of prostaglandin E₂ and leukotrienes, thereby attenuating bronchospasm and airway inflammation [25]. Clinical studies have demonstrated significant improvements in pulmonary function tests among asthmatic patients receiving standardized *N. sativa* oil supplementation [26].

Andrographis paniculata, commonly known as Kalmegh, is a traditional Ayurvedic herb widely recognized for its immunostimulatory properties. Its principal diterpene lactone, andrographolide, inhibits NF- κ B nuclear translocation, reduces the expression of intercellular adhesion molecule-1 (ICAM-1), and enhances cytotoxic T-lymphocyte activity, making it particularly relevant to viral respiratory infections [27]. *Boswellia serrata*, yielding boswellic acids including acetyl-11-keto-beta-boswellic acid (AKBA), selectively inhibits 5-lipoxygenase, the key enzyme in leukotriene biosynthesis, thereby offering a targeted mechanism for anti-asthmatic therapy [28]. Additional plants of pharmacological relevance include *Adhatoda vasica* (vasicine and vasicinone as bronchodilatory alkaloids), *Tylophora indica* (tylophorine with anti-asthmatic properties), and *Eucalyptus globulus* (1,8-cineole as a mucolytic and anti-inflammatory monoterpene) [29, 30].

4. Mechanisms of Action in Respiratory Conditions

The pharmacological mechanisms through which herbal constituents modulate respiratory pathophysiology are multifaceted and increasingly well characterized at the molecular level. Anti-inflammatory activity represents the most extensively studied mechanism and is primarily mediated through inhibition of pro-inflammatory transcription factors, particularly NF- κ B and AP-1 [14]. Curcumin and andrographolide inhibit inhibitory kappa B kinase (IKK), preventing phosphorylation and proteasomal

degradation of I κ B α and thereby blocking NF- κ B nuclear translocation and downstream cytokine gene transcription [23, 27]. This mechanism is directly analogous to the mode of action of corticosteroids, albeit through distinct molecular interactions, suggesting a potential for combination or dose-sparing strategies.

Bronchodilation by herbal agents is mediated through multiple complementary pathways. Vasicine and vasicinone derived from *Adhatoda vasica* act as beta-2 adrenoreceptor agonists and phosphodiesterase inhibitors, increasing intracellular cyclic AMP concentrations and promoting smooth muscle relaxation [29]. Thymoquinone and certain flavonoids derived from *Thymus vulgaris* exert calcium channel antagonism, reducing intracellular calcium influx in airway smooth muscle and thereby relieving bronchospasm [31]. The bronchodilatory effects of 1,8-cineole from *Eucalyptus globulus* have been attributed to inhibition of cytokine-mediated smooth muscle contraction and enhanced mucociliary clearance [30].

Antioxidant mechanisms constitute another critical therapeutic axis. Nrf2 pathway activation by curcumin, sulforaphane, and resveratrol upregulates the expression of antioxidant response element (ARE)-driven genes including HO-1, glutamate-cysteine ligase, and thioredoxin reductase, bolstering cellular defense against ROS-induced damage [18, 32]. These actions are of particular relevance in COPD, where oxidative stress is a central driver of airway destruction. Immunomodulatory effects include augmentation of natural killer cell activity, enhancement of interferon-gamma production, and promotion of regulatory T-cell responses, collectively contributing to improved host defense against respiratory pathogens while dampening excessive inflammatory responses [33].

5. Preclinical and Translational Research

Substantial preclinical evidence supports the therapeutic potential of herbal drugs in respiratory disorders. *in vitro* studies employing human bronchial epithelial cell lines, primary alveolar macrophages, and mast cell cultures have demonstrated concentration-dependent inhibition of cytokine secretion, reduction in reactive oxygen species, and modulation of cell signaling pathways by curcumin, thymoquinone, glycyrrhizin, and boswellic acids [22, 24, 25]. Ovalbumin-sensitized murine models of allergic asthma have provided *in vivo* evidence of reduced airway eosinophilia, decreased IgE levels, and attenuated bronchial hyperresponsiveness following administration of standardized herbal extracts [34]. Cigarette smoke-induced COPD models in rodents have demonstrated preservation of alveolar architecture and reduced neutrophilic infiltration with curcumin and resveratrol supplementation [35].

