

The Gut-Lung Axis in Chronic Obstructive Pulmonary Disease: Mechanistic Evidence and Traditional Chinese Medicine Interventions

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Abstract: Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung disorder accompanied by systemic immune, metabolic and mucosal dysfunction. We reviewed clinical and experimental evidence for the gut-lung axis and assessed how traditional Chinese medicine (TCM) interventions map onto defined biological nodes. Human studies consistently identify altered microbial functions and metabolites, whereas taxonomic signals vary with geography, diet, medication and disease state. Transfer, dietary, depletion and rescue experiments support a causal contribution of gut communities to experimental lung injury. Candidate mediators include short-chain fatty acids, epithelial barrier integrity, regulation of neutrophil extracellular trap formation involving GPR43, Th17/regulatory T-cell balance, NLRP3 signalling, tryptophan metabolites and trimethylamine N-oxide. Evidence for the reverse lung-to-gut route is weaker and is confounded by hypoxaemia, infection-associated inappetence and treatment exposure. Several TCM formulations engage these nodes in preclinical models, while early randomised studies link clinical outcomes to microbiome or metabolome changes. However, parallel biomarker shifts do not establish mediation, and no study yet connects treatment, mediator and clinical outcome within a prespecified causal model. Translation therefore requires hypothesis-driven trials stratified by TCM pattern and baseline microbial-metabolic state, with serial multi-compartment sampling and formal mediation analysis.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. The World Health Organization reports that COPD caused 3.4 million deaths in 2023, approximately 6% of all global deaths ^[1]. Contemporary GOLD guidance emphasises spirometric confirmation, individualised assessment of symptoms and exacerbation risk, and systematic management of comorbidities ^[2]. These priorities reflect a disease that extends beyond airflow

obstruction to malnutrition, skeletal-muscle dysfunction, cardiovascular disease, anxiety, depression and gastrointestinal impairment.

Persistent airway inflammation remains central to COPD, but a lung-restricted model cannot fully explain the systemic manifestations of COPD. Smoking, ageing, dietary change, physical inactivity, recurrent antibiotics and corticosteroids can simultaneously alter respiratory immunity, intestinal barrier function and microbial ecology. The gut-lung axis offers a bidirectional systems framework in which microbial functions, circulating metabolites, immune cells and neuroendocrine signals connect two mucosal compartments [3].

Several reviews have described gut dysbiosis in chronic lung disease, and a recent review surveyed multi-omics approaches to TCM in COPD [4]. The unresolved question is which microbial functions mediate treatment effects, and in whom. For multi-component TCM formulations, biomarker changes may reflect direct host pharmacology, microbiota-dependent activity or recovery itself.

This Review organises the COPD gut-lung literature by causal strength rather than by lists of altered taxa. It then translates TCM patterns and treatment principles into falsifiable microbial, metabolic and immunological hypotheses without treating historical concepts as biological equivalents. Finally, it defines a biomarker-enriched clinical pathway in which treatment, mediator and outcome are tested within one prospective causal model.

2. Review Scope and Evidence Framework

We conducted a structured narrative search of PubMed and Crossref/OpenAlex from database inception to 20 September 2026. Search concepts combined "chronic obstructive pulmonary disease" or "COPD" with "gut microbiota", "gut microbiome", "gut-lung axis", "metagenomics", "metabolomics", "short-chain fatty acids", "faecal microbiota transfer", "probiotic", "traditional Chinese medicine", "Chinese herbal medicine", "acupuncture", "mediation" and names of formulations identified during citation chaining. Reference lists of key mechanistic reviews and eligible primary studies were screened for additional reports.

We prioritised peer-reviewed human cohorts, prospective or longitudinal studies, randomised trials, mechanistic perturbation experiments and systematic reviews. Preclinical studies were retained when they tested microbiota dependence, metabolite mediation, host-target engagement or rescue, rather than reporting compositional change alone. Conference abstracts, non-peer-reviewed commentary and studies without a COPD-relevant biological or clinical endpoint were not used as primary evidence. Evidence from non-COPD respiratory models was included only when it clarified the lung-to-gut direction and is labelled as indirect. Bibliographic details were checked against DOI-indexed publisher or PubMed records when available.

