Association between polyphenols and inhalation-induced oxidative stress in chronic lung diseases: A systematic review

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Abstract. Chronic respiratory diseases associated with inhalation exposure represent a notable global health burden, and are characterized by persistent oxidative stress and inflammation. Plant-derived polyphenols may serve as modulators of redox-sensitive signaling pathways; however, their clinical relevance in inhalation-associated lung disease remains unclear. The present systematic review evaluated the effects of polyphenols on oxidative, inflammatory and clinical outcomes in chronic lung diseases associated with inhalation-induced oxidative stress. P`ubMed, Cochrane Library and Web of Science were searched up to January 2026 for experimental and clinical studies investigating plant-derived polyphenols in inhalation-associated lung injury or chronic airway disease. Eligible studies included *in vitro* studies, animal models and randomized clinical trials reporting oxidative stress, and inflammatory, functional or structural outcomes. Risk of bias was assessed using Risk of Bias 2 and Systematic Review Center for Laboratory Animal Experimentation tools. Due to notable heterogeneity between studies, findings were synthesized narratively. Preclinical studies consistently demonstrated attenuation of oxidative damage, suppression of inflammatory signaling and enhancement of endogenous antioxidant defenses, typically involving activation of nuclear factor erythroid 2-related factor 2 and modulation of NF-κB pathways. Structural and histopathological improvements were also reported across multiple exposure models. Clinical findings were more heterogeneous. Although several trials reported improvements in oxidative and inflammatory markers or symptom-associated outcomes, effects on spirometric parameters remained inconsistent. Overall, polyphenols demonstrate promising redox-modulating effects in experimental models of inhalation-induced lung injury; however, clinical trials remain limited, small in scale and short in duration, with inconsistent effects on functional outcomes. Therefore, these findings should be interpreted with caution and cannot be considered conclusive evidence of therapeutic benefit. Further well-designed clinical trials are required to clarify the potential role of polyphenols as adjunctive strategies in chronic respiratory disease.

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Abbreviations: COPD, chronic obstructive pulmonary disease; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species

Key words: polyphenols, oxidative stress, chronic lung disease, inhalation exposure, COPD, systematic review

Introduction

Chronic lung diseases linked to long-term inhalation exposure are a major challenge in occupational and environmental health. Continuous contact with particulate matter and occupational dust, including crystalline silica, coal dust and diesel exhaust particles, can sustain oxidative and inflammatory stress in the airways and lung parenchyma, contributing to epithelial injury, immune dysregulation and progressive structural remodeling (1-4). A key mechanism in this process is oxidative stress, defined as an imbalance between oxidant generation and antioxidant defenses that interferes with redox signaling and promotes molecular damage (5). Reactive oxygen species (ROS) and reactive nitrogen species are not only by-products of exposure-associated injury but also key signaling mediators: While physiological levels are required

for normal cell function, their excess may drive chronic inflammation and tissue damage (6).

Given the key role of redox imbalance in inflammatory lung diseases, antioxidant-based strategies are considered a potential approach for prevention and disease modification (7). Early research has primarily focused on classical antioxidant vitamins, such as vitamins C and E, based on their ability to scavenge ROS in experimental systems (8,9). However, accumulating clinical evidence has demonstrated limited or inconsistent benefits of vitamin supplementation in chronic diseases characterized by persistent oxidative injury, and in certain contexts has suggested adverse effects (10) such as increased mortality associated with β-carotene and vitamin E supplementation (11). These findings indicate that direct neutralization of reactive species may be insufficient to counteract complex redox disturbances associated with chronic inhalation exposure, where oxidative processes are sustained, compartmentalized and associated with inflammatory and immune signaling pathways in the lung, including NF-κB-dependent inflammatory activation (12-14). The proposed mechanistic framework linking inhalation-induced oxidative stress and chronic lung injury, along with potential modulatory effects of polyphenols, is illustrated in Fig. 1. Nevertheless, the effects of polyphenols are complex and context-dependent. Among naturally occurring antioxidants, polyphenols have received attention because, in addition to their antioxidant properties, they modulate redox-sensitive signaling pathways involved in oxidative stress and inflammation (15,16). Antioxidant activity observed in cell-free or *in vitro* systems does not necessarily translate into direct radical scavenging effects *in vivo*, where bioavailability, metabolism and tissue distribution are variable (17,18). In the respiratory system, polyphenols may therefore act predominantly through indirect mechanisms, including modulation of key redox-sensitive pathways, particularly nuclear factor erythroid 2-related factor 2 (Nrf2)/Keap1 axis and NF-κB signaling, which are critically involved in oxidative stress responses, inflammation and epithelial homeostasis in chronic inhalation-associated lung diseases (19,20). Experimental studies have suggested that specific polyphenols, such as quercetin, epigallocatechin gallate and resveratrol, can attenuate oxidative and inflammatory responses in pulmonary cells, although the extent to which these effects translate into clinical benefit remains uncertain (21-23). Interindividual variability in the metabolism and biological effects of polyphenols may be influenced by differences in gut microbiota composition, since intestinal microorganisms generate metabolites the activity of which may vary across individuals (24). Given their biological importance, it is useful to consider the major dietary sources of polyphenols. Polyphenols are widely distributed in plant-derived foods, including fruits such as apples, blueberries, chokeberries and rose-hips, and vegetables such as broccoli and onions, as well as olives (21,25). Epidemiological studies have also suggested that higher consumption of polyphenol-rich foods is associated with a decreased risk of cancer and cardiovascular diseases (26,27).

The biological effects of dietary polyphenols are determined by their bioavailability rather than solely by their concentration in foods (28,29). Bioavailability is influenced by multiple factors, including release from the food matrix (the physical and chemical environment of the food) during digestion, chemical stability, intestinal absorption and microbial biotransformation in the gut. As a result, a high polyphenol content does not necessarily translate into strong *in vivo* activity. An additional limitation relates to the generally low bioavailability of numerous dietary polyphenols. Following ingestion, these compounds undergo extensive metabolism in the intestine and liver, resulting primarily in conjugated and microbiota-derived metabolites rather than the parent compounds typically tested in experimental studies. This discrepancy between the bioactivity of parent polyphenols and circulating metabolites represents an important consideration when interpreting experimental findings. A potential solution to this problem is microencapsulation and microemulsions (30).

Evidence from experimental and clinical studies has suggested the potential relevance of polyphenols in respiratory conditions (23,31,32); however, to the best of our knowledge, their role in chronic lung diseases related to inhalation-induced oxidative stress has not been comprehensively evaluated. Existing studies vary regarding exposure types, disease phenotypes [including pneumoconiosis, chronic bronchitis and chronic obstructive pulmonary disease (COPD)], polyphenol source and assessed outcomes, making it difficult to draw coherent conclusions about their preventive or supportive value in respiratory pathology. Current literature predominantly addresses cardiovascular, metabolic and neurodegenerative outcomes, leaving a gap in the systematic evaluation of occupational and environmentally induced chronic lung disease (33). A systematic synthesis of the available data is therefore required to clarify the relevance of polyphenols in modulating oxidative stress-driven mechanisms in chronic lung disease associated with inhalation exposure.

The present review aimed to integrate available experimental and clinical evidence on the role of plant-derived polyphenols in chronic lung diseases associated with inhalation-induced oxidative stress, focusing on the underlying mechanisms, preventive potential and implications for disease management and rehabilitation.

Materials and methods

Population, intervention, comparison, outcome (PICO) question. The current study aimed to address the following research question: Do adult individuals with chronic lung diseases associated with inhalation-induced oxidative stress (P), who are exposed to plant-derived polyphenols (I), demonstrate improvements in oxidative stress-related, inflammatory and functional pulmonary outcomes (O), compared with individuals receiving no polyphenol intervention, placebo or standard care (C)? The systematic review focused on whether polyphenol exposure is associated with beneficial modulation of oxidative stress-driven pathogenic mechanisms and clinical outcomes in chronic lung diseases related to inhalation exposures.