Despite these promising preclinical findings, significant challenges impede the translation of herbal therapeutics into clinical practice. The bioavailability of many herbal phytochemicals is inherently limited by poor aqueous solubility, extensive first-pass metabolism, and rapid systemic elimination. Curcumin, for example, demonstrates extremely low oral bioavailability due to rapid glucuronidation and sulfation in the intestinal wall and liver [36]. Pharmacokinetic studies in humans have confirmed that unmodified curcumin achieves negligible plasma concentrations following oral administration, necessitating the development of enhanced delivery systems. Species variability in animal models, divergent immunological

profiles between rodents and humans, and the complex polypharmacological nature of herbal extracts further complicate the direct translation of preclinical findings. Rigorous dose-finding studies, validated biomarkers of therapeutic response, and mechanistically informed clinical trial designs are prerequisite for meaningful translational progress [37].

6. Clinical Evidence, Efficacy, and Safety

The clinical evidence base for herbal drugs in respiratory conditions has expanded considerably in recent decades, although robust randomized controlled trial (RCT) data remain limited for many agents. A systematic review and meta-analysis of *Nigella sativa* supplementation in asthmatic patients demonstrated significant improvements in forced expiratory volume in one second (FEV1), peak expiratory flow rate, and symptom scores compared with placebo, with a favorable safety profile [38]. Similarly, a double-blind RCT of *Andrographis paniculata* standardized extract in patients with uncomplicated upper respiratory tract infections reported significant reductions in symptom severity and duration compared with placebo, corroborating its traditional application [27].

Clinical studies of boswellic acids in asthma management have reported improvements in baseline FEV1 and reductions in the frequency of acute exacerbations over 12-week treatment periods [28]. *Glycyrrhiza* preparations have been investigated in the context of viral respiratory infections and cough suppression, with glycyrrhizin-containing compounds demonstrating antiviral activity against influenza and coronavirus in controlled clinical settings [22]. However, the heterogeneity of study designs, formulations, patient populations, and outcome measures across published trials precludes definitive meta-analytic conclusions for most herbal agents. The safety profiles of commonly used herbal drugs are generally favorable at recommended doses, though specific adverse effects must be acknowledged. Prolonged high-dose glycyrrhizin administration may induce pseudohyperaldosteronism, characterized by sodium retention, hypokalemia, and hypertension [21]. Rare hepatotoxic reactions have been reported with *Boswellia* and some *Andrographis* preparations, highlighting the necessity of rigorous post-marketing surveillance and pharmacovigilance [39]. Standardization of herbal preparations with respect to botanical identity, extraction methodology, and quantification of marker compounds is recognized as a critical prerequisite for consistent therapeutic outcomes and meaningful comparative clinical research [40].

7. Formulation and Delivery Approaches

The translation of herbal phytochemicals into effective therapeutic agents is critically dependent on advanced pharmaceutical formulation and drug delivery strategies. Nanotechnology-based delivery systems, including polymeric nanoparticles, solid lipid nanoparticles, liposomes, nanoemulsions, and phytosomes, have been engineered to overcome the bioavailability limitations inherent to many herbal compounds [36]. Curcumin-encapsulated polymeric nanoparticles have demonstrated approximately 20-fold enhancement in oral bioavailability compared with native curcumin in pharmacokinetic studies, with sustained plasma concentrations and improved tissue distribution [24]. Phytosomes, formed by the complexation of phytochemicals with phosphatidylcholine, have been successfully applied to

curcumin, boswellic acids, and green tea catechins to enhance intestinal absorption and systemic bioavailability.