Because the evidence spans heterogeneous designs and interventions, we did not perform a meta-analysis or claim PRISMA-compliant systematic coverage. Instead, an interpretive evidence ladder was used: tier 1, cross-sectional or clinical association; tier 2, temporal or functional coherence across longitudinal or multi-omics measurements; tier 3, perturbation demonstrating partial necessity, sufficiency or rescue; and tier 4, randomised human clinical mediation linking treatment to a prespecified mediator and outcome. This ladder grades support for a gut-lung mechanism, not the overall efficacy of a therapy. No included TCM study yet meets tier 4.

3. Evidence for a Bidirectional Gut-Lung Axis in COPD

3.1. Human Microbial and Metabolic Signatures

Human studies support an association between COPD and altered gut microbial ecology, but not

a universal disease-specific community. Integrated faecal microbiome and metabolome profiling identified differences in microbial species and in lipid, xenobiotic and amino-acid pathways between patients with COPD and healthy participants^[5]. Subsequent cohorts associated gut community structure with COPD severity and lower faecal short-chain fatty acids (SCFAs)^[6]. A one-year follow-up study associated changes in gut microbial communities with lung-function decline^[7]. Shotgun metagenomics has further identified functional markers that distinguish severity groups and support faecal classifiers^[8].

Recent studies sharpen the functional and phenotype-level signal. A 2026 analysis of 74 patients and 30 controls identified differences in community structure, microbial functions, and faecal and serum metabolites^[9]. Reduced serum riboflavin correlated with pulmonary function, although the diagnostic candidates require external validation. A cross-sectional multi-omics study associated GOLD A/B/E clinical groups with microbial functions and serum O-phosphoethanolamine^[10]. These groups reflect symptoms and exacerbation risk; the proposed *Clostridium ljungdahlii*-metabolite axis remains associative. In a prospective multicentre study sampling the upper airway, lower airway and stool, the gut and lung microbiomes remained compositionally distinct^[11]. Bacterial modules identified within individual compartments were associated with forced expiratory volume in 1 s, exacerbation history and inhaled corticosteroid use^[11]. Together, these studies favour coordinated host-environment effects and functional crosstalk over simple microbial migration.

Substantial between-study heterogeneity limits the generalisability of taxonomic signatures across chronic lung diseases^[12]. Cross-cohort validation should prioritise microbial functions and metabolites while accounting for clinical, environmental and analytical differences.

3.2. Gut-to-Lung Influence: From Association to Perturbation

Experimental transfer provides the strongest evidence that gut communities can modify lung injury. Microbiota from patients with COPD aggravated COPD-like changes in recipient mice^[6]. Faecal microbial transfer and complex-carbohydrate supplementation reduced experimental lung injury and motivated an exploratory placebo-controlled inulin study in patients^[13]. *Parabacteroides goldsteinii* and its structurally distinct lipopolysaccharide suppressed smoke-related inflammation in mice^[14]. Antibiotic-induced dysbiosis worsened lung pathology and regulatory T-cell dysfunction, whereas faecal transfer restored gut homeostasis and attenuated these effects^[15].

Function-led organism selection is also emerging. A colon-mimetic screen identified *Lactobacillus fermentum* as a candidate intervention and linked administration in smoke-exposed mice to increased faecal SCFAs and improved pulmonary phenotypes^[16]. These effects depend on the experimental setting and do not establish clinical efficacy.

3.3. Lung-to-Gut Influence: An Under-Tested Route

The reverse arm of the axis is less developed but biologically credible. In smoke-exposed mice, impaired pulmonary gas exchange coincided with early colonic hypoxia and inflammation. Intestinal barrier dysfunction emerged after prolonged exposure, supporting a potentially hypoxia-mediated route to gut injury^[17]. In non-COPD respiratory infection models, influenza and respiratory syncytial virus changed the gut microbiota largely through immune-driven inappetence, demonstrating that altered food intake can mediate an apparent lung-to-gut effect^[18]. In patients with COPD, acute infection, hypoxaemia, anorexia, antibiotics, systemic corticosteroids and reduced activity are therefore competing or interacting drivers that must be measured rather than treated as background noise.

Airway dysbiosis independently tracks disease progression, and longitudinal airway data

associate community disruption with accelerated lung-function decline ^[19]. Current evidence does not, however, establish routine direct seeding between the airway and intestine. The most defensible model is a bidirectional host-mediated network in which systemic inflammation, hypoxia, behaviour and treatment connect distinct microbial ecosystems.