Inclusion and exclusion criteria. Studies were included if they met the following criteria: i) They involved adult participants (age, ≥18 years) with chronic lung diseases associated with inhalation-induced oxidative stress, or consisted of experimental studies using relevant *in vitro* or *in vivo* models of inhalation-associated oxidative or inflammatory lung injury;

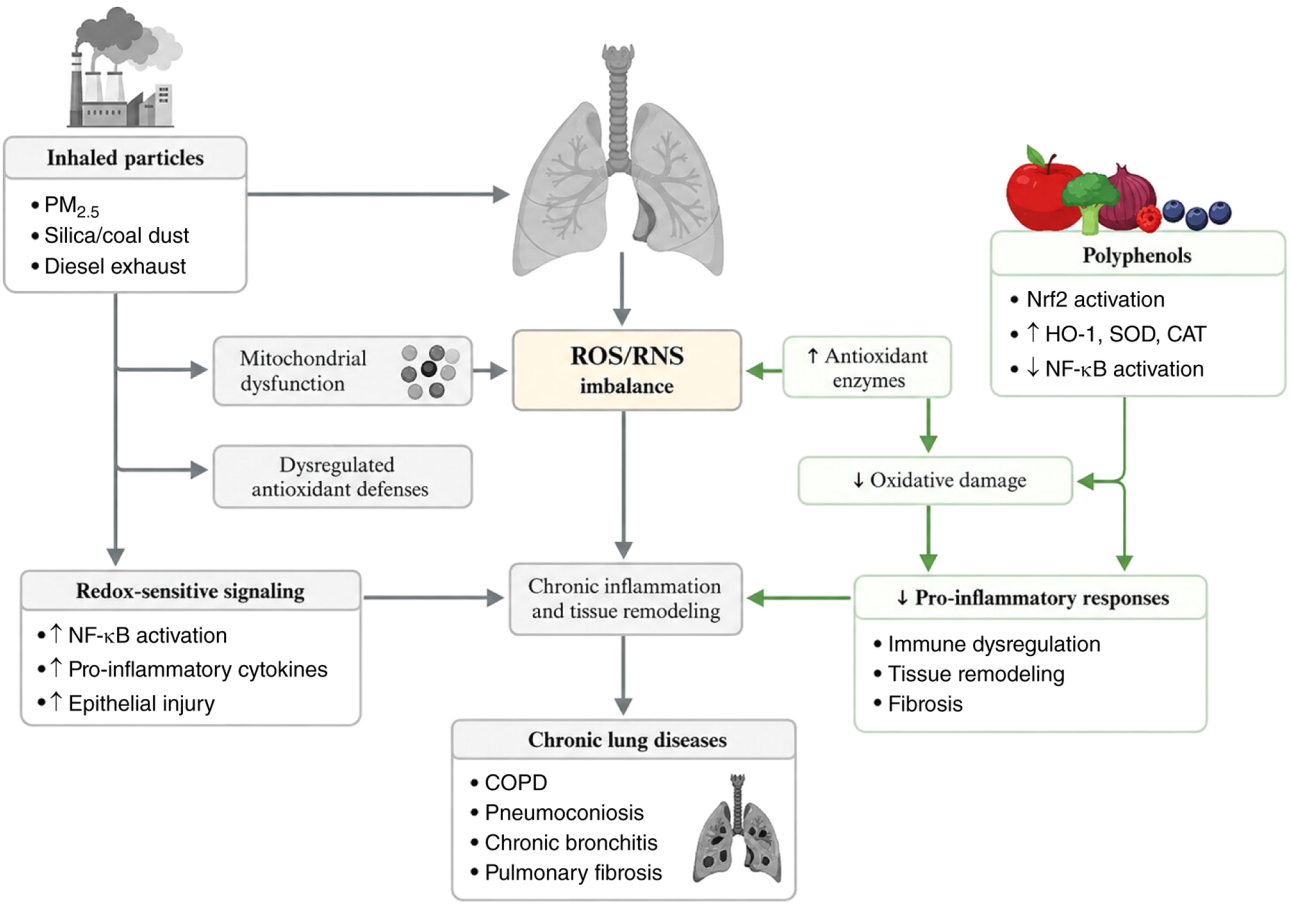

Figure 1. Mechanistic overview of inhalation-induced oxidative stress and potential polyphenol-mediated modulation in chronic lung disease. $PM_{2.5}$, fine particulate matter; ROS, reactive oxygen species; RNS, reactive nitrogen species; COPD, chronic obstructive pulmonary disease; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; SOD, superoxide dismutase; CAT, catalase.

ii) they evaluated plant-derived polyphenols administered as isolated compounds, polyphenol-rich extracts or dietary intervention; iii) they reported outcomes related to oxidative stress, inflammation, pulmonary function or lung tissue alterations; iv) the experimental (*in vitro* or *in vivo*) or clinical studies were published as original research articles; v) they were published in peer-reviewed journals; and vi) they were published in English.

The exclusion criteria were as follows: i) The studies involved pediatric populations or acute respiratory conditions; ii) they focused exclusively on vitamin or mineral antioxidants; iii) they addressed lung diseases not primarily associated with inhalation-induced oxidative stress; iv) they lacked relevant oxidative or pulmonary outcomes; or v) they were reviews, editorials, conference abstracts or case reports.

The inclusion of *in vitro* studies, animal studies and clinical trials was intended to provide complementary mechanistic and clinical evidence on the biological effects of polyphenols, rather than to compare findings across different experimental models and clinical settings. This approach allowed for a comprehensive evaluation of the available evidence related to chronic lung disease associated with inhalation-induced oxidative stress.

Search strategy. A systematic literature search was conducted in PubMed (pubmed.ncbi.nlm.nih.gov/), Cochrane Library (cochranelibrary.com/) and Web of Science (https://www.webofscience.com/wos/) to identify studies eligible for inclusion published from database inception to January 2026. The search strategy used free-text terms associated with polyphenols, oxidative stress and chronic lung disease associated with inhalation exposure. Search terms were adapted for each database as appropriate (Table SI). Core search terms included combinations of 'polyphenols', 'flavonoids', 'resveratrol', 'quercetin', 'curcumin', 'oxidative stress', 'chronic lung disease', 'COPD', 'chronic bronchitis', 'pneumoconiosis', 'particulate matter', 'dust exposure' and 'inhalation'. Reference lists of included studies were screened for additional relevant publications. Study selection was based on the predefined eligibility criteria and the PICO framework.

Study selection. A total of two reviewers independently screened titles and abstracts, and assessed full texts against the eligibility criteria. Disagreements were resolved by discussion, with involvement of a third reviewer when necessary. The study selection process followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations (34). Data were extracted using a standardized form and included study characteristics such as author, year, country, study design, sample size, exposure type, polyphenol intervention, relevant outcome measures and main findings. The protocol of the present systematic review was registered on PROSPERO with ID CRD420261321751 (crd.york.ac.uk/prospero/).

Risk of bias assessment. Risk of bias assessment was performed for randomized controlled clinical trials using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (35,36). The assessment covered the following domains: Bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of outcomes and bias in the selection of the reported result. Overall risk of bias judgment was assigned based on Cochrane guidance. *In vivo* studies were assessed using the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) risk of bias tool (37), which is specifically designed for experimental animal research. *In vitro* studies were narratively assessed because no universally accepted standardized risk of bias tool is currently available. Quality assessment was conducted independently by two reviewers, with disagreements resolved by consensus or consultation with a third reviewer.

Results

Study screening and selection. A total of 1,738 records were identified through database searches, including 897 from PubMed, 824 from Web of Science and 17 from Cochrane Library, with no additional records obtained from other sources. Following removal of 1,023 duplicates, 715 records were screened based on titles and abstracts. In total, 662 records were excluded, including 238 review articles and 424 studies not relevant to the topic. Full texts were sought for 53 articles, of which two could not be retrieved, leaving 51 studies for eligibility assessment. Of these, 32 studies were excluded due to insufficient or incomplete data (n=20) or outcomes not relevant to the aims of the review (n=12). In total, 19 studies met the predefined inclusion criteria and were included in the final systematic review (Fig. 2) (38-56).

Characteristics of included studies. In total, 19 studies published from 2006 to 2025 were included in the present systematic review (Tables I and II). The evidence comprised preclinical *in vivo* and *in vitro* studies and clinical trials, providing a translational overview of the effects of plant-derived polyphenols in chronic lung diseases associated with inhalation-induced oxidative stress. Sample sizes ranged from small animal cohorts to clinical trials enrolling up to 60 patients. Most included studies were preclinical, employing established models of oxidative and inflammatory lung injury induced by inhaled or airway-targeted stressors, including cigarette smoke, lipopolysaccharide, elastase, chemotherapeutic agents, sulfur mustard and environmental toxicants. These models captured key pathological features shared across chronic lung diseases, such as oxidative stress, inflammation, epithelial injury, protease imbalance and tissue remodeling. Several studies integrated animal models with complementary *in vitro* systems, including airway epithelial cells and macrophages, to explore underlying cellular mechanisms (40,43,51,52,54-56). Clinical evidence was provided by randomized controlled trials and early-phase studies conducted in patients with chronic obstructive and COPD-like airway diseases, in which polyphenols were administered as adjuncts to standard therapy. A diverse range of polyphenolic compounds was investigated, with outcomes primarily assessing oxidative stress markers, inflammatory responses, structural lung injury and functional parameters. The studies investigated several major classes of plant-derived polyphenols, predominantly flavonoids, followed by stilbenes, phenolic acids, curcuminoids and polyphenol-rich plant extracts.