For respiratory indications specifically, inhaled delivery via nebulization, dry powder inhalers, or metered-dose inhaler formulations represents a particularly advantageous route of administration, enabling direct deposition of therapeutic concentrations at the site of airway disease while minimizing systemic exposure [37]. Thymoquinone nanoemulsions formulated for nebulization have demonstrated enhanced pulmonary deposition and anti-inflammatory efficacy in murine asthma models. Mucoadhesive microsphere formulations designed for intranasal delivery of andrographolide have been evaluated for upper respiratory tract infections, achieving prolonged local drug retention and improved therapeutic outcomes in preclinical studies. Standardized standardized phytopharmaceutical dosage forms, including enteric-coated tablets, standardized liquid extracts, and soft gel capsules with validated content uniformity, are essential for ensuring reproducible clinical outcomes and facilitating regulatory review [40].

8. Regulatory, Safety, and Ethical Considerations

The regulatory landscape governing herbal medicines is highly heterogeneous across jurisdictions, creating significant challenges for standardization, quality assurance, and evidence-based clinical integration. In the European Union, herbal medicinal products are regulated under Directive 2004/24/EC, which distinguishes between well-established herbal medicines supported by bibliographic evidence and traditional herbal medicines relying on documented traditional use [39]. The United States Food and Drug Administration classifies most herbal preparations as dietary supplements under the Dietary Supplement Health and Education Act of 1994, imposing limited pre-market efficacy requirements but establishing current Good Manufacturing Practice standards for manufacturing quality. In contrast, several Asian regulatory authorities, including those in India and China, have developed dedicated frameworks for traditional medicine registration that incorporate pharmacopoeial standards for herbal ingredients. A critical concern in herbal medicine practice is the potential for pharmacokinetic and pharmacodynamic herb-drug interactions. Inducers or inhibitors of cytochrome P450 enzymes, particularly CYP3A4 and CYP1A2, present among herbal constituents may significantly alter the plasma concentrations and efficacy of co-administered conventional drugs. Curcumin, for example, has been reported to inhibit

CYP3A4 and P-glycoprotein, potentially elevating plasma concentrations of substrate drugs including certain corticosteroids and immunosuppressants [33]. Ethical considerations specific to herbal medicine research include the need for culturally informed consent in ethnopharmacological studies, equitable benefit-sharing arrangements with indigenous communities that serve as custodians of traditional knowledge, compliance with the Nagoya Protocol on Access and Benefit Sharing, and transparency in reporting of both therapeutic benefits and adverse effects in clinical trial publications [9].

9. Conclusions and Future Directions

Herbal drugs represent a scientifically substantiated and clinically relevant complementary modality in the therapeutic armamentarium for respiratory disorders. A growing body of preclinical and clinical evidence supports the anti-inflammatory, bronchodilatory, antioxidant, and immunomodulatory properties of key medicinal plants and their bioactive constituents. Curcumin, thymoquinone, glycyrrhizin, andrographolide, boswellic acids, and vasicine each offer distinct and mechanistically validated therapeutic actions targeting the central pathological processes of asthma, COPD, and respiratory infections. Advanced pharmaceutical formulation technologies have substantially improved the biopharmaceutical profiles of these compounds, enhancing their translational prospects.

Nevertheless, significant scientific and regulatory challenges must be addressed before herbal medicines can be fully integrated into evidence-based respiratory care. The current evidence base is undermined by methodological heterogeneity, inadequate sample sizes, variable extract standardization, and insufficient long-term safety data. Future research priorities should include well-designed, multi-center randomized controlled trials with standardized phytopharmaceutical preparations, validated surrogate and clinical endpoints, and rigorous pharmacovigilance protocols. Mechanistic studies employing omics technologies, organ-on-a-chip platforms, and systems pharmacology approaches are warranted to delineate the molecular networks engaged by herbal polypharmacology in respiratory disease. Collaborative frameworks engaging traditional medicine practitioners, clinical pharmacologists, regulatory scientists, and patient communities will be essential to realize the therapeutic potential of herbal drugs in respiratory medicine in a safe, equitable, and evidence-based manner.

