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## ***Curcuma longa* and curcumin affect respiratory and allergic disorders, experimental and clinical evidence: A comprehensive and updated review**

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### Abstract

*Curcuma longa* and its constituents, mainly curcumin, showed various of pharmacological effects in previous studies. This review article provides updated and comprehensive experimental and clinical evidence regarding the effects of *C. longa* and curcumin on respiratory, allergic, and immunologic disorders. Using appropriate keywords, databases including PubMed, Science Direct, and Scopus were searched until the end of October 2021. *C. longa* extracts and its constituent, curcumin, showed the relaxant effect on tracheal smooth muscle, which indicates their bronchodilatory effect in obstructive pulmonary diseases. The preventive effects of extracts of *C. longa* and curcumin were shown in experimental animal models of different respiratory diseases through antioxidant, immunomodulatory, and anti-inflammatory mechanisms. *C. longa* and curcumin also showed preventive effects on some lung disorders in the clinical studies. It was shown that the effects of *C. longa* on pulmonary diseases were mainly due to its constituent, curcumin. Pharmacological effects of *C. longa* extracts and curcumin on respiratory, allergic, and immunologic disorders indicate the possible therapeutic effect of the plant and curcumin on these diseases.

### Abbreviations

**15d-PGJ2**

15-deoxy-D12,14-prostaglandin J2

**ALI**

acute lung injury

**BCL-2**

B-cell lymphoma 2

***C. longa****Curcuma longa***CAT**

catalase

**COPD**

chronic obstructive pulmonary disorder

**COVID-19**

coronavirus disease-19

**DEN**

diethylnitrosamine

**FEV1**

first second of forced expiration

**GMCSF**

Granulocyte/Macrophage Colony Stimulating Factor

**HRQoL**

health-related quality of life

**IAV**

influenza A virus

**IFN- $\gamma$** interferon- $\gamma$ **LPMP**

large porous microparticle

**LSCC**

lung squamous cell carcinoma

**MCA**

3-methylcholanthrene

**MDA**

malondialdehyde

**MVV**

maximal voluntary ventilation

**NF- $\kappa$ B**

nuclear factor kappa B

**Nrf2**

nuclear factor (erythroid-derived 2)-like 2

**OVA**

ovalbumin

**PEF**

peak expiratory flow

**PGE2**

prostaglandin E2

**ROS**

reactive oxygen species

**SJC**

swollen joint count

**TCID<sub>50</sub>**

tissue culture infectious dose

**TGF- $\beta$**

transforming growth factor-beta

**Th2**

type 2 helper cell

**TJC**

tender joint count

**TNF- $\alpha$**

factor-alpha

**TSM**

tracheal smooth muscle

**UCA1**

urothelial cancer-associated 1

**VC**

vital capacity

**VEGF**

vascular endothelial growth factor

**WBC**

white blood cell

**$\alpha$ -SMA**

$\alpha$ -smooth muscle actin

## 1 INTRODUCTION

Man has been using herbs and plant products for combating diseases since times immemorial. Among plants known for medicinal value, the plants of genus *Curcuma* belonging to the family Scitaminae are significant for their therapeutic potentials. Turmeric, with the scientific name of *Curcuma longa*, is a perennial and herbaceous plant from the family Zingiberaceae that grows in East Asia, such as China and India. *C. longa* showed various health beneficate effects, and it was used as one of the main ingredients for food additives.<sup>1,2</sup> *C. longa* or turmeric is one of the main plants used in traditional Chinese medicine and Indian Ayurvedic medicine. Ample evidence from previous studies indicates that *C. longa* has been used for the treatment of inflammatory diseases, menstrual difficulties, hematuria, hemorrhage, colic, urticarial, skin allergy, viral hepatitis, inflammatory conditions of joints, sore throat, wounds, jaundice, liver disorders, anorexia, rheumatism, diabetic wounds, runny nose, cough, and sinusitis as well as asthma, allergic, gastric, hepatic, gynecological, and infectious diseases.<sup>3-6</sup> Different pharmacological effects such as antioxidant,<sup>7</sup> anti-inflammatory,<sup>8</sup> antitumor,<sup>9</sup> antitussive,<sup>10</sup> anti-diabetic,<sup>11</sup> anticonvulsant,<sup>12</sup> and hepatoprotective effects<sup>13</sup> were also shown for *C. longa*. In addition, similar pharmacological and therapeutic effects<sup>14-19</sup> such as antibacterial<sup>20</sup> and antiulcer activities<sup>21</sup> were shown for curcumin as the main constituent of *C. longa*.

In this review article, updated and comprehensive experimental and clinical evidence regarding the effects of *C. longa* and its constituent, curcumin, on respiratory, allergic and immunologic disorders were provided.

### 1.1 Chemical constituents of *C. longa*

*C. longa* contains protein (6.3%), fat (5.1%), minerals (3.5%), carbohydrates (69.4%) and moisture (13.1%).<sup>22</sup> Chemical constituents of *C. longa* such as phenolic compounds, terpenes, fatty acids, and various compounds have been indicated.<sup>23</sup> Gas chromatography–mass spectrometry (GC–MS) analysis of the methanolic extract of *C. longa* showed the presence of 50 compounds, where the major compounds were ar-turmerone, β-sesquiphellandrene, curcuminol, 2-methoxy-4-vinylphenol, cis-β-elemenone, isolongifolol, geranyl-*p*-cumene, β-turmerone, β-curcumene, β-vatirenene, β-caryophyllene, α-curcumene, furanodiene, γ-curcumene, α-turmerone, and α-cedrene.<sup>24</sup> Curcuminoids, including curcumin, demethoxycurcumin, and bisdemethoxycurcumin, are the major polyphenolic compounds in turmeric rhizomes.<sup>25</sup> Curcumin, as the main constituent of *C. longa* was discovered main coloring principle of *C. longa* rhizome in the 19th century.<sup>22</sup> Curcumin is usually a mixture of three curcuminoids. For example, the composition of a commercial “curcumin” is about 71.5% curcumin (curcumin I), 19.4% demethoxycurcumin (curcumin II), and 9.1% bisdemethoxycurcumin (curcumin III).<sup>26</sup> Different chemical constituents of *C. longa* are indicated in Table 1.

TABLE 1. Different constituents of *Curcuma longa*

| Chemical                | Constituents                                                                                                                                                                                                                                                                              | References |
|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Phenolic compounds      | Diarylheptanoids, diarylpentanoids, phenylpropenes, vanillic acid, and vanillin                                                                                                                                                                                                           | 23         |
| Terpenes                | Monoterpenes, sesquiterpenes, diterpenes, and triterpenoids                                                                                                                                                                                                                               | 23         |
| Fatty acids             | Linoleic acid, 8,11-octadecadienoic acid, methyl ester, palmitic acid (n-hexadecanoic acid), oleic acid and stearic acid), steroids (β-sitosterol, stigmasterol, gitoxygenin and 20-oxopregn-16-en-12-yl acetate                                                                          | 23         |
| Miscellaneous compounds | Curcuma-J, 2-(20-methyl-10 -propenyl)-4, 6-dimethyl-7-hydroxyquinoline, 2,3,5-trimethylfuran, (1,2,3-trimethyl-cyclopent-2-enyl)-metha nol, dicumyl peroxide, 1-(3-cyclopentylpropyl)-2,4-dimethy-benzene, 1,4-dimethyl-2-(2-methylpropyl)-benzene, cyclohexyl formate and methyl eugenol | 23         |

## 2 METHODS

Experimental and clinical studies regarding the effect of *C. longa* and curcumin on

respiratory, allergic, and immunologic disorders were searched using online databases such as PubMed, Science Direct, and Scopus until the end of October 2021. For this purpose, keywords including (*Curcuma longa*, *C. longa*, or turmeric), (curcumin), and (respiratory, pulmonary or lung diseases) were used. Furthermore, the effects of the plant and curcumin on obstructive pulmonary disorders (COPD), asthma, bronchitis, lung disorders induced by noxious agents, lung cancer, lung infection, and allergic disorders were covered in the present review article.