Quality and risk of bias assessment. According to the RoB 2.0 assessment for clinical studies (Table SII), none of the included randomized controlled trials was judged to be at an overall high risk of bias. One trial was classified as low risk of bias across all domains (38), while the remaining studies were judged as having some concerns overall, primarily due to limited reporting of randomization procedures or prespecified analysis plans. Domains associated with deviations from intended interventions and measurement of the outcome were consistently assessed as low risk. The missing outcome data domain was assessed as low risk in most studies, although concerns were identified in two trials (44,53). Overall judgments followed Cochrane guidance without the use of numerical scoring.

Animal studies assessed using the SYRCLE tool (Table SIII) showed a predominance of unclear risk of bias across several domains, primarily reflecting insufficient reporting of methodological details (39-42,45-47,50,52,54,56). Information on allocation concealment, random housing and blinding procedures was typically lacking, resulting in unclear risk classifications for these domains. By contrast, incomplete outcome data were typically assessed as low risk, whereas reporting bias was typically unclear because of insufficient information. High risk of bias was limited to a single domain within one study (46). No composite risk of bias score was calculated and results were interpreted descriptively in accordance with SYRCLE guidance.

Effects of polyphenols on oxidative stress and inflammatory outcomes. Across the included studies, polyphenol exposure was associated with changes in oxidative stress and inflammation-associated outcomes in models of inhalation-induced lung injury and chronic airway disease. Reported effects most commonly included decreases in oxidative damage markers, attenuation of inflammatory responses and partial restoration of endogenous antioxidant defenses (Tables I and II).

In preclinical *in vivo* models, diverse polyphenolic compounds were associated with decreased lipid peroxidation and ROS, alongside increased activity or expression of antioxidant enzymes such as superoxide dismutase, catalase, glutathione and heme oxygenase-1. These effects were reported across multiple models of lung injury induced by cigarette smoke, elastase, lipopolysaccharide, bleomycin, cyclophosphamide, and environmental or chemical toxicants. Most animal studies also reported decreased airway and lung inflammation, including lower bronchoalveolar lavage inflammatory cell counts and decreased levels of pro-inflammatory cytokines. Several studies described improvements in histopathological features of lung injury, such as decreased alveolar damage, inflammatory infiltration, edema and fibrosis (39,41,42,45-47).

In vitro studies provide complementary evidence, showing that polyphenols attenuated oxidative stress-induced cell responses, suppressed pro-inflammatory mediator release, and supported

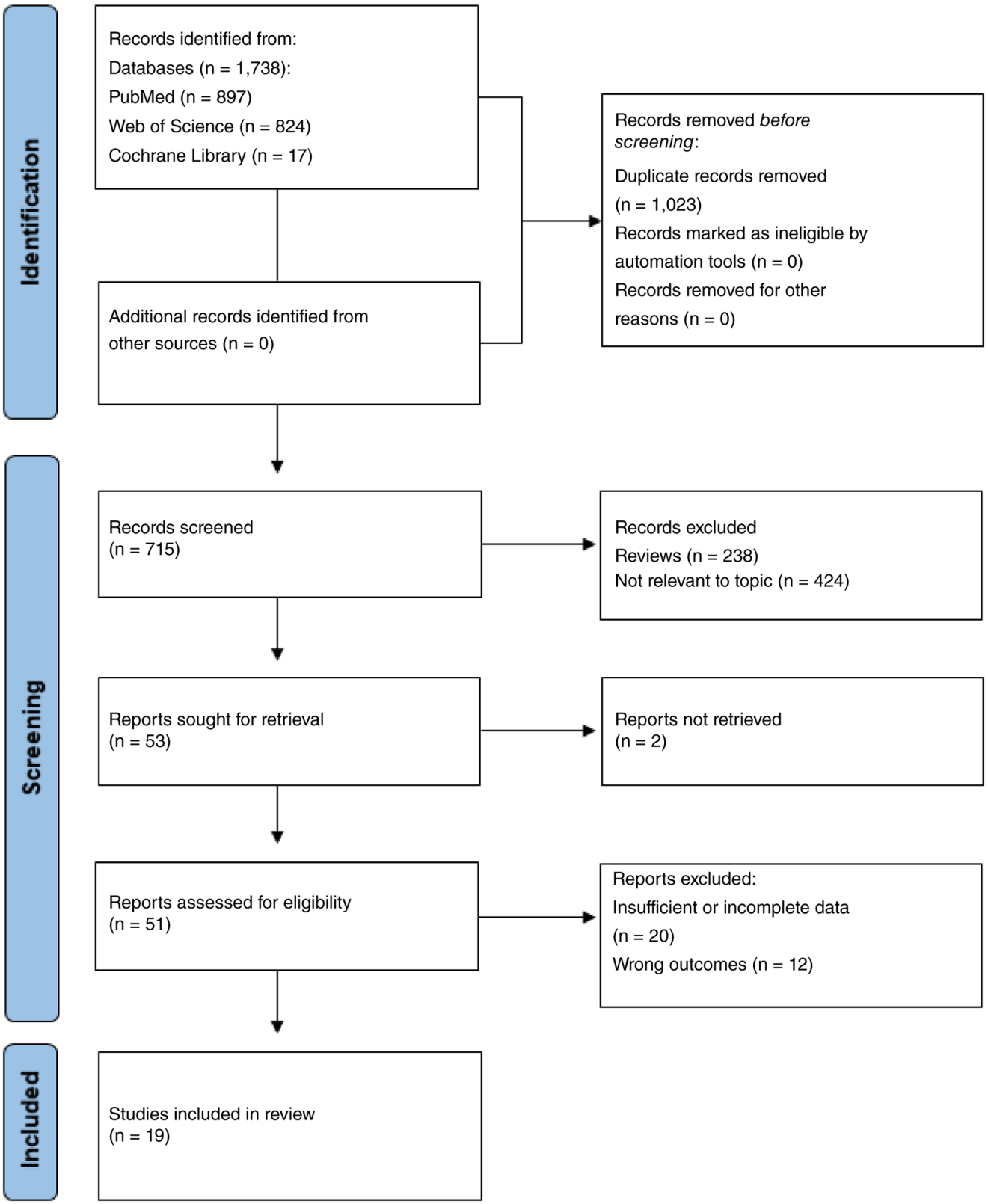

Figure 2. Search methods and findings according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

epithelial resilience or repair under controlled experimental conditions. These observations were directionally aligned with findings reported in *in vivo* models. Clinical studies showed more heterogeneous results. While certain trials reported improvements in oxidative stress markers, inflammatory parameters or symptom-related outcomes, effects on lung function were variable and spirometric improvements were not consistently observed. Heterogeneity may be attributable to differences in disease characteristics, exposure patterns, polyphenol formulation and dosing, intervention duration and outcome measures.

Table I. Characteristics of included clinical studies.

First author, year	Study type	Model/population	Inhalation exposure/disease	Polyphenols	Dose/exposure	Comparison	Key outcomes	(Refs.)
Cerdá *et al*, 2006	Clinical RCT (double-blind, placebo-controlled)	Male patients with stable COPD (n=30; GOLD II-IV)	Stable COPD (smokers/ex-smokers)	PJ polyphenols (ellagitannins, ellagic acid, anthocyanins)	400 ml/day for 5 weeks (2.66 g total polyphenols/day)	PJ vs. placebo	No significant effect on lung function, oxidative stress markers or clinical symptoms; high interindividual variability in polyphenol metabolism	(38)
Panahi *et al*, 2014	Clinical trial (RCT, double-blind, placebo-controlled)	Male patients (n=89) with sulfur mustard-induced bronchiolitis obliterans (COPD-like)	Chronic pulmonary complications following sulfur mustard inhalation	Curcuminoids (with piperine)	1,500 mg/day curcuminoids + 15 mg/day piperine for 4 weeks (adjunct to standard therapy)	Curcuminoids + standard therapy vs. placebo + standard therapy	Increased antioxidant status (increased GSH, decreased MDA); improved symptoms and quality of life (decreased CAT and SGRQ); antioxidant and anti-inflammatory effects with enhanced bioavailability via piperine	(44)
Lu *et al*, 2018	Clinical trial (RCT, double-blind, placebo-controlled)	Patients with stable COPD (n=27)	Chronic COPD (stable phase)	Oligomeric proanthocyanidins (grape seed extract)	150 mg/day oral for 8 weeks	OPC vs. placebo	Decreased oxidative stress (decreased MDA and SOD activity); improved lipid profile (increased HDL-C, decreased TC/HDL-C ratio); no improvement in lung function (FEV_1, FVC); antioxidant effects via free radical scavenging and inhibition of lipid peroxidation	(48)
Han *et al*, 2020	Clinical trial (phase I, randomized, double-blind, placebo-controlled)	Patients with stable COPD (mild-severe; n=9)	Chronic COPD (stable phase)	Quercetin	500-2,000 mg/day oral for 7 days (dose escalation)	Quercetin vs. placebo	Well tolerated up to 2,000 mg/day; no significant change in lung function or clinical safety parameters; efficacy not assessed	(49)

Table I. Continued.