Figures

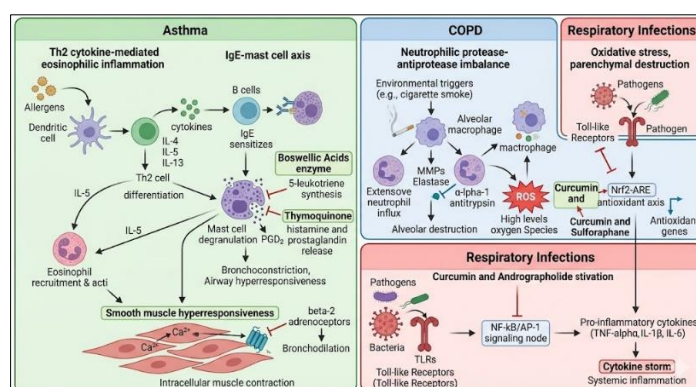


Fig 1: Major pathological mechanisms involved in respiratory disorders and the pharmacological intervention points of herbal drugs

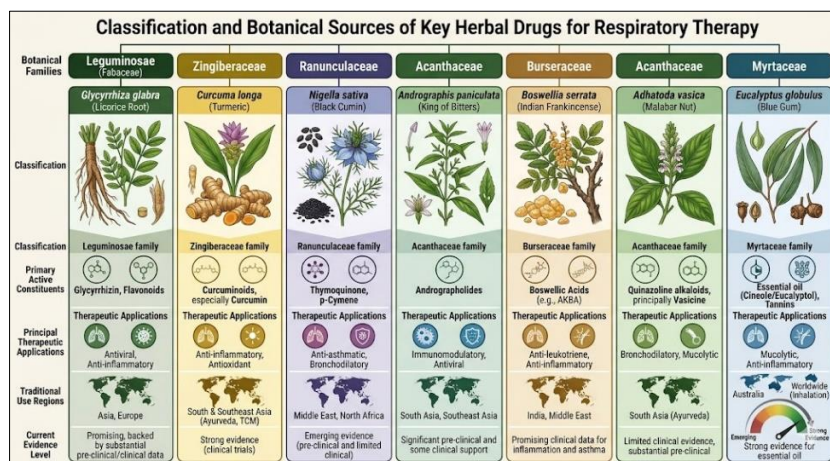


Fig 2: Classification and botanical sources of key herbal drugs used in respiratory therapy

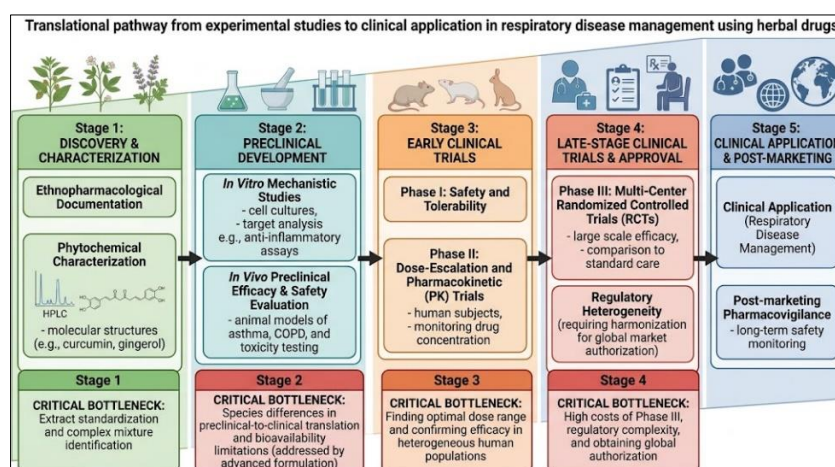


Fig 3: Translational pathway from experimental studies to clinical application in respiratory disease management using herbal drugs