The inclusion eligibility criteria in this review were: (1) in vitro, animal and human studies, (2) the interventions related to *C. longa* and curcumin supplementation, (3) use of *C. longa* and curcumin alone or in combination with other compounds for the treatment of respiratory disorders, (4) the effect of *C. longa* and curcumin on respiratory and allergic disorders, and (5) articles published in English language. The exclusion criteria in this review were: (1) the interventions unrelated to *C. longa* and curcumin, (2) the effect of *C. longa* and curcumin on other diseases, and (3) articles published in a non-English language. A total of 164 articles were selected and reviewed from the above databases based on the above inclusion and exclusion criteria.

## 3 RESULTS

### 3.1 Possible bronchodilatory or relieving effects

#### 3.1.1 *C. longa* extracts and essential oil

##### ***Experimental evidence***

The relatively potent relaxant effects of *C. longa* extract were shown on tracheal smooth muscle (TSM) pre-contracted by methacholine or KCl in nonincubated or incubated tissues with different substances. In tissues incubated with propranolol, diltiazem, L-NAME, glibenclamide, atropine, chlorpheniramine, indomethacin, and papaverine, the hydro-ethanolic extract of *C. longa* showed significant concentration-dependent relaxant effects. The relaxant effects of *C. longa* were comparable to those of theophylline, which could be due to the presence of methylxanthines or its possible interaction with the nonadrenergic noncholinergic nervous system.<sup>27</sup>

In rabbit TSM, *C. longa* crude extract concentration-dependently inhibited the carbachol (1  $\mu$ M) and high K<sup>+</sup> (80 mM)-induced contractions.<sup>28</sup> Hydro-ethanolic extract of *C. longa* decreased tracheal responsiveness (TR) to methacholine and ovalbumin (OVA) in OVA-sensitized rats, which was similar or even more than the effect of dexamethasone.<sup>29</sup>

##### ***Clinical evidence***

In a randomized, double blind, placebo-controlled clinical trial, patients with asthma received 30 mg/kg/day of *C. longa* for 6 months. Administration of powdered *C. longa* roots did not affect the expiratory volume in the first second of forced expiration (FEV1) in

children and adolescents with persistent asthma. However, the results showed better control of asthma, less use of short-acting  $\beta$ -adrenergic agonists, and frequent nocturnal awakenings in the treated group.<sup>30</sup>

### 3.1.2 Curcumin

#### *Experimental evidence*

The reports indicated a relatively potent relaxant effect of curcumin on TSM, which was less marked than the effect of theophylline. A significant difference was observed in  $EC_{50}$  between atropine-incubated and nonincubated tissues, indicating the contribution of muscarinic receptor inhibition in the relaxant effect of curcumin in TSM.<sup>31</sup>

In isolated rabbit trachea, *C. longa* fractions, petroleum spirit (Cl.Pt) and aqueous (Cl.Aq), as well as curcumin relaxed the carbachol (1  $\mu$ M) and high  $K^+$  (80 mM)-induced contractions. In this study, Cl.Aq showed similar potency to that of the plant crude extract, whereas Cl.Pt showed 5–15 times less potency than the plant crude extract. Moreover, more than 10 times more selectivity was seen for the inhibitory effect of curcumin against  $K^+$ -induced TSM contractions.<sup>28</sup>

In OVA-sensitized mice, the prophylactic treatment of curcumin decreased airway resistance (Raw) during methacholine-induced constriction.<sup>32</sup> In a similar study, treatment with curcumin 24 h before allergen challenge inhibited OVA-induced airway hyperreactivity in mice.<sup>33</sup> Curcumin showed preventive effects on TR in asthmatic rats by the significant reduction of TR to methacholine and OVA.<sup>34</sup> In a guinea pig model of airway hyperresponsiveness, curcumin treatment significantly inhibited OVA-induced airway constriction and airway hyperreactivity.<sup>35</sup> The effect of curcumin on airway responsiveness may also indicate its relaxant property on TSM.

The effect of curcumin on the pharmacokinetics of theophylline was investigated in rabbits. For combined treatment, the rabbits were fed with freshly prepared curcumin solution at a dose of 200 mg/kg in glycofurol before theophylline administration (25 mg/kg). Curcumin only increased the absorption half-life of theophylline, and other pharmacokinetic parameters were not affected. It indicated that co-administration of curcumin delayed the onset of theophylline but would not result in the acute intoxication of theophylline.<sup>36</sup>

#### *Clinical evidence*

Oral administration of a soft gelatin capsule containing 15 mg of curcumin (from *C. longa*, 2.2% curcumin) significantly increased FEV1% and peak expiratory flow rate (PEFR) in 63 asthmatic patients aged 18–60 years with at least a 1-year history of bronchial asthma.<sup>37</sup> In patients with mild to moderate bronchial asthma, curcumin therapy resulted in a significant improvement in the mean FEV1 values without any adverse effect.<sup>38</sup> In 23 patients with chronic bronchial asthma, curcumin supplementation produced a significant increase in the values of FEV1, FVC, and peak expiratory flow (PEF) compared with values in patients

receiving standard bronchial asthma therapy. The ratio of FEV1/FVC was also increased by 12.7% in patients on curcumin supplementation.<sup>39</sup>

In a preliminary clinical study, 15 adult patients with stable and persistent asthma with evidence of allergic sensitization were randomly received curcumin (1000 mg, twice daily) or placebo for 6 months. The treatment did not affect post-bronchodilator FEV1 (primary endpoint) and rescue use of bronchodilators.<sup>40</sup>

In 20 patients with purulent septic lung injury, treatment with curcumin capsules significantly increased vital capacity (VC), maximal voluntary ventilation (MVV), and FEV1 levels.<sup>41</sup>

Overall, in vitro and in vivo experimental studies showed the relaxant effects of *C. longa* extracts and curcumin on methacholine, OVA, KCl, or carbachol-induced TSM constriction or airway hyperreactivity. Calcium channel blocking or potassium channel opening properties of curcumin may be responsible for TSM relaxation. In addition, curcumin increased the absorption half-life of theophylline in rabbits. These results demonstrated that *C. longa* and curcumin are effective in relieving airway obstruction in experimental studies. Moreover, clinical studies showed that treatment of asthmatic patients with *C. longa* and curcumin increased PFT values indicating their bronchodilatory effect in obstructive pulmonary disease.

Whereas all experimental and most clinical studies suggested that curcumin can be used as a bronchodilator agent in the treatment of obstructive pulmonary disorders, two clinical studies demonstrated that *C. longa* extracts and curcumin treatment did not affect post-bronchodilator FEV1 and rescue use of bronchodilators. Therefore, more detailed clinical studies are needed to clarify this discrepancy. The bronchodilatory effects of *C. longa* and curcumin and their possible mechanisms are summarized in Table 2 and Figure 1.

TABLE 2. The possible bronchodilatory effects of *Curcuma longa* and curcumin

| Study type | Study design | Preparations            | Dose                         | Effects                                                                                         | References |
|------------|--------------|-------------------------|------------------------------|-------------------------------------------------------------------------------------------------|------------|
| Exp.       | Rat TSM      | Hydro-ethanolic extract | 6.25, 12.5, 25, and 50 mg/ml | Relaxant effect on precontracted TSM, effect on nonadrenergic and noncholinergic nervous system | 27         |
|            | Rabbit TSM   | Crude extract           | 0.03–0.3 mg/ml               | Inhibition of carbachol and high K <sup>+</sup> -induced TSM contractions                       | 28         |

| Study type | Study design | Preparations | Dose                       | Effects                                                                                                                 | References         |
|------------|--------------|--------------|----------------------------|-------------------------------------------------------------------------------------------------------------------------|--------------------|
|            | Rat TSM      | Curcumin     | 12.5, 25, 50 and 100 mg/ml | Relaxant effect on KCl-induced TSM contraction<br><br>Increased methacholine EC <sub>50</sub> in atropine-incubated TSM | <a href="#">31</a> |
|            | Rabbit TSM   | Cl.Pt        | 0.003–3 mg/ml              | Relaxant effect on carbachol and high K <sup>+</sup> -induced TSM contractions                                          | <a href="#">28</a> |
|            |              | Cl.Aq        | 0.003–3 mg/ml              |                                                                                                                         |                    |

Abbreviations: BID, 2 times/day; Cl.Aq, curcumin aqueous spirit; Cl.Pt, curcumin petroleum spirit; Clin., clinical; Exp., experimental; FEV1/FVC: the ratio of forced expiratory volume in 1 s to forced vital capacity; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MVV, maximal voluntary ventilation; OVA, ovalbumin; PEF, peak expiratory flow; PEFR, peak expiratory flow rate; Ref, reference; TID, 3 times/day; TR, tracheal responsiveness; TSM, tracheal smooth muscle; VC, vital capacity.