First author, year	Study type	Model/population	Inhalation exposure/disease	Polyphenols	Dose/exposure	Comparison	Key outcomes	(Refs.)
Zare'i *et al*, 2024	Clinical trial (RCT, double-blind, placebo-controlled)	Patients with severe-very severe COPD (GOLD III-IV; n=60)	Advanced COPD (smoking-associated)	Nano-curcumin	80 mg/day oral for 3 months (adjunct to standard therapy)	Nano-curcumin + standard therapy vs. placebo + standard therapy	Increased lung function (increased FEV_1, FVC and FEV_1/FVC); decreased systemic inflammation (decreased IL-6); well tolerated; anti-inflammatory and antioxidant effects via NF-κB inhibition and Nrf2 activation	(53)

CAT, catalase; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity; GOLD, Global Initiative for Obstructive Lung Disease; GSH, glutathione; HDL-C, high-density lipoprotein cholesterol; PJ, pomegranate juice; MDA, malondialdehyde; Nrf2, nuclear factor erythroid 2-related factor 2; OPC, oligomeric proanthocyanidin; RCT, randomized clinical trial; SGRQ, St. George's Respiratory Questionnaire; SOD, superoxide dismutase; TC, total cholesterol.

Disease and exposure-specific findings

COPD and cigarette smoke-associated models. In models of COPD and cigarette smoke-associated airway injury, polyphenol exposure was consistently associated with attenuation of oxidative stress and inflammatory responses. Preclinical studies reported decreased airway and parenchymal inflammation and oxidative damage and partial preservation of lung structure following administration of compounds such as resveratrol, quercetin, curcumin, luteolin, gallic acid and related polyphenols. These effects were commonly accompanied by improvements in antioxidant defenses, and decreased protease activity or emphysematous changes. Clinical evidence in COPD was more variable. While several trials reported improvements in oxidative stress markers, inflammatory parameters, symptom burden or quality of life measures, effects on spirometric outcomes were inconsistent. In some studies, polyphenol supplementation was well-tolerated and associated with biochemical or symptomatic benefits without measurable improvements in lung function.

Chemically and toxicant-induced lung injury. In experimental models of chemically induced lung injury, including bleomycin, cyclophosphamide and sulfur mustard-related pulmonary damage, polyphenols were associated with marked decreases in oxidative stress and inflammatory injury. Studies consistently reported attenuation of fibrotic or structural lung changes, decreased inflammatory cell infiltration and modulation of oxidative damage markers following treatment with polyphenol-rich extracts or isolated compounds. In the clinical setting, limited evidence from patients with chronic pulmonary complications following toxic inhalation suggested polyphenol supplementation may improve antioxidant status and symptom-associated outcomes when used as an adjunct to standard therapy. However, data on functional respiratory outcomes remain limited.

Particulate matter and environmental exposure models. Animal and cell models of lung injury induced by particulate matter, heavy metals or environmental toxicants demonstrate the protective effects of polyphenols against oxidative and inflammatory damage. Findings included decreased ROS generation, inflammatory mediator release, epithelial injury and apoptosis, alongside enhancement of endogenous antioxidant responses. *In vitro* studies further supported these observations, showing improved epithelial resilience and modulation of macrophage activation under oxidative stress conditions.

Clinical outcomes. Across the included clinical studies, polyphenol supplementation was generally well-tolerated and did not raise safety concerns when administered as an adjunct to standard therapy. Several trials reported improvements in systemic or pulmonary oxidative stress markers, inflammatory parameters or patient-reported outcomes, including symptom burden or quality of life measures.

The effects on objective pulmonary function outcomes were inconsistent. While certain studies reported improvements in spirometric parameters (44,53), most trials did not demonstrate significant or uniform changes in lung function indices despite favorable biochemical or symptomatic responses. Given the modest number of available trials, their small cohorts and short follow-up periods, these clinical

Table II. Characteristics of included preclinical studies.

First author, year	Study type	Model/population	Inhalation exposure/disease	Polyphenols	Dose/exposure	Comparison	Key outcomes	(Refs.)
Iraz *et al*, 2006	Preclinical (*in vivo)*	Male Sprague-Dawley rats (n=29)	BLM-induced lung injury/fibrosis (intratracheal BLM, 2.5 mg/kg)	*Ginkgo biloba* extract (flavonoid-rich)	100 mg/kg/day, oral; prophylactic (from 1 day before BLM to day 14)	BLM vs. BLM + *G. biloba*	Decreased lung fibrosis (decreased hydroxyproline and Ashcroft score), preserved lung histology; decreased BAL neutrophils and total cells; decreased oxidative stress (decreased MDA, nitrite and MPO); partial restoration of antioxidant defenses (increased catalase and SOD); antioxidant attenuation of oxidative and neutrophilic injury	(39)
Ganesan *et al*, 2010	Preclinical (*in vivo* and *in vitro*)	C57BL/6 mice (n=4-14/group); murine alveolar macrophages	ET/LPS-induced COPD (intranasal elastase + LPS)	Quercetin (flavonoid)	*In vivo:* 10 mg/kg/day oral for 10 days (post-exposure); *in vitro:* 25 μM	COPD vs. COPD + quercetin	Attenuated emphysema progression; decreased lung (± sirtinol) inflam-mation, oxidative stress, goblet cell metaplasia and MMP9/MMP12 expression and activity; SIRT1-dependent suppression of NF-κB-driven MMP transcription via histone deacetylation	(40)
Sahin *et al*, 2011	Preclinical (*in vivo*)	Wistar-Albino rats (n=35)	Chronic CS-induced COPD (passive smoke exposure, 20 weeks)	Resveratrol (stilbene polyphenol)	20 mg/kg i.p. daily for 21 days (post-exposure)	Smoke + resveratrol vs. smoke + DMSO; smoke + theophylline vs. smoke + physiolo-gical saline; healthy control	Decreased systemic inflammation (decreased serum TNF-α) and lung injury score; improved lung histopathology (decreased alveolar duct dilatation, inflammatory infiltration, epithelial proliferation and vascular congestion); restorationof alveolar-capillary ultrastructure; anti-inflammatory/antioxidant effects	(41)

Table II. Continued.

First author, year	Study type	Model/population	Inhalation exposure/disease	Polyphenols	Dose/exposure	Comparison	Key outcomes	(Refs.)
Hamdy *et al*, 2012	Preclinical (*in vivo*)	Male albino Wistar rats (n=8-20/group)	CP-induced lung injury/fibrosis (systemic CP causing oxidative lung damage)	Curcumin; GTE (catechin-rich, including EGCG)	Curcumin: 200 mg/kg/day oral; GTE: 150 mg/kg/day oral (concomitant with CP, pre- and post-exposure)	CP vs. CP + curcumin or GTE (comparators: NAC, vehicle)	Attenuated lung fibrosis (decreased hydroxyproline and elastin deposition); decreased oxidative stress (decreased MDA, increased GSH) and inflammatory mediators (decreased TGF-β, IL-1β and histamine); improved BALF profile; attenuated fibrosis via antioxidant and anti-inflammatory mechanisms	(42)
Flores *et al*, 2013	Preclinical (*in vitro*)	Human small airway epithelial cells	Cigarette smoke extract-induced oxidative stress	Guava (*Psidium friedrichsthalianum*) ethyl acetate fraction (phenolic-rich)	5-100 μg/ml; pre- or co-treatment with CSE (24 h)	CSE vs. CSE + extract	Decreased pro-inflammatory response (decreased IL-8) and MMP-1 expression; strong antioxidant capacity; phenolic antioxidant activity reducing ROS-driven inflammatory and protease responses	(43)
Impellizzeri *et al*, 2015	Preclinical (*in vivo*)	Male CD-1 (ICR) mice (n=60)	BLM-induced lung injury/fibrosis (intratracheal BLM)	Resveratrol; mangiferin; quercetin; dihydroquercetin	Oral administration for 7 days post-BLM (resveratrol 50 mg/kg; others 10 mg/kg)	BLM vs. BLM + polyphenols	Decreased lung inflammation and fibrosis (decreased histological score and edema), BAL inflammatory cells and MPO and oxidative/nitrosative stress (decreased nitrotyrosine and iNOS); suppression of MAPK/NF-κB inflammatory signaling.	(45)
Zhang *et al*, 2016	Preclinical (*in vivo*)	Male Sprague-Dawley rats (n=38)	Cigarette smoke + LPS-induced COPD	Curcumin	100 mg/kg/day oral for 30 days (post-exposure)	COPD vs. COPD + curcumin	Decreased BAL inflammatory cells and cytokines (IL-6, IL-8, TNF-α) and emphysema severity (decreased MLI and MAN); improved lung histopathology and ultrastructure; decreased epithelial apoptosis; attenuation of oxidative stress-induced mitochondrial apoptosis via p66Shc downregulation	(46)

Table II. Continued.