Tables

Table 1: Comparison of herbal drugs, their sources, bioactive constituents, and mechanisms of action in respiratory disorders

Herbal Drug	Botanical Source	Bioactive Constituent	Mechanism of Action	Respiratory Application
Licorice	<i>Glycyrrhiza glabra</i>	Glycyrrhizin, 18-beta-glycyrrhetic acid	NF-kB inhibition; antiviral; IL-6/TNF-alpha suppression	Bronchitis, viral URTI, cough suppression
Turmeric	<i>Curcuma longa</i>	Curcumin	NF-kB/AP-1/COX-2 inhibition; Nrf2 activation; Th1/Th2 modulation	Asthma, COPD, airway inflammation
Black Seed	<i>Nigella sativa</i>	Thymoquinone	Mast cell stabilization; histamine/PGE2 inhibition; Ca2+ antagonism	Asthma, allergic rhinitis, bronchospasm
Kalmegh	<i>Andrographis paniculata</i>	Andrographolide	NF-kB blockade; ICAM-1 downregulation; T-cell activation	Viral URTI, influenza, immunostimulation
Indian Frankincense	<i>Boswellia serrata</i>	Boswellic acids (AKBA)	Selective 5-lipoxygenase inhibition; leukotriene synthesis blockade	Asthma, exercise-induced bronchospasm
Malabar Nut	<i>Adhatoda vasica</i>	Vasicine, vasicinone	Beta-2 agonism; PDE inhibition; bronchodilation	Asthma, bronchitis, cough
Eucalyptus	<i>Eucalyptus globulus</i>	1,8-cineole	Mucociliary clearance enhancement; cytokine-mediated bronchoconstriction inhibition	Sinusitis, COPD, mucolysis

Table 2: Advantages, limitations, and clinical considerations of herbal therapies in respiratory disease treatment

Category	Advantages	Limitations	Clinical Considerations
Pharmacological Profile	Pleiotropic mechanisms; simultaneous modulation of multiple pathways; polypharmacological synergy	Mechanistic complexity; difficulty in attributing effects to single constituents	Combinatorial phytochemistry requires holistic pharmacological profiling
Safety and Tolerability	Generally favorable safety profile at therapeutic doses; lower incidence of systemic adverse effects compared with corticosteroids	Herb-drug interactions (CYP450); rare hepatotoxicity; pseudohyperaldosteronism (glycyrrhizin)	Screen for co-medications; monitor liver function; avoid high-dose glycyrrhizin in hypertensive patients
Standardization and Quality	Advanced extraction techniques permit enrichment of active fractions; phytopharmaceutical standards improving	Batch-to-batch variability; species adulteration; lack of universal pharmacopoeial standards	Require validated marker compound quantification; botanical authentication mandatory
Bioavailability	Nanoformulations and phytosomes significantly enhance bioavailability; inhaled delivery optimizes pulmonary targeting	Poor aqueous solubility; rapid first-pass metabolism; short plasma half-life for many compounds	Formulation-specific dosing required; bioequivalence studies necessary across formulations
Clinical Evidence	Growing body of RCT data for <i>Nigella sativa</i> , <i>Andrographis</i> , and <i>Boswellia</i> ; positive systematic review outcomes	Small sample sizes; heterogeneous outcomes; short follow-up periods; publication bias	Multi-center trials with standardized preparations and validated endpoints required for regulatory acceptance
Regulatory Framework	Established traditional use frameworks (EU Directive 2004/24/EC); pharmacopoeial monographs available for key plants	Inconsistent global regulations; inadequate pre-market efficacy requirements in many jurisdictions	Engage regulatory agencies early; pursue phytopharmaceutical status where evidence supports; full pharmacovigilance compliance

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