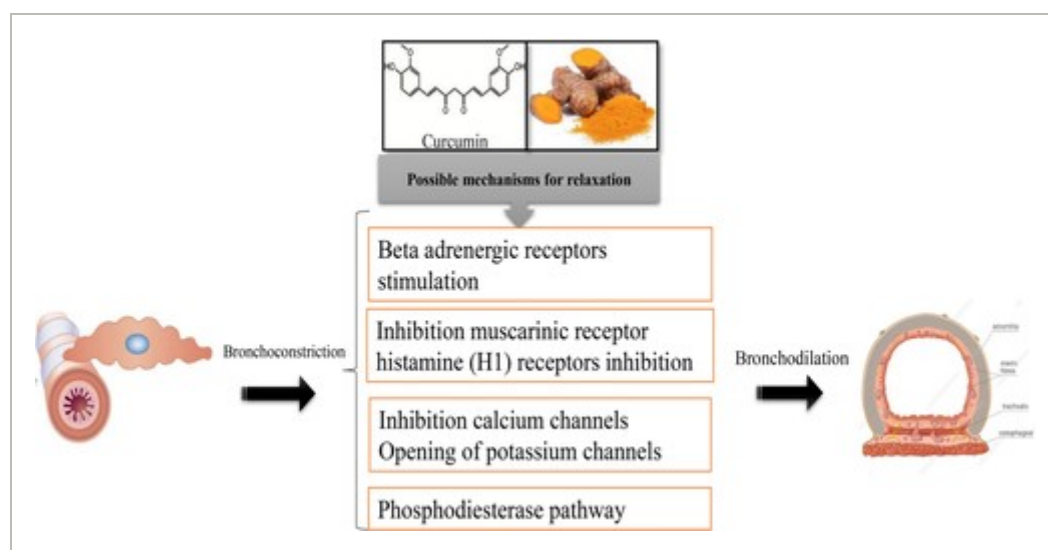


**FIGURE 1**

[Open in figure viewer](#) | [Download PowerPoint](#)

Possible mechanisms of the relaxant effect of *Curcuma longa* and curcumin on tracheal smooth muscles

## 3.2 Preventive effects on asthma

### 3.2.1 *C. longa* extracts and essential oil

#### *Experimental evidence*

Administration of *C. longa* (0.75, 1.50, and 3.00 mg/ml) and curcumin (0.15, 0.30, and 0.60

mg/ml) decreased nitrite (NO<sub>2</sub>), nitrate (NO<sub>3</sub>), and malondialdehyde (MDA) levels, as well as total and differential white blood cell (WBC), counts and enhanced superoxide dismutase (SOD) and catalase (CAT) activities and thiol level in asthmatic rats.<sup>42</sup> Hydro-ethanolic extract *C. longa* (150, 300, and 600 mg/kg/day) markedly improved pathological changes 20%–70%, such as interstitial fibrosis, and decreased TR in OVA-sensitized rats.<sup>29</sup>

The administration of *C. longa*, *Zingiber officinale*, and *Alpinia galangal* combination as capsules (62.5, 125, and 250 mg/kg) suppressed the accumulation of total WBC and eosinophils neutrophils and lymphocytes and inhibited IgE and showed a bronchodilatory effect in OVA-sensitized mice.<sup>43</sup> *C. longa* (0.75, 1.50, and 3.00 mg/ml) reduced eosinophils, neutrophils, and monocytes inflammatory cells, indicating this plant's anti-inflammatory effect. Total and differential WBC in the blood, as well as TR to methacholine and OVA, were also reduced by *C. longa*, indicating its anti-inflammatory properties in a rat model of asthma.<sup>44</sup> Administration *C. longa* extract (100 mg/kg) for 16 days, inhibited IgE, IgG1, and mMCP-1 levels, reduced type 2 helper cell (Th2)-related cytokines and enhanced a Th1-related cytokine in an OVA-induced allergic asthma animal model.<sup>45</sup> The levels of IgE, IgG1, IL-4, IL-17A, IFN- $\gamma$ , Granulocyte/Macrophage Colony Stimulating Factor (GM-CSF), and Th1 were decreased by oral administration of *C. longa* rhizoma in asthmatic mice.<sup>46</sup> Treatment with *C. longa* (0.75, 1.50, and 3.00 mg/ml) in a rat model of asthma reduced WBC count, NO<sub>2</sub>, NO<sub>3</sub>, and MDA levels but increased SOD, CAT activities, and thiol level.<sup>47</sup> *C. longa* (0.75, 1.50, and 3.00 mg/ml) also improved total and differential WBC count, inflammatory mediators such as phospholipase A2 (PLA2) and total protein (TP), oxidative stress markers including NO<sub>2</sub>, NO<sub>3</sub>, MDA, SOD, CAT, and thiol well as IFN- $\gamma$ , IL-4, and IgE levels in the BALF of rats model of asthma.<sup>48</sup>

### Clinical evidence

Administration of *C. longa* (30 mg/kg/day) for 6 months reduced frequent nighttime awakenings and frequent use of short-acting  $\beta$ -adrenergic agonists in asthmatic patients.<sup>30</sup>

## 3.2.2 Curcumin

### Experimental evidence

Treatment with curcumin (5 mg/kg) regulated IgE, EPO, IL-4, and IL-5 levels in the BALF and also reduced airway smooth muscle thickening and mucus secretion in an asthma model of mice.<sup>49</sup> Reactive oxygen species (ROS) in the BALF, serum NO<sub>2</sub> level, the phosphorylation of c-Jun N-terminal kinases (JNK), ERK1/2, p38, COX-2 expression, and nuclear factor kappa B (NF- $\kappa$ B) activation of lung tissue were reduced in asthmatic rats by intranasal administration of curcumin.<sup>50</sup> Curcumin (200 mg/kg) improved airway inflammation and inhibited Notch1–GATA3 signaling pathway in asthmatic mice.<sup>51</sup> Treatment with curcumin activated Wnt/ $\beta$ -catenin signaling pathway and decreased inflammation factors in the BALF of mice model of asthma.<sup>52</sup> Administration of curcumin reduced eosinophil count, recovered IL-17A level, increased IL-10 level in the BALF, and improved histological changes in the lung tissue, and balanced Treg/Th17 I ratio in OVA-induced animal model of asthma.<sup>32</sup> Curcumin-solid lipid

nanoparticles (curcumin-SLNs) suppressed the expression of Th2-type cytokines in the BALF in a rat model of asthma.<sup>53</sup> Treatment with curcumin (10 and 20 mg/kg) improved pathological changes in the chronic asthma model.<sup>54</sup> The expression of pro-inflammatory parameters such as IL-6, IL-8, IL-1 $\beta$ , and factor-alpha (TNF- $\alpha$ ) in immortalized human airway basal cell line were improved by treatment with curcumin encapsulated in niosomes (Nio-Curc).<sup>55</sup> Administration of curcumin-containing poly(lactic-co-glycolic acid) decreased epithelial hyperplasia and goblet cells in the airway of the murine asthma model.<sup>56</sup> Decreasing in Th2 and Th17 cells, serum levels of IL-4 and IL-13, as well as increasing in the mRNA expression level of M1 macrophage-related inflammatory factors including IL-6, iNOS, and IL-1 $\beta$  were indicated by treatment with curcumin (200 mg/kg) in asthmatic mice.<sup>57</sup> Intranasal administration of curcumin (2.5 and 5.0 mg/kg) improved airway inflammation and airway obstruction mainly by modulating cytokine levels (IL-4, 5, IFN- $\gamma$ , and TNF- $\alpha$ ) and sPLA2 activity, thereby inhibiting PGD2 release and COX-2 expression in the murine model of asthma.<sup>58</sup> Administration of curcumin (2.5  $\mu$ L) suppressed airway inflammation and pulmonary fibrosis, and decreased  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA), MMP-9, and TIMP-1 expression in ovalbumin-induced chronic asthma.<sup>59</sup> MCP-1, MUC5AC, and peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) expression, as well as the phosphorylation of NF- $\kappa$ B p65 and NF- $\kappa$ B p65 DNA-binding activity, were regulated by curcumin in both in vivo and in vitro studies.<sup>60</sup>