First author, year	Study type	Model/population	Inhalation exposure/disease	Polyphenols	Dose/exposure	Comparison	Key outcomes	(Refs.)
Wang *et al*, 2017	Preclinical (*in vivo*)	Male Wistar rats (n=30)	Cigarette smoke + LPS-induced COPD	Resveratrol	50 mg/kg/day oral for 20 days (pre-/co-exposure)	COPD vs. COPD + resveratrol	Decreased lung inflammation, emphysema, BAL and serum inflammatory markers (IL-6, IL-8) and oxidative stress (decreased MDA, increased SOD); improved lung histopathology; Activation of SIRT1/PGC-1α signaling, enhancing antioxidant defense and suppressing NF-κB-mediated inflammation	(47)
Singla *et al*, 2021	Preclinical (*in vivo*)	Balb/c mice; 5 groups (n=5-6/group)	Elastase + LPS-induced COPD exacerbation model	Gallic acid	200 mg/kg/day i.p. for 28 days (prophylactic)	ET + LPS vs. ET + LPS + gallic acid	Decreased airway inflammation, neutrophilic infiltration and oxidative stress (decreased ROS and MDA); restored antioxidant defenses (increased GSH, SOD and catalase); antioxidant and anti-inflammatory effects via Nrf2 activation and NF-κB suppression	(50)
Coco *et al*, 2022	Preclinical (*in vitro*)	Human lung epithelial cells (NCI-H441, A549)	Oxidative stress-induced epithelial injury (tBHP)	Baru nut ethanolic extract (phenolic-rich)	0.5-10.0 μg/ml (pre-/co-treatment)	tBHP vs. tBHP + extract	Decreased ROS under basal and oxidative stress conditions; enhanced epithelial wound closure; phenolic antioxidant activity reducing ROS and supporting epithelial repair	(51)
Liu *et al*, 2024	Preclinical (*in vivo* and *in vitro*)	CS + LPS-induced COPD rats (n=6/group); RAW264.7 macrophages; BEAS-2B epithelial cells	CS + LPS-induced COPD	Magnolol	*In vivo*: 50 mg/kg/day intragastric (weeks 3-6); *In vitro*: 5-40 μM	COPD vs. COPD + magnolol (positive control: Dexamethasone)	Decreased lung inflammation, emphysema, pro-inflammatory cytokines and oxidative stress (decreased ROS and MDA); increased antioxidant enzymes (SOD, HO-1, NQO1); activation of Nrf2 signaling with concomitant inhibition of MAPK pathways	(52)

Table II. Continued.

First author, year	Study type	Model/population	Inhalation exposure/disease	Polyphenols	Dose/exposure	Comparison	Key outcomes	(Refs.)
Zhou *et al*, 2023	Preclinical (*in vivo* and *in vitro*)	CS + LPS-induced COPD mice (n=40); A549 epithelial cells	CS + LPS-induced COPD; CSE-induced epithelial oxidative stress	Lut (flavonoid)	*In vivo:* 50-100 mg/kg/day oral for 28 days; *in vitro:* 15-30 μM	*In vivo*: Control, COPD (CS + LPS), COPD + Lut-L, COPD + Lut-H; *in vitro*: Control, CSE, CSE + Lut-L, CSE + Lut-H	Decreased lung injury, emphysema, and systemic and cell oxidative stress (decreased ROS and MDA); increased antioxidant defenses (increased SOD, CAT, GSH); attenuation of oxidative stress via TRPV1/SIRT6 and CYP2A13/Nrf2 pathway modulation	(54)
Jiang and Somavarapu, 2025	Preclinical (*in vitro*)	RAW 264.7 murine macrophages	IL-4-induced macrophage polarization (COPD-relevant immune remodeling)	Icariin	10-25 μg/ml (pretreatment, 24-72 h); inhalable micellar formulation	IL-4 vs. IL-4 + icariin	73% decrease in IL-4-induced CD206 expression; decreased M2 macrophage polarization (decreased CD206 expression); enhanced cell uptake with micellar delivery; modulation of IL-4-dependent macrophage signaling, suppressing profibrotic/anti inflammatory M2 phenotype	(55)
Min *et al*, 2025	Preclinical (*in vivo* and *in vitro*)	Pb/Cd-exposed mice (n=3-18/group); mice with ET-induced emphysema (n=3-6/group); alveolar macrophages and lung epithelial cells	Heavy metal (Pb/Cd) inhalation-induced lung injury; elastase-induced emphysema	Gaylussacin (stilbene glycoside)	*In vivo:* 40 mg/kg oral (5 weeks); *in vitro:* 10 μM	Injury vs. injury + gaylussacin	Decreased emphysema, mucus hypersecretion, oxidative stress, apoptosis, MMP activity (notably MMP-12) and inflammatory cytokines; improved lung mechanics; SIRT1 activation with suppression of macrophage-driven inflammation and protease activity	(56)

BALF, bronchoalveolar lavage fluid; BLM, bleomycin; COPD, chronic obstructive pulmonary disease; CP, cyclophosphamide ; CSE, cigarette smoke extract; EGCG, epigallocatechin gallate; ET, elastase; GSH, glutathione; GTE, green tea extract; HO-1, heme oxygenase-1; iNOS, inducible nitric oxide synthase; i.p., intraperitoneal; LPS, lipopolysaccharide; Lut-L, low-dose luteolin; Lut-H, high-dose luteolin; MAN, mean alveolar number; MDA, malondialdehyde; MLI, mean linear intercept; MPO, myeloperoxidase; NAC, N-acetylcysteine; NQO1, NAD(P)H quinone dehydrogenase 1; Nrf2, nuclear factor erythroid 2-related factor 2; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1-α; ROS, reactive oxygen species; SIRT, sirtuin; SOD, superoxide dismutase; tBHP, tert-butyl hydroperoxide.

findings warrant a conservative interpretation and should not be considered conclusive evidence of functional benefit.

Discussion

The present systematic review integrates experimental and clinical evidence on the role of plant-derived polyphenols in chronic lung disease associated with inhalation-induced oxidative stress. Preclinical studies consistently demonstrated attenuation of oxidative stress, suppression of inflammatory signaling and partial preservation of lung structure following polyphenol exposure (40,42,45,47,52,56). By contrast, clinical findings were more heterogeneous, with relatively consistent improvements in biochemical and inflammatory markers but variable effects on spirometric outcomes. These findings suggested that polyphenols reliably modulate redox-sensitive and inflammatory pathways under controlled experimental conditions, whereas translation into measurable functional improvement in humans remains uncertain (12,57). This may reflect the complex and long-standing nature of structural lung damage, which may not be easily reversible even when oxidative and inflammatory pathways are modulated (58).

Notably, oxidative stress and inflammatory markers appeared more responsive to polyphenol intervention than established functional endpoints. This suggests that polyphenols may preferentially influence upstream molecular and inflammatory processes, potentially affecting disease trajectory rather than acutely reversing airflow limitation (59,60). No consistent safety concerns were identified, supporting further investigation of polyphenols as adjunctive strategies in chronic inhalation-associated lung disease.