4. Mechanistic Nodes and Unresolved Causal Links

4.1. SCFAs: Production is Not Equivalent to Pulmonary Exposure

SCFAs are generated primarily by microbial fermentation of dietary fibre. Acetate, propionate and butyrate can signal through G-protein-coupled receptors, inhibit histone deacetylases, support epithelial barrier integrity and alter immune-cell differentiation. Plasma SCFA concentrations are associated with COPD and specific phenotypes, but a cross-sectional measurement cannot resolve directionality or source ^[20]. Experimental data provide a more direct bridge: SCFAs suppressed neutrophil extracellular trap formation through a pathway involving G-protein-coupled receptor 43 (GPR43) and reduced lung inflammation in COPD models ^[21]. Microbial butyrate also inhibited type 2 innate lymphoid cell-dependent airway inflammation ^[22].

The central compartment problem is often overlooked. Faecal SCFAs reflect the balance among production, absorption and colonic use; plasma concentrations reflect absorption and systemic clearance; neither establishes exposure within lung tissue. An oral intervention can increase faecal butyrate without increasing circulating or pulmonary butyrate, and an anti-inflammatory pulmonary effect could still arise through local intestinal receptor activation, immune-cell programming or direct phytochemical action. Compartment-resolved measurements and stable-isotope tracing are needed to test pulmonary exposure.

4.2. Barrier Failure, Adaptive Immunity and Inflammasome Activation

Patients with COPD showed increased intestinal permeability and impaired nutrient absorption in a small observational study ^[23]. Barrier failure may increase systemic exposure to microbial products and amplify chronic inflammation. Within this network, imbalance between T helper 17 and regulatory T (Th17/Treg) cells, NLRP3 inflammasome activation, innate lymphoid cells and neutrophil-dominant inflammation are plausible convergence points. These pathways recur in TCM intervention studies, including the SCFA-GPR43-NLRP3 axis and Th17/Treg balance ^[24,25].

Most experiments, however, measure barrier proteins, inflammatory mediators and microbial composition at one terminal time point. Such designs cannot determine whether barrier restoration precedes pulmonary improvement or accompanies recovery. Gut-selective perturbations, time-resolved sampling, receptor-specific blockade and rescue are needed to establish sequence and necessity.

Antibiotic depletion deserves particular caution. A weakened herbal effect after antibiotics is consistent with microbiota dependence, but antibiotics can directly alter host immunity, epithelial metabolism and mitochondrial function. Conversely, persistence of benefit after depletion does not exclude activity of residual organisms or microbial products. The microbiota-dependent fraction should therefore be separated from direct pharmacology by combining germ-free or defined-consortium models, metabolite rescue, exposure measurements and host-cell assays using chemically characterised formulations.

4.3. Metabolite Networks and Clinical Phenotypes

Beyond SCFAs, COPD-associated profiles include lipids, amino acids, bile acids, tryptophan

derivatives and xenobiotic pathways^[5,9]. Higher trimethylamine N-oxide (TMAO) concentrations at admission were associated with long-term all-cause mortality after COPD exacerbation in unadjusted analyses^[26]. The association was no longer significant after multivariable adjustment, limiting its interpretation as an independent prognostic marker. Bidirectional Mendelian-randomisation studies have proposed causal links between selected microbial features, metabolites and COPD^[27]; these findings remain hypothesis-generating because instruments for microbiome traits can be weak and population-specific.

Independent validation should distinguish stable disease from acute exacerbation and account for medication, renal function, diet and sampling compartment.

5. From TCM Theory to Falsifiable Biological Hypotheses

In TCM, COPD overlaps with lung distension, dyspnoea, cough and phlegm-fluid retention. Stable disease is commonly classified into patterns such as lung-spleen qi deficiency, lung-kidney qi deficiency, phlegm-turbidity obstructing the lung and phlegm-blood stasis; acute exacerbation is more often attributed to phlegm-heat, external pathogens or impaired bowel movement. These pattern labels are clinical constructs and are not biological equivalents of enterotypes, mucosal immunity or metabolic endotypes.