### **Clinical evidence**

In a prospective randomized controlled interventional study, 23 asthmatic patients were assigned to receive conventional therapy for asthma plus curcumin capsules for 2 months. The results revealed significant improvement in FEV1 and FEV1/forced vital capacity (FVC) in patients after 2 months.<sup>61</sup> A placebo-controlled, single-blind study on 150 nonsmokers patients with asthma showed an improvement in FEV1% after 3-month treatment with curcumin.<sup>62, 63</sup>

In Asian older adults, increasing levels of curcumins-rich curry intake (at least once monthly) were associated with higher mean adjusted FEV1 and FEV1/FVC%. There were more considerable differences in FEV1 and FEV1/FVC% between curry intake and noncurry intake, especially among current and past smokers. The mean adjusted FEV1 associated with curry intake was 9.2% higher among current smokers, 10.3% higher among past smokers, and 1.5% higher among nonsmokers.<sup>64</sup>

Administration of curcumin capsules in asthmatic patients (1000 mg, for 30 days) significantly improved the mean FEV1 values and hematological parameters.<sup>38</sup> Treatment with curcumin (1000 mg) decreased exhaled NO, serum IgE, total WBC, and blood eosinophils in patients with persistent atopic asthma.<sup>40</sup> Suppression of IL-4, IL-8, and TNF- $\alpha$  levels and increased production of IL-10 were observed in patients with perennial allergic rhinitis.<sup>65</sup>

Based on the findings above, curcumin and *C. longa* affect oxidative damage, inflammation,

and immune system by affecting total and differential WBC counts, IgG, IgE, and suppression of T cells in the asthma model and activation of signaling pathways such as Notch1–GATA3. The airway inflammation was reduced by improvement of several mediators such as IL-4, IL-5, IFN- $\gamma$ , and TNF- $\alpha$  as well as COX enzymes. *C. longa* and curcumin could reduce oxidative damage by decreased MDA and NO levels and increased expression of MCP-1, MUC5AC, PPAR $\gamma$ , and NF- $\kappa$ B p65 DNA-binding activity, and prevent pulmonary function tests. Moreover, the tissue fibrosis was improved by treatment with *C. longa* extract. Therefore, *C. longa* and curcumin might be promising targets in the therapeutic strategy of asthma. Preventive effects of *C. longa* and curcumin and their possible mechanisms on asthma are summarized in Table 3 and Figure 2.

TABLE 3. The effects of *Curcuma longa* and curcumin on asthma

| Study type | Study design                          | Preparations                                                          | Dose                                    | Effects                                                                         | References |
|------------|---------------------------------------|-----------------------------------------------------------------------|-----------------------------------------|---------------------------------------------------------------------------------|------------|
| Exp.       | OVA-sensitized rats                   | Hydro-ethanolic extract                                               | 150, 300, and 600 mg/kg)                | Decreased TR to methacholine and OVA                                            | 29         |
|            | CIMCD in rats, OVA-induced AI in mice | <i>C. longa</i> , <i>A. galanga</i> and <i>Z. officinale</i> extracts | 50, 100 g/g/g<br>250 and 500 mg, 7 days | Protection of mast cell degranulation, inhibition of cell infiltration, and IgE | 43         |
|            | Asthmatic rats                        | Curcumin                                                              | 0.15, 0.30, 0.60 mg/ml, orally          | Decreased TR to methacholine and OVA                                            | 34         |
|            | Asthmatic mice                        | Curcumin                                                              | 50, 100, and 200 mg/kg, orally          | Decreased Raw during methacholine-induced TSM contraction                       | 32         |
|            | Asthmatic mice                        | Curcumin                                                              | 25, 50 mg/kg, 4 times                   | Inhibited OVA-induced TR                                                        | 33         |
|            | Asthmatic guinea pigs                 | Curcumin                                                              | 10, 20, and 40 mg/kg, orally            | Inhibited OVA-induced airway constriction and TR                                | 35         |
|            | Asthmatic rats                        | Ethanolic extract                                                     | 0.75, 1.50, and 3.00 mg/kg              | Decreased NO <sub>2</sub> , NO <sub>3</sub> , and MDA, differential WBC         | 42         |

Abbreviations: AI, airway inflammation; BALF, bronchoalveolar lavage; CAT, catalase; CIMCD, clonidine-induced mast cell degranulation in rats; Clin, clinical; COX, cyclooxygenase; Exp., experimental; FEV1, first second of forced expiration; i.n., intranasal; IFN- $\gamma$ , interferon gamma; IgE, Immunoglobulin E; IL-4, interleukin 4; MDA, malondialdehyde;

mMCP-1, mucosal mast cell protease-1; NF- $\kappa$ B, nuclear factor kappa B; NO<sub>2</sub>, nitrogen dioxide; PGD<sub>2</sub>, prostaglandin D<sub>2</sub>; PLA<sub>2</sub>, Phospholipase A<sub>2</sub>; Raw, airway resistance; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF, tumor necrosis factor; TR, tracheal responsiveness; WBC, with blood cell.

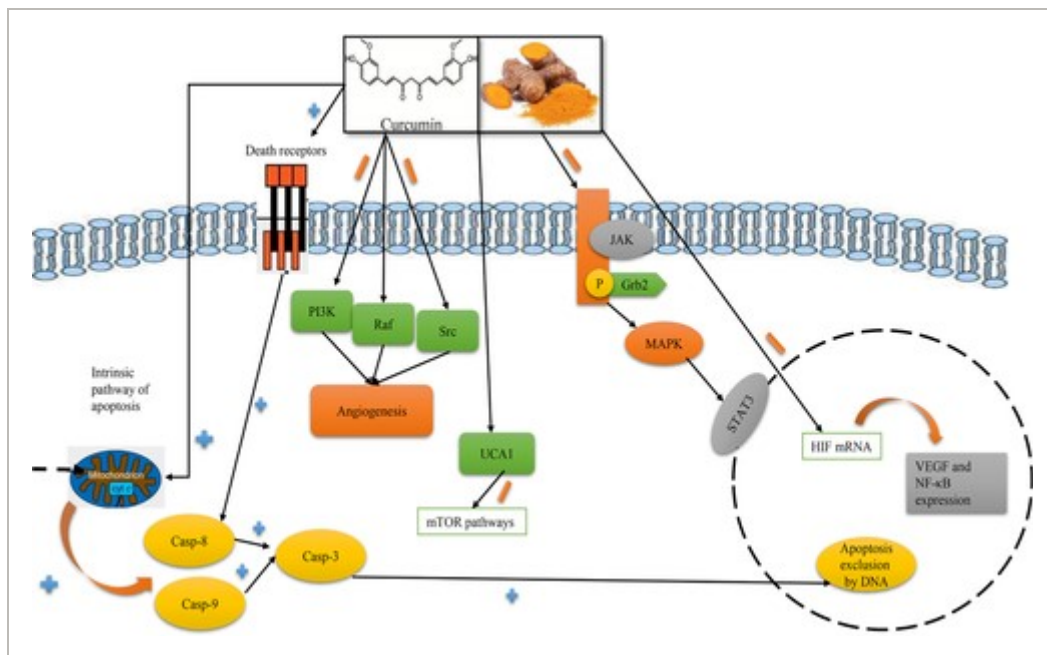


**FIGURE 2**

[Open in figure viewer](#) | [PowerPoint](#)

Possible mechanisms of the preventive effects of *Curcuma longa* and curcumin on asthma, COPD, and noxious agents-induced lung injury