The consistency of findings across preclinical models supports the hypothesis that polyphenols primarily act via modulation of redox-sensitive signaling pathways (61). In certain *in vivo* and *in vitro* systems, activation of Nrf2-associated antioxidant responses and attenuation of NF-κB-mediated inflammatory signaling were recurrent mechanistic themes (62,63). This aligns with the hypothesis that chronic inhalation-induced lung injury is driven not only by excess ROS, but also by dysregulated redox signaling networks that amplify inflammatory and remodeling cascades (58,64). Although Nrf2 activation and NF-κB inhibition were recurrent mechanistic themes, comparison of the included studies indicates that different polyphenols do not act through a single conserved signaling pathway. Distinct compounds were associated with modulation of different molecular targets. Several polyphenols, including gallic acid, magnolol and luteolin, were more frequently associated with Nrf2-associated antioxidant signaling, whereas curcumin predominantly modulated inflammatory pathways. Curcumin attenuates inflammation and oxidative stress through modulation of the PTEN/PI3K/AKT/NF-κB signaling pathway (65). By contrast, resveratrol and the stilbene derivative gaylussacin were more consistently associated with sirtuin 1 (SIRT1)-associated signaling, while quercetin demonstrated SIRT1-dependent regulation of MMP expression. However, because structurally related compounds were not systematically compared under standardized experimental conditions, definitive structure-activity associations cannot yet be established. These observations may explain why classical antioxidant supplementation has yielded limited clinical benefit. Direct neutralization of reactive species is unlikely to sufficiently address sustained, compartmentalized oxidative stress or downstream transcriptional activation. By contrast, polyphenols may influence endogenous antioxidant defenses and inflammatory pathways more broadly, supporting a more integrated regulation of redox balance.

However, the translational gap between mechanistic efficacy and clinical impact remains evident (31). While experimental models capture early oxidative and inflammatory processes, clinical populations typically represent advanced disease stages characterized by established structural remodeling, airway narrowing and irreversible parenchymal damage (66). Under such conditions, modulation of oxidative pathways alone may not translate into substantial improvements in spirometric indices, even if biochemical and symptomatic benefits are observed (67,68). The mechanistic evidence supports biological plausibility for polyphenols as modulators of inhalation-induced redox imbalance, but also underscores the need to consider disease stage, timing of intervention and combination strategies in future clinical investigations.

The effects of polyphenols differed according to disease context and exposure model. In COPD and cigarette smoke-associated models, preclinical studies consistently demonstrated attenuation of oxidative stress and inflammation (40,42,45), whereas clinical trials show more variable effects, particularly on spirometric outcomes (32,53). This may reflect the limited reversibility of established structural damage despite modulation of upstream redox and inflammatory pathways (69). In chemically or toxicant-induced lung injury models, polyphenols exerted more pronounced effects on inflammatory and fibrotic parameters, potentially due to the more defined oxidative drivers of injury in these systems (39,56,70). However, clinical evidence in toxic inhalation-associated disease remains limited, and functional respiratory outcomes are not consistently improved. Overall, disease stage, exposure characteristics and endpoint selection may influence the observable impact of polyphenol interventions.

The present review integrates clinical and preclinical evidence within a unified mechanistic framework, enabling translational interpretation across biological levels. Risk of bias was assessed using validated tools appropriate to each study design and findings were synthesized descriptively in line with established methodological standards. However, clinical evidence base remains limited, with most randomized trials including small sample sizes and relatively short intervention durations. These factors decrease the likelihood of detecting changes in structural or functional respiratory endpoints. The findings should be interpreted in the context of the risk of bias assessment. Although none of the included randomized clinical trials were judged to be at high risk of bias, most were assessed as having some concerns, decreasing confidence in the reported clinical benefits. Similarly, the predominance of unclear risk of bias among the preclinical studies, primarily reflecting incomplete methodological reporting, warrants cautious interpretation of the mechanistic findings. Several factors contributed to the substantial heterogeneity across the included studies. First, different polyphenols and polyphenol classes were investigated, ranging from flavonoids and stilbenes to curcuminoids and

polyphenol-rich extracts. Second, considerable variation existed in formulations, dosing regimens and intervention duration. Third, the included evidence comprised *in vitro* studies, animal models and clinical trials, each providing complementary but different types of evidence. Finally, studies differed in disease phenotypes, exposure model and outcome measures. These methodological differences limit direct comparisons between studies, preclude quantitative meta-analysis, and should be considered when interpreting the consistency and clinical applicability of the available evidence.

Extrapolation from animal and *in vitro* models to human disease must be approached cautiously due to differences in exposure duration, metabolism and disease chronicity (37,71). In addition, most studies evaluated polyphenols as adjunctive interventions and long-term clinical outcomes such as disease progression or exacerbation frequency were rarely assessed (38,44,48). Consequently, conclusions regarding sustained disease modification remain preliminary. Overall, confidence in the preclinical oxidative and inflammatory findings was greater than confidence in the clinical functional evidence, which was limited by heterogeneity, small trial sizes and methodological concerns.

The present review suggested that polyphenols may represent a biologically plausible adjunctive strategy in chronic lung diseases characterized by inhalation-induced oxidative stress (72). While consistent modulation of oxidative and inflammatory markers has been demonstrated across experimental systems, clinical benefits are modest and may depend on disease stage, intervention timing and endpoint selection. Polyphenols are therefore unlikely to reverse established structural lung damage but may contribute to modulation of ongoing redox and inflammatory activity within a multimodal therapeutic framework. However, a biologically plausible mechanism does not establish therapeutic value, particularly when the available clinical evidence remains limited. The clinical trials underlying this evidence base are few, generally small, of short duration and have reported inconsistent functional outcomes. Accordingly, the present data are not sufficient to support the broad clinical use of polyphenols in chronic lung diseases associated with inhalation-induced oxidative stress. Nonetheless, given the growing global burden of occupational and environmental lung disease (73,74), strategies targeting redox-sensitive pathways may hold relevance in high-exposure populations where preventive or adjunctive approaches are needed (75).

Future clinical research should prioritize adequately powered randomized trials with longer intervention durations and clearly defined patient populations. Improved standardization of polyphenol formulations, dosing regimens, intervention duration and outcome assessment is key, as variability in these methodological aspects remains a major limitation for translating experimental findings into clinical practice. Consistent intervention protocols, outcome measures and reporting standards will also be critical to reduce heterogeneity and improve comparability across studies. Greater emphasis on clinically meaningful endpoints such as exacerbation frequency, symptom burden and disease progression may clarify whether redox modulation translates into sustained functional benefit. Mechanistic studies that better integrate pharmacokinetics, bioavailability and tissue distribution in chronic exposure settings are also warranted. Bridging experimental and clinical research through well-designed translational studies may determine whether targeting redox sensitive pathways can meaningfully alter the trajectory of inhalation-associated lung disease.

In conclusion, plant-derived polyphenols are biologically plausible modulators of inhalation-induced oxidative stress. However, their clinical benefit remains unproven. Given the limited number, small size and heterogeneity of the available clinical trials, current evidence does not support recommending a specific polyphenol, formulation or dosage for routine clinical use in chronic lung disease. Future adequately powered randomized controlled trials using standardized, bioavailability-optimized formulations are needed to determine optimal dosing strategies and clarify the efficacy of individual polyphenols in specific chronic lung diseases.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

AEG and MN confirm the authenticity of all the raw data. AEG and MN conceptualized the study, performed the literature review and prepared the initial draft of the manuscript. MN and AI contributed to the methodology and investigation. NK performed the literature review. SAK, MBB, KT and SK performed the literature review and interpreted data. ZS, AKu and AN analyzed data. AEG and MN reviewed and edited the manuscript. SS contributed to interpretation of data and constructed figures. AI supervised the study. AKo designed the study and revised the manuscript. MBB contributed to funding acquisition. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