Their scientific value lies in generating predictions that can fail. One hypothesis is that lung-spleen qi deficiency identifies a subgroup with reduced microbial fermentative capacity, lower effective SCFA exposure and impaired intestinal barrier function. A second is that phlegm-heat during exacerbation co-occurs with an inflammatory microbial-metabolic state, but only after infection, diet and recent antibiotics are modelled. A third is that baseline community configuration, including reproducible enterotype-like strata, and metabolite availability modify responses to qi-tonifying, heat-clearing or bowel-directed formulations.

These are interaction hypotheses, not claims that a microbial signature validates a TCM pattern. They require reproducible pattern diagnosis by trained, blinded assessors; prespecified molecular features; and tests of pattern-by-treatment and baseline-biomarker-by-treatment interaction. A microbial model should add predictive value beyond age, sex, smoking, lung function, exacerbation history, diet and medication. Failure to replicate would refute or narrow the proposed correspondence, which is a strength rather than a threat to integration.

6. TCM Interventions Targeting the Gut-Lung Axis

6.1. Preclinical Convergence and Microbiota Dependence

Preclinical formulations converge on several pathway classes despite differing composition. Bufe Jianpi formula altered microbiota, SCFAs and GPR43-NLRP3 signalling while improving lung and colonic pathology in COPD rats^[24]. Xuanbai Chengqi decoction reduced pulmonary inflammation alongside microbial restructuring and correction of Th17/Treg imbalance^[25]. Qi-Huo-Yi-Fei formula altered tyrosine-, taurine- and tryptophan-related pathways^[28]. Lifei decoction affected microbial profiles and NF-kappaB-related inflammation^[29], while Seabuckthorn Wuwei Pulvis improved tight-junction markers, SCFA-associated features and lung injury^[30].

The strongest dependency experiment used Jianpiyifei II in a virus-triggered acute exacerbation model. Microbiota depletion partially attenuated benefit and implicated microbial metabolites and JAK-STAT signalling^[31]. The partial effect suggests a microbiota-dependent component without excluding direct host pharmacology. Electroacupuncture has also reduced airway remodelling in COPD rats alongside changes in gut and lung microbiota, endotoxaemia, inflammation and epithelial-mesenchymal transition^[32]. Because that study relied on sham comparison and

correlation rather than transfer or rescue, it supports pathway convergence but not microbial mediation. No intervention has yet identified an indispensable strain-metabolite-target chain.

Preclinical studies should report botanical identity, preparation, dose, batch chemistry and pharmacokinetics, including colonic exposure and microbial biotransformation.

6.2. Clinical Evidence: Early Signals and a Platform for Mediation Trials

Human evidence directly linking TCM treatment to the gut-lung axis is at an early but productive stage. A randomised trial in stable COPD reported improved respiratory health status with compound Caoshi silkworm granules^[33]. However, stool was sampled only before treatment, precluding assessment of treatment-induced microbial changes. A double-blind placebo-controlled trial of Yihuo Huatan formula in 96 patients with stable COPD and a prespecified TCM pattern combined clinical outcomes with metabolomics and 16S ribosomal RNA gene sequencing^[34]. These studies do not establish mediation, but they show that pattern definition, randomisation and biological sampling can coexist in a feasible protocol.

Larger multicentre studies provide the clinical scaffold for the next step. In a 270-participant trial, tiotropium plus pattern-based TCM reduced exacerbations over 52 weeks compared with tiotropium alone^[35]. Symptoms and exercise capacity also improved, while an exploratory substudy assessed serum metabolites. That substudy compared intervention-group samples before and after treatment with healthy controls, rather than comparing both randomised groups. The metabolomic findings therefore remain exploratory and do not establish a gut-microbial mechanism. A prospective multicentre randomised trial of Guilou Tongluo formula in COPD with pulmonary hypertension reported cardiopulmonary benefit alongside gut metagenomic and plasma metabolomic changes^[36]. This phenotype-focused design offers useful enrichment, although generalisation to uncomplicated COPD requires replication.

Pairwise and network meta-analyses suggest that several Chinese herbal medicines may improve selected outcomes when added to standard care^[37-39]. Heterogeneity in formulation, comparator, pattern diagnosis and outcome reporting limits ranking certainty, and these syntheses do not test gut-lung mediation. A multicentre sham-controlled acupuncture protocol incorporates microbiome, metabolome and inflammatory measurements, but it remains a protocol rather than efficacy evidence^[40]. Outside TCM, a small double-blind trial randomised 50 patients with mild-to-moderate COPD to a multistrain probiotic or placebo^[41]. Among 44 completers, the intervention reduced interleukin-6 and improved COPD Assessment Test scores, whereas between-group spirometric differences were not significant.