## 3.3 Preventive effects on COPD and chronic bronchitis

### 3.3.1 Curcumin

#### *Experimental evidence*

Administration of curcumin (curcumin 78.1%, demethoxycurcumin 17.7%, and bisdemethoxycurcumin 4.2%) at 0.5% of diet showed a robust biological effect in inhibition of *Hemophilus influenza* (NTHi)-induced COPD-like inflammation and significantly inhibited the increase of the neutrophil chemoattractant keratinocyte-derived chemokine and neutrophils in BALF of wild type (WT) C57BL/6 and CC-LR mice.<sup>66</sup> Curcumin (100 mg/kg) significantly enhanced mitochondrial enzyme activities of cytochrome C oxidase, succinate dehydrogenase, Na<sup>+</sup>/K<sup>+</sup>-ATPase and Ca<sup>2+</sup>-ATPase, mRNA and protein expression of PGC-1 $\alpha$  and SIRT3. It decreased oxidative stress and inflammation by improving the levels of MDA, SOD, glutathione peroxidase (GPx), CAT, IL-6, and TNF- $\alpha$  in a rat model of COPD.<sup>67</sup> Treatment with curcumin alleviated the airway inflammation and airway remodeling via inhibition of the BEAS-2B cells proliferation, suppression of NF- $\kappa$ B and COX-2 expression, and reduced neutrophils and lymphocytes in the BALF of a mouse model of COPD.<sup>68</sup> The in vitro studies

suggested that curcumin (100  $\mu$ M) markedly blocks mRNA expression of IL-8, MCP-1, or MIP-2 $\alpha$  in the AEC II, and this component induces anti-inflammation by modulating HDAC2 expression in the cells of a rat model of COPD.<sup>69</sup> The *in vivo* and *in vitro* experiments demonstrated that treatment with curcumin (2.5, 5, and 7.5  $\mu$ M) improved the CSE-induced cell viability and inflammation via upregulating of PPAR $\gamma$ , inhibiting of NF- $\kappa$ B activation and diminished production of TNF- $\alpha$  and IL-6 in the BALF and serum. Treatment with curcumin (100 mg/kg) improved FEV1/FVC, FRC, MMEF, and PEF cigarette smock (CS)-exposed rats.<sup>70</sup> Curcumin treatment (50, 100, and 150 mg/kg) increased the expression of SIRT1, LC3-I, LC3-II, and Beclin1, and reduced the expression of CHOP and GRP78, promoting autophagy and inhibiting ERS via SIRT1 in a rat model of COPD.<sup>71</sup> Administration of curcumin (100 mg/kg) decreased total and differential WBC counts in the BALF of CS and LPS-induced a rat model of COPD and also markedly reduced IL-6, IL-8, and TNF- $\alpha$  levels in the serum and BALF of rats, and diminished protein expression of p66Shc and p-p66Shc in alveolar epithelia in COPD model cells. Curcumin also ameliorated emphysema and ultrastructural damage of alveolar epithelial cells.<sup>72</sup> Treatment with curcumin (100 mg/kg) significantly inhibited the increase of neutrophils, and macrophages in the BALF, 12 weeks after CS exposure, and decreased inflammation and emphysema in mice.<sup>73</sup>

### **Clinical evidence**

Administration of curcumin in COPD patients reduced free radicals such as SOD and NO, moderated main signaling pathways mediated via NF- $\kappa$ B and mitogen-activated protein kinase pathways, and down-regulated the expression of iNOS, MMP-9, CAMs, IL-8, TNF- $\alpha$ , IL-1b, AKT, p38 mitogenactivated protein kinase, ERK, and PKC matrix metalloproteinases, adhesion molecules, and growth factor receptor genes and up-regulated HDAC2.<sup>74</sup>

Curcuminoids (1500 mg/day)-piperine combination could improve the clinical symptoms and health-related quality of life (HRQoL), increase glutathione, and decrease MDA in patients exposed to sulfur mustard.<sup>75</sup> A clinical study reported that administration of curcumin (for 24 weeks) decreased the levels of atherosclerotic  $\alpha$ 1-antitrypsin-low-density lipoprotein (AT-LDL) in subjects with stages I-II COPD.<sup>76</sup> Curcumin at concentrations up to 1 mM showed antioxidant effects, decreased HDAC2 protein expression, and inhibited MG132 in patients with COPD.<sup>77</sup> Treatment with curcumin improved NF- $\kappa$ B, cytokines (IL-6 and TNF- $\alpha$ ), adhesion molecules (ICAM-1), and enzymes (MMPs) that play a major role in inflammation. These findings indicate that curcumin is an effective component for the treatment of pulmonary disease.<sup>78</sup> Curcumin (10  $\mu$ M) reduced the concentrations of oxygen radicals and IL-8, increased glutathione level, and modulated NF- $\kappa$ B and AP-1 activation in alveolar epithelial cells.<sup>79</sup>

Two clinical studies were indicated that curcumin (500 mg) administration improved the levels of MDA, IL-6, IL-8, TNF- $\alpha$ , transforming growth factor-beta (TGF- $\beta$ ), C-reactive protein, calcitonin gene-related peptide, macrophage chemotactic protein-1, and spirometric parameters such as FVC, FEV1, and FEV1/FVC ratio.<sup>75, 80</sup>

The above findings indicated that treatment with curcumin improved spirometric parameters and downregulated oxidative parameters and inflammatory mediators levels as well as suppressed the expression of different parameters such as CHOP, GRP78, p66Shc, and p-p66Shc but increased the expression of SIRT1, LC3-I, LC3-II, and Beclin1 in COPD models. Administration of curcumin improved pathological damages in the emphysema model and ameliorated epithelial damage. Therefore, curcumin could be a treatment strategy for COPD and similar lung disorders. The preventive effects of curcumin on COPD and chronic bronchitis are summarized in Table 4 and Figure 2.

**TABLE 4.** The effects of *Curcuma longa* and curcumin on COPD and chronic bronchitis disorders

| Study type | Study model                                | Preparations | Dose                                                                 | Effects                                                                                                                                                                                         | References |
|------------|--------------------------------------------|--------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Exp.       | <i>Hemophilus influenza</i> -infected mice | Curcumin     | Curcumin78.1%, demethoxycurcumin 17.7% and bisdemethoxycurcumin 4.2% | Decreased neutrophil chemoattractant keratinocyte-derived chemokine and neutrophils                                                                                                             | 66         |
|            | COPD rats                                  | Curcumin     | 100 mg/kg, orally                                                    | Enhanced mitochondrial enzyme activities, Na <sup>+</sup> /K <sup>+</sup> -ATPase and Ca <sup>2+</sup> -ATPase, mRNA, PGC-1α and SIRT3 expression, improved MDA, SOD, GPx, CAT, IL-6, and TNF-α | 67         |
|            | CS-exposed rats                            | Curcumin     | 100 μM, orally, for 10 days                                          | Blocked mRNA expression of IL-8, MCP-1, or MIP-2α, moduled HDAC2 expression                                                                                                                     | 68         |
|            | CS-exposed rats                            | Curcumin     | 2.5, 5, and 7.5 μM                                                   | Up-regulated PPARγ and inhibited NF-κB                                                                                                                                                          | 69         |

Abbreviations: CAT, catalase; Clin., clinical; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein CSE, cigarette smoke exposure; Exp., experimental; FVC, forced vital capacity; FVC, forced vital capacity; GPx, glutathione Peroxidase; GRP78, binding immunoglobulin protein; GSH, glutathione; HDAC2, histone deacetylase 2; HRQoL, health-related quality of life; i.g., intragastric; IL-6, interleukin 6; MDA, malondialdehyde; NF-κB, nuclear factor kappa-light-

chain-enhancer of activated B cells; PPAR $\gamma$ , peroxisome proliferator-activated receptor gamma; SOD, superoxide dismutase; TGF- $\beta$ , transforming growth factor-beta; TNF, tumor necrosis factor; TNF- $\alpha$ , tumor necrosis factor.