References

1. De Matteis S, Heederik D, Burdorf A, Colosio C, Cullinan P, Henneberger PK, Olsson A, Raynal A, Rooijackers J, Santonen T, *et al*: Current and new challenges in occupational lung diseases. Eur Respir Rev 26: 170080, 2017.
2. Tran HM, Lai CH, Chen WL, Wang CC, Liang CW, Chien CY, Pan CH, Chuang KJ and Chuang HC: Effects of occupational exposure to metal fume $PM_{2.5}$ on lung function and biomarkers among shipyard workers: A 3-year prospective cohort study. Int Arch Occup Environ Health 97: 401-412, 2024.
3. Vanka KS, Shukla S, Gomez HM, James C, Palanisami T, Williams K, Chambers DC, Britton WJ, Ilic D, Hansbro PM and Horvat JC: Understanding the pathogenesis of occupational coal and silica dust-associated lung disease. Eur Respir Rev 31: 210250, 2022.
4. Sherekar P, Suke SG, Dhok A, Malegaonkar S and Dhale SA: Global scenario of silica-associated diseases: A review on emerging pathophysiology of silicosis and potential therapeutic regimes. Toxicol Rep 14: 101941, 2025.
5. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, Squadrito F, Altavilla D and Bitto A: Oxidative stress: Harms and benefits for human health. Oxid Med Cell Longev 2017: 8416763, 2017.
6. Mittal M, Siddiqui MR, Tran K, Reddy SP and Malik AB: Reactive oxygen species in inflammation and tissue injury. Antioxid Redox Signal 20: 1126-1167, 2014.
7. Victoni T, Barreto E, Lagente V and Carvalho VF: Oxidative imbalance as a crucial factor in inflammatory lung diseases: Could antioxidant treatment constitute a new therapeutic strategy? Oxid Med Cell Longev 2021: 6646923, 2021.
8. McCall MR and Frei B: Can antioxidant vitamins materially reduce oxidative damage in humans? Free Radic Biol Med 26: 1034-1053, 1999.
9. Traber MG and Stevens JF: Vitamins C and E: Beneficial effects from a mechanistic perspective. Free Radic Biol Med 51: 1000-1013, 2011.
10. Halliwell B: Reactive oxygen species (ROS), oxygen radicals and antioxidants: Where are we now, where is the field going and where should we go? Biochem Biophys Res Commun 633: 17-19, 2022.
11. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG and Gluud C: Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane Database Syst Rev 2012: CD007176, 2012.
12. Rahman I and Adcock IM: Oxidative stress and redox regulation of lung inflammation in COPD. Eur Respir J 28: 219-242, 2006.
13. Forman HJ and Zhang H: Author Correction: Targeting oxidative stress in disease: Promise and limitations of antioxidant therapy. Nat Rev Drug Discov 20: 652, 2021.
14. Wang J, Huang J, Wang L, Chen C, Yang D, Jin M, Bai C and Song Y: Urban particulate matter triggers lung inflammation via the ROS-MAPK-NF-κB signaling pathway. J Thorac Dis 9: 4398-4412, 2017.
15. Chen H, Jia H, Wang W, Cai Q, Sun J and Cui C: Polyphenol-functionalized biosensors for real-time monitoring of oxidative stress and inflammation. Ind Crops Prod 235: 121658, 2025.
16. Fraga CG, Oteiza PI, Hid EJ and Galleano M: (Poly)phenols and the regulation of NADPH oxidases. Redox Biol 67: 102927, 2023.
17. Serreli G and Deiana M: In vivo formed metabolites of polyphenols and their biological efficacy. Food Funct 10: 6999-7021, 2019.
18. Shen Y, Zhang H, Cheng L, Wang L, Qian H and Qi X: In vitro and in vivo antioxidant activity of polyphenols extracted from black highland barley. Food Chem 194: 1003-1012, 2016.
19. Kostenko V, Akimov O, Gutnik O, Kostenko H, Kostenko V, Romantseva T, Morhun Y, Nazarenko S and Taran O: Modulation of redox-sensitive transcription factors with polyphenols as pathogenetically grounded approach in therapy of systemic inflammatory response. Heliyon 9: e15551, 2023.
20. Rudrapal M, Rakshit G, Singh RP, Garse S, Khan J and Chakraborty S: Dietary polyphenols: Review on chemistry/sources, bioavailability/metabolism, antioxidant effects, and their role in disease management. Antioxidants (Basel) 13: 429, 2024.
21. Cione E, La Torre C, Cannataro R, Caroleo MC, Plastina P and Gallelli L: Quercetin, epigallocatechin gallate, curcumin, and resveratrol: From dietary sources to human MicroRNA modulation. Molecules 25: 63, 2019.
22. Wang D, Wang T, Zhang Z, Li Z, Guo Y, Zhao G and Wu L: Recent advances in the effects of dietary polyphenols on inflammation in vivo: Potential molecular mechanisms, receptor targets, safety issues, and uses of nanodelivery system and polyphenol polymers. Curr Opin Food Sci 48: 100921, 2022.
23. Zhu XD, Lei XP and Dong WB: Resveratrol as a potential therapeutic drug for respiratory system diseases. Drug Des Devel Ther 11: 3591-3598, 2017.
24. Tomás-Barberán FA, Selma MV and Espín JC: Interactions of gut microbiota with dietary polyphenols and consequences to human health. Curr Opin Clin Nutr Metab Care 19: 471-476, 2016.
25. Denev P, Kratchanova M, Ciz M, Lojek A, Vasicek O, Nedelcheva P, Blazheva D, Toshkova R, Gardeva E, Yossifova L, *et al*: Biological activities of selected polyphenol-rich fruits related to immunity and gastrointestinal health. Food Chem 157: 37-44, 2014.
26. Arts IC and Hollman PC: Polyphenols and disease risk in epidemiologic studies. Am J Clin Nutr 81 (1 Suppl): 317S-325S, 2005.
27. Del Bo' C, Bernardi S, Marino M, Porrini M, Tucci M, Guglielmetti S, Cherubini A, Carrieri B, Kirkup B, Kroon P, *et al*: Systematic review on polyphenol intake and health outcomes: Is there sufficient evidence to define a health-promoting polyphenol-rich dietary pattern? Nutrients 11: 1355, 2019.
28. Manach C, Williamson G, Morand C, Scalbert A and Rémésy C: Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. Am J Clin Nutr 81 (1 Suppl): 230S-242S, 2005.
29. D'Archivio M, Filesi C, Varì R, Scazzocchio B and Masella R: Bioavailability of the polyphenols: Status and controversies. Int J Mol Sci 11: 1321-1342, 2010.
30. Lippolis T, Cofano M, Caponio GR, De Nunzio V and Notarnicola M: Bioaccessibility and bioavailability of diet polyphenols and their modulation of gut microbiota. Int J Mol Sci 24: 3813, 2023.
31. Emran TB, Eva TA, Zehravi M, Islam F, Khan J, Kareemulla S, Arjun UVNV, Balakrishnan A, Taru PP, Nainu F, *et al*: Polyphenols as therapeutics in respiratory diseases: Moving from preclinical evidence to potential clinical applications. Int J Biol Sci 20: 3236-3256, 2024.
32. Fu YS, Kang N, Yu Y, Mi Y, Guo J, Wu J and Weng CF: Polyphenols, flavonoids and inflammasomes: The role of cigarette smoke in COPD. Eur Respir Rev 31: 220028, 2022.
33. Cory H, Passarelli S, Szeto J, Tamez M and Mattei J: The role of polyphenols in human health and food systems: A mini-review. Front Nutr 5: 87, 2018.
34. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, *et al*: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372: n71, 2021.
35. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, *et al*: RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 366: l4898, 2019.
36. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ and Welch VA: Front matter. In: Cochrane Handbook for Systematic Reviews of Interventions. 1st Edition. Wiley, 2019.
37. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M and Langendam MW: SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol 14: 43, 2014.
38. Cerdá B, Soto C, Albaladejo MD, Martínez P, Sánchez-Gascón F, Tomás-Barberán F and Espín JC: Pomegranate juice supplementation in chronic obstructive pulmonary disease: A 5-week randomized, double-blind, placebo-controlled trial. Eur J Clin Nutr 60: 245-253, 2006.
39. Iraz M, Erdogan H, Kotuk M, Yağmurca M, Kilic T, Ermis H, Fadillioğlu E and Yildirim Z: Ginkgo biloba inhibits bleomycin-induced lung fibrosis in rats. Pharmacol Res 53: 310-316, 2006.
40. Ganesan S, Faris AN, Comstock AT, Chattoraj SS, Chattoraj A, Burgess JR, Curtis JL, Martinez FJ, Zick S, Hershenson MB and Sajjan US: Quercetin prevents progression of disease in elastase/LPS-exposed mice by negatively regulating MMP expression. Respir Res 11: 131, 2010.