6.3. From Concurrent Changes to Causal Mediation: Integrating Safety Assessment

A post-treatment microbiome shift should not be assumed to mediate benefit. A convincing chain requires five linked observations: treatment reproducibly changes a microbial function; the predicted metabolite or exposure changes in the relevant compartment; a host target is engaged; selective disruption or rescue alters the biological effect; and the mediator statistically and biologically explains a clinically meaningful outcome. Few TCM studies currently meet more than two or three links.

Safety must be treated as an outcome, not a footnote. Multi-herb formulations may alter exposure to bronchodilators, corticosteroids, anticoagulants and drugs used for cardiovascular comorbidity. Trials should document botanical identity, contaminants, batch chemistry, adverse events, liver and kidney indices, adherence and concomitant medication. Microbiome-focused monitoring should also consider loss of colonisation resistance, expansion of pathobionts and antimicrobial-resistance genes, particularly in older, frequently antibiotic-exposed or

immunosuppressed patients. These are risks to be measured, not established harms of the reviewed formulations.

7. A Translational Research Agenda

7.1. Biomarker-Enriched, Hypothesis-Driven Trials

The next-generation trial should retain guideline-based COPD therapy and use a randomised, blinded, placebo-controlled design whenever feasible. One clinically meaningful endpoint, such as moderate-to-severe exacerbation rate, should anchor the study. COPD Assessment Test score, modified Medical Research Council dyspnoea grade, six-minute walk distance and lung function can serve as prespecified secondary outcomes. Serial sampling should begin before treatment and span early biological response, steady exposure and exacerbation.

A small number of mediators should be selected before unblinding. For an SCFA hypothesis, this could include a strain-resolved fermentation pathway, a specific plasma SCFA, GPR43 target engagement and a neutrophil phenotype. Randomisation should be stratified by COPD state and the prespecified TCM pattern; baseline microbial or metabolic state can be used for enrichment only after analytical validation. The primary mechanistic analysis should estimate natural or interventional indirect effects, report treatment-mediator and mediator-outcome assumptions, and test whether the effect persists after adjustment for diet, antibiotics, inhaled corticosteroids and stool consistency. Temporal ordering and sensitivity analyses are essential to assess mediation and address mediator-outcome confounding.

7.2. Compartment-Resolved Validation and Global External Validity

Mechanistic studies should collect stool, plasma and respiratory samples contemporaneously. Shotgun metagenomics and metatranscriptomics can define function, targeted metabolomics can quantify exposure, and host profiling can test receptor or immune engagement. Stable-isotope tracing is particularly valuable for closing the SCFA compartment gap. Candidate organisms or metabolites should then be examined using defined consortia, gut-selective delivery, receptor blockade and rescue.

External validation should include diverse populations and diets, harmonised sampling and region-stratified analyses. Candidate responder signatures should predict treatment response beyond geography and standard clinical variables, rather than being assumed transferable from Chinese cohorts.

Formulations require the same external-validity discipline. Botanical sourcing, processing, chemical fingerprints and exposure should be harmonised across centres. Core outcomes and adverse-event definitions should be registered prospectively, and de-identified sequencing and metabolomics data should be deposited with sufficient metadata for independent reanalysis.

8. Limitations

This is a structured narrative review, not a systematic review; study selection and evidence grading are interpretive, and formal risk-of-bias tools were not applied. The literature is also vulnerable to publication bias, small cohorts, analytical flexibility and incomplete reporting of diet, medication and stool characteristics. Most causal evidence derives from rodents, while human microbiome studies remain predominantly observational.

9. Conclusions

Experimental perturbation supports a contribution of gut communities to COPD-like lung injury, whereas human evidence remains predominantly associative. Evidence for lung-to-gut effects is less direct and requires separation of hypoxia, inflammation, behaviour and treatment exposure. TCM formulations affect candidate gut-lung pathways in preclinical models, and early trials provide a basis for clinical investigation. The next step is to test whether microbial or metabolic changes mediate clinically meaningful benefit. Prespecified mediation analyses, reproducible formulations and external validation are essential before these findings can guide precision integrative COPD care.

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