### 3.4 Preventive effects on lung fibrosis and LPS-induced lung injury

#### 3.4.1 *C. longa* extracts and essential oil

##### *Experimental evidence*

Treatment with *C. longa* extract (10–30  $\mu$ g/ml) showed a protective effect on LPS-induced cytotoxicity in Raw 264.7 cells and lung injury in mice with COPD. This effect was demonstrated by reducing accumulation of immune cells and pathophysiological regulation of caspase 3, elastin, and collagen in lung tissues.<sup>81</sup> Administration of hydro-ethanolic extract of *C. longa* (0.75, 1.50, and 3.00 mg/ml) significantly improved the pathological changes from 20% to 70%, including interstitial fibrosis in rats.<sup>29</sup> In addition, lung interstitial fibrosis, lung injury, and inflammatory cell infiltrate were improved by treatment with *C. longa* (300 mg/kg) in mosquito coil smoke-exposure rats.<sup>82</sup>

#### 3.4.2 Curcumin

##### *Experimental evidence*

Reduction of total protein concentration and the number of inflammatory cells in the BALF, pathological changes of lung tissues including pulmonary edema, TNF- $\alpha$  and IL-6 in the serum and the BALF as well as macrophage infiltration, inflammatory gene expression, and MAPKs phosphorylation was observed in LPS-induced rats due to curcumin treatment.<sup>83</sup> Administration of curcumin (200 mg/kg in vivo and 30  $\mu$ M in vitro) diminished the production of TNF- $\alpha$ , MIP-2, and IL-6, and the accumulation of neutrophil in the BALF reduced pulmonary myeloperoxidase levels and the wet/dry weight ratio, and increased AMPK activity through the modulation of CaMKK activity in macrophages in LPS-induced mice.<sup>84</sup> Treatment with curcumin (10 mg/kg) downregulated oxidative stress markers such as NO and MDA levels and upregulated anti-oxidative enzymes such as SOD and CAT in LPS-induced acute lung injury (ALI).<sup>85</sup>

Treatment with curcumin analog C66 (5 and 10 mg/kg) inhibited LPS-induced inflammatory cytokine expression in the BALF, serum, and lung tissue. In vitro results demonstrated LPS-induced production of TNF- $\alpha$  and IL-6 and gene expression of TNF- $\alpha$ , IL-6, IL-1 $\beta$ , and COX-2 were inhibited by the pretreatment with C66. It was found that C66 and SP600125 could inhibit LPS-induced phosphorylation of JNK.<sup>85</sup>

Administration of mono-carbonyl analogs of curcumin (MACs) reduced mRNA expression of TNF- $\alpha$ , IL-6, IL-1 $\beta$ , and VCAM-1 in Beas-2B cells after LPS administration.<sup>86</sup> A novel series of di-carbonyl analogs of curcumin (DACs, 10 mg/kg) potentially inhibited LPS-induced production of TNF- $\alpha$  and IL-6 as suppressed neutrophil infiltration and inhibited the

activation of macrophages by the suppression of MAPK signaling and nuclear translocation of NF- $\kappa$ B in LPS-induced ALI model.<sup>87</sup> Curcumin (1.5, 3.0, and 6.0 mg/kg) improved lung function by increasing PaO<sub>2</sub>, decreasing lung wet/dry weight ratio, upregulation of the PPAR $\gamma$  activity, and expression of HO1 in lung tissues. In addition, it was able to increase the levels of HMGB1, RAGE, TNF- $\alpha$ , IL-6, and TGF- $\beta$ 1 in the BALF and lung tissues and improved the complication of the LPS-induced ALI model of rats.<sup>88</sup> Administration of curcumin (5–20  $\mu$ M) in idiopathic pulmonary fibrosis (IPF) inhibited the TGF- $\beta$  signaling pathway in mice.<sup>89</sup> Treatment with curcumin (200 mg/kg) inhibited the activation of NF- $\kappa$ B, decreased pulmonary inflammatory responses and oxidative stress, and diminished the synthesis of NO and prostaglandin E2 (PGE2) in lung fibrosis of diabetic or LPS-induced rats.<sup>90</sup> Curcumin (300 mg/kg) could suppress the bleomycin (BLM)-induced alveolar macrophage production of TNF- $\alpha$ , superoxide, and NO.<sup>91</sup> Inhalation of curcumin large porous microparticles (LPMPs) significantly decreased lung injury, hydroxyproline contents, and the synthesis of collagen I, and inhibited the expression of TNF- $\alpha$ , TGF- $\beta$ 1, NF- $\kappa$ B p65, and MMP9. LPMPs showed higher anti-fibrotic activity than curcumin powders, and it was an effective component for the treatment of IPF.<sup>92</sup>

### ***Clinical evidence***

Administration of curcumin showed anti-fibrinolysis and apoptosis by downregulation of the p53 PAI-1 expression in alveolar epithelial cells with parallel apoptosis, and it demonstrated a protective mechanism against ALI in patients with IPF.<sup>93</sup>

Treatment with curcumin in paraquat poisoning patients could reduce MMP-9 and TIMP-1 levels, decrease pulmonary fibrosis and delay the progression of the disease and prolong survival time in patients.<sup>94</sup>

Curcumin markedly reduced oxidant levels in the blood and suppressed NF- $\kappa$ B activation and the genes of COX-2, iNOS, MMP-9, IL-8, cell surface adhesion molecules, and anti-apoptotic proteins and cyclin D1 in smoker patients lung epithelial cells.<sup>95</sup>

Curcumin treatment (0–50  $\mu$ M) in patients with lung fibroblasts (CCD-19Lu cells) could promote the ECM-degrading activities of cathepsins, thereby relieving the detrimental accumulation of extracellular matrix, upregulation of cathepsins B and L via stimulation of nuclear PPAR $\gamma$ , activated PPAR $\gamma$  and improved NF- $\kappa$ B, STAT3, nuclear factor (erythroid-derived 2)-like 2 (Nrf2), and COX-2 levels.<sup>96</sup>

Based on the mentioned above studies, administration of curcumin improved pathological changes or damages as well as lung function by increasing PaO<sub>2</sub>. It could relieve cellular parameters and mediate levels of cytokines by activating signaling pathways, including nuclear PPAR $\gamma$ , MAPK, and TGF- $\beta$  pathways. It has been demonstrated that curcumin reduced WBC and inflammatory mediators in the BALF of lung fibrosis model and downregulated expressions of essential genes such as COX-2, iNOS, MMP-9, IL-8, and cell surface adhesion molecules. Therefore, curcumin might be promising targets in the

therapeutic strategy of lung fibrosis and other similar disorders. Preventive effects of *C. longa* and curcumin and their possible mechanisms on lung fibrosis and other similar lung diseases (e.g., LPS-induced lung disorders) are summarized in Table 5 and Figure 2, respectively.

**TABLE 5.** The effects of *Curcuma longa* and curcumin on pulmonary fibrosis and other lung disorders

| Study type | Study model                   | Preparations            | Dose                                 | Effects                                                                                                                              | References |
|------------|-------------------------------|-------------------------|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|------------|
| Exp.       | Mice model of COPD            | <i>C. longa</i> root    | 10–30 µg/ml                          | Reduced immune cells and pathophysiological regulation of caspase 3, elastin, and collagen                                           | 81         |
|            | Interstitial fibrosis in rats | Hydro-ethanolic extract | 150, 300 and 600 mg/kg/day           | Improved pathological changes from 20 to 70% including interstitial fibrosis                                                         | 29         |
|            | LPS-exposed mice              | Curcumin                | 200 mg/kg in vivo and 30 µM in vitro | Diminished TNF-α, MIP-2, and IL-6, neutrophil, pulmonary myeloperoxidase and wet/dry weight ratio                                    | 82         |
|            | LPS-induced ALI mice          | Curcumin                | 10 mg/kg, i.n.                       | Down-regulated oxidative NO and MDA, up-regulated SOD and CAT                                                                        | 85         |
|            | LPS-exposed                   | C66                     | 5 and 10 mg/kg                       | Inhibited TNF-α and IL-6 TNF-α, IL-6, IL-1β, and COX-2 gene expression                                                               | (159)      |
|            | LPS-induced ALI               | DACs                    | 10 mg/kg, i.p, for 6 h               | Decrease TNF-α and IL-6, neutrophil infiltration and inhibited the activation of macrophages and also nuclear translocation of NF-κB | 87         |

Abbreviations: ALI, acute lung injury; CAT, catalase; CCD-19Lu, human lung fibroblasts cells; Clin., clinical; COX, cyclooxygenase; COX-2, cyclooxygenase; DACs, di-carbonyl analogs of curcumin; Exp., experimental; IL-6, interleukin 6; IPF, idiopathic pulmonary fibrosis; LPS, lipopolysaccharide; MDA, malondialdehyde; MIP-2, macrophage inflammatory protein 2; NF-κB, nuclear factor kappa B; NO, Nitric oxide; peroxisome proliferator-activated receptor gamma; PF, pulmonary fibrosis; PGE2, prostaglandin E2; PPARγ; SOD, Superoxide dismutase; STAT3, signal transducer and activator of transcription 3; TGF-β1, transforming growth factor-beta 1.