41. Şahi˙n M, Yildiz F, Şi˙rvanci S, Ercanb F, Şahinc D, Boyacia H, Başyiğita I and Ilgazli A: Comparison of anti-inflammatory effects of theopylline and resveratrolin in chronic bronchitic rats. Turkiye Klinikleri J Med Sci 31: 559-567, 2011.
42. Hamdy MA, El-Maraghy SA and Kortam MAEA: Modulatory effects of curcumin and green tea extract against experimentally induced pulmonary fibrosis: A comparison with N-acetyl cysteine. J Biochem Mol Toxicol 26: 461-468, 2012.
43. Flores G, Dastmalchi K, Wu SB, Whalen K, Dabo AJ, Reynertson KA, Foronjy RF, D Armiento JM and Kennelly EJ: Phenolic-rich extract from the Costa Rican guava (Psidium friedrichsthalianum) pulp with antioxidant and anti-inflammatory activity. Potential for COPD therapy. Food Chem 141: 889-895, 2013.
44. Panahi Y, Ghanei M, Hajhashemi A and Sahebkar A: Effects of curcuminoids-piperine combination on systemic oxidative stress, clinical symptoms and quality of life in subjects with chronic pulmonary complications due to sulfur mustard: A randomized controlled trial. J Diet Suppl 13: 93-105, 2016.
45. Impellizzeri D, Talero E, Siracusa R, Alcaide A, Cordaro M, Maria Zubelia J, Bruschetta G, Crupi R, Esposito E, Cuzzocrea S and Motilva V: Protective effect of polyphenols in an inflammatory process associated with experimental pulmonary fibrosis in mice. Br J Nutr 114: 853-865, 2015.
46. Zhang M, Xie Y, Yan R, Shan H, Tang J, Cai Y, Yin J, Chen M, Zhang J, Yang X, *et al*: Curcumin ameliorates alveolar epithelial injury in a rat model of chronic obstructive pulmonary disease. Life Sci 164: 1-8, 2016.
47. Wang XL, Li T, Li JH, Miao SY and Xiao XZ: The effects of resveratrol on inflammation and oxidative stress in a rat model of chronic obstructive pulmonary disease. Molecules 22: 1529, 2017.
48. Lu MC, Yang MD, Li PC, Fang HY, Huang HY, Chan YC and Bau DT: Effect of oligomeric proanthocyanidin on the antioxidant status and lung function of patients with chronic obstructive pulmonary disease. In Vivo 32: 753-758, 2018.
49. Han MK, Barreto TA, Martinez FJ, Comstock AT and Sajjan US: Randomised clinical trial to determine the safety of quercetin supplementation in patients with chronic obstructive pulmonary disease. BMJ Open Respir Res 7: e000392, 2020.
50. Singla E, Puri G, Dharwal V and Naura AS: Gallic acid ameliorates COPD-associated exacerbation in mice. Mol Cell Biochem 476: 293-302, 2021.
51. Coco JC, Ataide JA, Sake JA, Tambourgi EB, Ehrhardt C and Mazzola PG: In vitro antioxidant and wound healing properties of baru nut extract (Dipteryx alata Vog.) in pulmonary epithelial cells for therapeutic application in chronic pulmonary obstructive disease (COPD). Nat Prod Res 36: 4469-4475, 2022.
52. Liu S, Huang C, Wu Z, Mei X, Li S, Xing Y, Zhong Y, Mi B, Wang Y and Tang X: Magnolol alleviates inflammation and oxidative stress in COPD via MAPK and Nrf2 signaling pathways. Curr Res Biotechnol 8: 100264, 2024.
53. Zare'i M, Rabieepour M, Ghareaghaji R, Zarrin R and Faghfouri AH: Nanocurcumin supplementation improves pulmonary function in severe COPD patients: A randomized, double blind, and placebo-controlled clinical trial. Phytother Res 38: 1224-1234, 2024.
54. Zhou L, Jian T, Wan Y, Huang R, Fang H, Wang Y, Liang C, Ding X and Chen J: Luteolin alleviates oxidative stress in chronic obstructive pulmonary disease induced by cigarette smoke via modulation of the TRPV1 and CYP2A13/NRF2 signaling pathways. Int J Mol Sci 25: 369, 2023.
55. Jiang C and Somavarapu S: Trehalose-stabilized micelle-in-microparticles of icariin targeting IL-4 pathway in chronic obstructive pulmonary disease. Eur J Pharm Sci 212: 107223, 2025.
56. Min HY, Sim JY, Ahn JH, Kang NW, Boo HJ, Kim J, Yu NY, Bottacin M, Huh J, Park CS, *et al*: Gaylussacin, a stilbene glycoside, inhibits chronic obstructive pulmonary disease in mice. Redox Biol 85: 103744, 2025.
57. Izzi V, Masuelli L, Tresoldi I, Sacchetti P, Modesti A, Galvano F and Bei R: The effects of dietary flavonoids on the regulation of redox inflammatory networks. Front Biosci (Landmark Ed) 17: 2396-2418, 2012.
58. Wang Y, Xu J, Meng Y, Adcock IM and Yao X: Role of inflammatory cells in airway remodeling in COPD. Int J Chron Obstruct Pulmon Dis 13: 3341-3348, 2018.
59. Rodríguez-Pérez J, Andreu-Martínez R, Daza R, Fernández-Arroyo L, Hernández-García A, Díaz-García E, Cubillos-Zapata C, Lozano-Diez A, Morales A, Ramos D, *et al*: Oxidative stress and inflammation in hypoxemic respiratory diseases and their comorbidities: Molecular insights and diagnostic advances in chronic obstructive pulmonary disease and sleep apnea. Antioxidants (Basel) 14: 839, 2025.
60. Morton L and Braakhuis AJ: The effects of fruit-derived polyphenols on cognition and lung function in healthy adults: A systematic review and meta-analysis. Nutrients 13: 4273, 2021.
61. Vrankova S, Cebova M, Klimentova J and Pechanova O: Redox paradox of polyphenols: Bioavailability, hormesis, and safety concerns. Phytother Res 40: 2437-2455, 2026.
62. Gao W, Guo L, Yang Y, Wang Y, Xia S, Gong H, Zhang BK and Yan M: Dissecting the crosstalk between Nrf2 and NF-κB response pathways in drug-induced toxicity. Front Cell Dev Biol 9: 809952, 2022.
63. Li W, Khor TO, Xu C, Shen G, Jeong WS, Yu S and Kong AN: Activation of Nrf2-antioxidant signaling attenuates NFkappaB-inflammatory response and elicits apoptosis. Biochem Pharmacol 76: 1485-1489, 2008.
64. Van Der Vliet A, Janssen-Heininger YMW and Anathy V: Oxidative stress in chronic lung disease: From mitochondrial dysfunction to dysregulated redox signaling. Mol Aspects Med 63: 59-69, 2018.
65. Liu K, Shi M, Li X, Zeng X and Liu X: Curcumin modulates the PTEN/PI3K/AKT pathway to alleviate inflammation and oxidative stress in PM2.5-induced chronic obstructive pulmonary disease. Food Chem Toxicol 201: 115460, 2025.
66. Pan M and Zhou X: Airway remodeling in chronic obstructive pulmonary disease: Characteristics and opportunities. Front Med (Lausanne) 12: 1556868, 2025.
67. Decramer M, Rutten-van Mölken M, Dekhuijzen PR, Troosters T, van Herwaarden C, Pellegrino R, van Schayck CP, Olivieri D, Del Donno M, De Backer W, *et al*: Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (bronchitis randomized on NAC cost-utility study, BRONCUS): A randomised placebo-controlled trial. Lancet 365: 1552-1560, 2005.
68. Wu D, Dong Y, Zhang D, Wang T, Ye H and Zhang W: Efficacy and safety of dietary polyphenol supplements for COPD: A systematic review and meta-analysis. Front Immunol 16: 1617694, 2025.
69. Cazzola M, McDonald VM, Stolz D, Rogliani P and Matera MG: Emerging therapeutics in COPD: Mapping innovation to treatable traits. Lung 203: 92, 2025.
70. Amin F, Roohbakhsh A, Memarzia A, Kazerani HR and Boskabady MH: Immediate and late systemic and lung effects of inhaled paraquat in rats. J Hazard Mater 415: 125633, 2021.
71. Ghorani V, Boskabady MH, Khazdair MR and Kianmeher M: Experimental animal models for COPD: A methodological review. Tob Induc Dis 15: 25, 2017.
72. Narayanan K, Deviani Pakan P, Kokkinis S, Kumar Chellappan D, Chang D, Mutalik S, Kaur IP, Oliver BG, Paudel KR and Dua K: Emerging trends and advances in antioxidant-based plant derived nano formulations in alleviating lung diseases. J Drug Deliv Sci Technol 119: 108131, 2026.
73. Cohen RA, Go LHT and Rose CS: Global trends in occupational lung disease. Semin Respir Crit Care Med 44: 317-326, 2023.
74. Murgia N, Akgun M, Blanc PD, Costa JT, Moitra S, Muñoz X, Toren K and Ferreira AJ: Issue 3-the occupational burden of respiratory diseases, an update. Pulmonology 31: 2416808, 2025.
75. Cullinan P, Muñoz X, Suojalehto H, Agius R, Jindal S, Sigsgaard T, Blomberg A, Charpin D, Annesi-Maesano I, Gulati M, *et al*: Occupational lung diseases: From old and novel exposures to effective preventive strategies. Lancet Respir Med 5: 445-455, 2017.