## 3.5 Therapeutic effects on lung cancer

### 3.5.1 *C. longa* extracts and essential oil

#### *Experimental evidence*

In an in vitro model of lung cancer, the inhibitory effect of n-hexane extract of *C. longa* on telomerase in A549 lung cancer cell line was shown in a dose-dependent manner.<sup>97</sup> Curcuminoids derived from *C. longa* extract significantly decreased the viability/proliferation of lung cancer cells dose-dependently. Crude extract of the plant in combination with cisplatin augmented the decrease in the viability of cancer cells compared with single compound treatment in A549 lung cancer cells. Total extract of *C. longa* could be regarded as being more effective against lung cancer cells in vitro than its separated compounds.<sup>98</sup>

Inhibition of lung cancer cells A549 and H460 by curcuminoid extracts and nanoemulsions prepared from *C. longa* was observed. A dose-dependent increase in cyclin B expression was shown for A549 cells for both treatments, while a reversed trend was found for H460 cells. Both mitochondria and death receptor pathways may be responsible for the apoptosis of both A549 and H460 cells.<sup>99</sup>

### 3.5.2 Curcumin

#### *Experimental evidence*

Curcumin has been reported to possess anti-tumor effects on multiple cancers, including lung cancer.<sup>100</sup> However, the mechanisms of its anti-tumor effect on lung cancer have not been fully elucidated.

Several studies attempted to identify the effect of curcumin on A549 cells and explore its potential mechanism. In nude mice with lung cancer A549 cell subsets side population (SP) and non-SP (NSP) cells, curcumin decreased the tumor weight and size, downregulated the expression of Notch and HIF-1 mRNA, and suppressed the VEGF and NF- $\kappa$ B expression. These results indicated that curcumin inhibits lung cancer growth through the regulation of angiogenesis mediated by VEGF signaling.<sup>101</sup>

It has been suggested that curcumin exhibits its interventional effect on lung cancer stem cells via inhibition of Wnt/ $\beta$ -catenin and Sonic Hedgehog pathways.<sup>102</sup> Curcumin also inhibited Wnt and mTOR pathways through downregulation of urothelial cancer-associated 1 (UCA1),<sup>100</sup> In this way, curcumin inhibited the growth of A549 cells through the downregulation of UCA1. In addition, curcumin inhibited LIN-28A through the activation of miRNA-98 in the lung cancer cell line A549.<sup>103</sup>

Nano-encapsulated curcumin-Fe<sub>3</sub>O<sub>4</sub> and pure curcumin reduced proliferation and hTERT gene expression in the A549 lung cancer cell line. Compared to pure form, nano-encapsulated curcumin caused a further decline in the expression levels of the gene.<sup>104</sup> Furthermore, facile synthetic nano-curcumin encapsulated bio-fabricated nanoparticles

induced ROS-mediated apoptosis and migration blocking of human lung cancer cells.<sup>105</sup>

To assay the effect of curcumin on lung squamous cell carcinoma (LSCC) and its potential mechanisms of action, curcumin was applied to a human NCI-H292 LSCC cell line. Curcumin treatment inhibited human NCI-H292 cells growth by increasing FOXA2 expression via regulation of STAT3 signaling pathways.<sup>106</sup> Curcumin also triggered DNA damage and inhibited expression of DNA-repair-associated proteins in NCI-H460 cells.<sup>107</sup> In addition to inhibition on the proliferation and colony formation of lung cancer cells, curcumin reduced tumorspheres of H460 cells. Moreover, curcumin inhibited JAK2 activity and reduced tumor spheres via inhibiting the JAK2/STAT3 signaling pathway. In a lung cancer xenograft nude mouse model, curcumin strongly repressed tumor growth.<sup>108</sup>

It was shown that curcumin enhanced the inhibitory effect of gefitinib, an epidermal growth factor receptor (EGFR) inhibitor, on primary gefitinib-resistant nonsmall cell lung cancer (NSCLC) cell lines H157 and H1299. The data indicate that the synergism of curcumin on gefitinib was autophagy dependent. Curcumin can be used as a sensitizer to enhance the efficacy of EGFR-TKIs and overcome the EGFR-TKI resistance in NSCLC patients with wild-type EGFR or KRAS mutation.<sup>109</sup>

In small cell lung cancer (SCLC) cells, curcumin inhibited cell proliferation, which was associated with upregulation of the cyclin-dependent kinase inhibitors, p27 and p21, and downregulation of cyclin D1. In addition, curcumin induced the expression of forkhead box protein O1 (FOXO1) through activation of extracellular signal-regulated kinase 1/2 signaling.<sup>51</sup>

Some studies indicated that curcumin potently inhibits the cell growth of NSCLC cells by inducing both apoptosis and autophagy by inhibition of the PI3K/Akt/mTOR pathway<sup>110-113</sup> and involvement of the calcium signaling pathway.<sup>114</sup> In addition, curcumin inhibited the migratory and invasive ability of A549 cells via the inhibition of adiponectin expression by blocking the adiponectin receptor 1. Curcumin treatment also inhibited the in vivo tumor growth of A549 cells and adiponectin expression. The effect of curcumin in decreasing the migratory and invasive ability of A549 cells by inhibiting adiponectin expression is probably mediated through NF- $\kappa$ B/MMP pathways.<sup>115</sup>

The data of the in vitro experiments showed that curcumin converts the lung cancer patient-isolated regulatory T (Treg) to T helper (Th)-1 cells via repressing the gene transcription of forkhead protein-3 (Foxp3) and increasing the expression of interferon- $\gamma$  (IFN- $\gamma$ ). The frequency of peripheral Treg cells was markedly higher in lung cancer patients than that in healthy subjects, which was suppressed after treating with curcumin for two weeks.<sup>116</sup>

It is indicated that oxidative stress is involved in the curcumin-induced reduction of A549 viability.<sup>117</sup> In another similar study, curcumin exerted cytotoxicity dependent on ROS accumulation in NSCLC cells. Curcumin decreased mitochondrial transmembrane potential and induced ROS production, thereby activating the DNA damage/repair pathway and

mitochondrial apoptosis.<sup>118</sup> Furthermore, curcumin could inhibit NSCLC proliferation via the Wnt/ $\beta$ -catenin pathway.<sup>117</sup>

A novel synthetic curcumin derivative MHMM-41 induced ROS-mediated apoptosis and migration blocking of human lung cancer cells A549 was shown, which had better anti-proliferative activity than curcumin in A549 cells.<sup>119</sup>

In an ectopic xenograft model, tumor size and tumor weight were reduced by curcumin treatment. Similarly, in an orthotopic xenograft model, curcumin reduced tumor weight and improved the survival rate of mice. In an in vitro assays, curcumin (30  $\mu$ mol/L) inhibited cell migration and tube formation of NCI-H460 cells. However, transfection with pMXs-Stat3C, a dominant active mutant, could abolish the inhibitory effects of curcumin on the cells, suggesting curcumin inhibited tumor angiogenesis of NCI-H460 cells through the inactivation of STAT3.<sup>120</sup>

In large cell lung carcinoma (LCLC) 801D cell line, low-toxic levels of curcumin could efficiently inhibit migration and invasion of lung cancer cells through inhibition of Rac1/PAK1 signaling pathway as well as MMP-2 and MMP-9 expression.<sup>121</sup>

The effect of curcumin powders inhalation and liposomal curcumin dry powder inhalers (LCDs) on primary lung cancer induced by pulmonary delivery of 3-methylcholanthrene (MCA) and diethylnitrosamine (DEN) in rats was investigated. Findings showed that curcumin powders and LCDs reduced the levels of TNF- $\alpha$  in BALF, MDA, and caspase-3 in lung tissues, and the expression of VEGF, and B-cell lymphoma 2 (BCL-2), as well as improved histopathological changes. However, the anticancer effects of LCDs were higher than curcumin powders.<sup>122</sup>

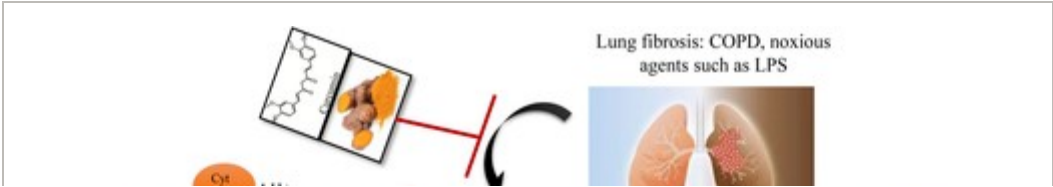
Extensive in vitro and in vivo studies documented that *C. longa* and curcumin attenuate cancer cell proliferation and promote apoptosis in different cancer cell lines. Apart from transcription factors and apoptosis, emerging studies shed light on latent targets of curcumin against EGFR, microRNAs (miRNA), autophagy, and cancer stem cells. These studies suggested the therapeutic effect of *C. longa* and supported the potential use of curcumin as a novel candidate in the treatment of human lung cancer.

The effect of curcumin on inhibiting cancer has been recognized, but the mechanism remains elusive. Curcumin has been demonstrated to interact with multiple molecules and signal pathways, which makes it a potential adjuvant anticancer agent to chemotherapy. Curcumin could be effective in treating cancers by regulating oncogenes such as p53, egr-1, c-myc, bcl-XL, transcription factors like NF- $\kappa$ B, STAT-3, and AP-1; protein kinases like MAPK; and enzymes like COX and LOX. Curcumin could also show synergism to chemotherapy. Therefore, EGFR-, miRNA-, autophagy- and cancer stem cell-based therapy in the presence of curcumin might be promising mechanisms and targets in the therapeutic strategy of lung cancer. The effects of *C. longa* and curcumin and their possible mechanisms on lung cancer are summarized in Table 6 and Figure 3, respectively.

TABLE 6. The effects of *Curcuma longa* and curcumin on lung cancer

| Study type | Study design                                 | Preparations       | Dose                             | Effects                                                                                                                                         | References |
|------------|----------------------------------------------|--------------------|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Exp.       | A549 lung cancer cell line                   | N-Hexane extract   | 0.028–0.199 mg/ml                | Inhibited telomerase activity                                                                                                                   | 97         |
|            | A549 lung cancer cell line                   | Total extract, VCF |                                  | Reduced viability/proliferation of cancer cells                                                                                                 | 98         |
|            | A549 and H460 lung cancer cell lines         | VCF                | 0.1, 0.5, 1, 5, 10, and 15 µg/mL | Increased cyclin B expression, A549 cells, caspase-3, caspase-8, and caspase-9 activities, cytochrome C expression, decrease in CDK1 expression | 99         |
|            | Lung cancer subsets SP and NSP cells in mice | Curcumin           | 100 mg/kg, for 8 days            | Decrease in tumor weight and size, downregulated Notch and HIF-1 mRNA expression, inhibited of VEGF and NF-κB expression                        | 101        |
|            | A549 and H1299 lung cancer cell lines        | Curcumin           |                                  | Reduced tumorsphere formation, number of CD133-positive cells, lung CSC markers expression, induced apoptosis, suppressed Met/EGFR activation   | 102        |

Abbreviations: BID, 2 times/day; BRCA1, breast cancer susceptibility gene-1; CP, curcumin powders; DEN, diethylnitrosamine; EOX, Etopic and orthotopic xenograf Exp., experimental; FCEBFNP, Facile synthetic nano-curcumin encapsulated Bio-fabricated nanoparticles; FOXO1, forkhead box protein O1; Foxp3, forkhead protein-3; i.h., inhaler; IFN-γ, interferon-γ; IP3R, inositol 1,4,5-trisphosphate receptor; LCLC, large cell lung carcinoma; LCP, liposomal curcumin dry powder; LSCC, lung squamous cell carcinoma; MCA, 3-methylcholanthrene; MDC1, mediator of DNA damage checkpoint-1; MGMT, O6-methylguanine-DNA methyltransferase; mTOR, mammalian target of rapamycin; NCF, Nanoencapsulated curcumin-Fe<sub>3</sub>O<sub>4</sub>; NSCLC, nonsmall-cell lung cancer; PI3K, phosphatidylinositol 3-kinase; QD, once a day; Th1, T helper-1; Treg, regulatory T; VCF, various curcumin formulations.



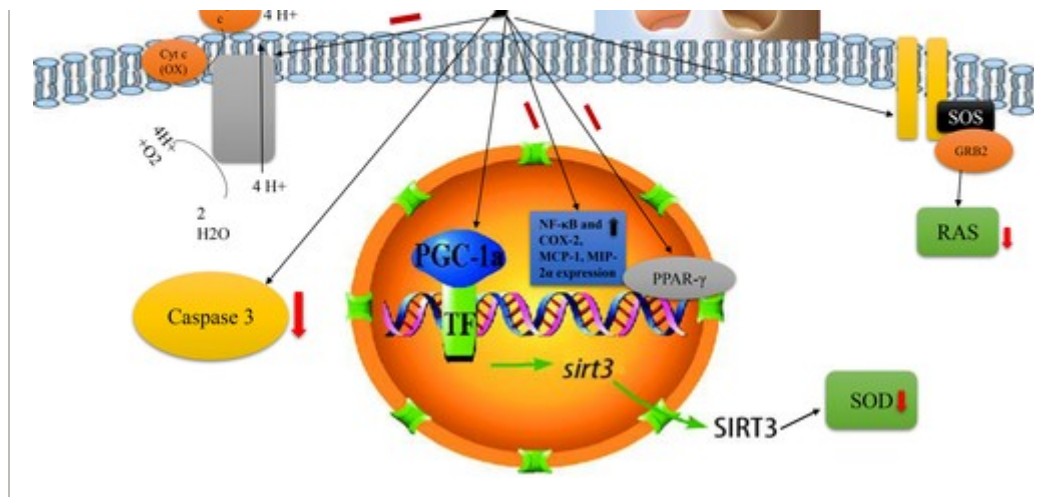


**FIGURE 3**

[Open in figure viewer](#) | [PowerPoint](#)

Possible mechanisms of the preventive effects of *Curcuma longa* and curcumin on lung cancer

## 3.6 Therapeutic effects on lung infections

### 3.6.1 *C. longa* extracts and curcumin

#### *Experimental evidence*

The isolation and identification of bisabolane-type sesquiterpenoids from *C. longa*, and their antiviral activity against H1N1 was investigated in vitro. The findings indicated that these compounds could inhibit the expression of inflammatory cytokines induced by the virus and regulate the activity of NF-κB/MAPK and RIG-1/STAT-1/2 signaling pathways in vitro.<sup>123</sup>

### 3.6.2 Curcumin

#### *Experimental evidence*

To investigate the anti-influenza role of curcumin in vitro and in vivo, the effect of curcumin on replication of influenza A virus (IAV) was examined in human lung cancer cell line A549, as well as in a mouse model. Curcumin could inhibit IAV in vitro and alleviate the severity of the disease in the mouse after infection with IAV. Curcumin could also trigger expression of Heme oxygenase-1 in vivo and attenuate IAV-induced injury to the lung tissues. Furthermore, curcumin could regulate immune response following IAV infection by inhibiting the production of local inflammatory cytokines.<sup>124</sup>

In human macrophages or mice infected by IAV, curcumin treatment downregulated cytokines production in a dose-dependent manner. Curcumin inhibited NF-κB signaling pathway via promoting the expression of NF-κ light polypeptide gene enhancer in B-cells inhibitor (IκBα), and inhibiting the translocation of p65 from the cytoplasm to nucleus.<sup>125</sup>

It has been reported that curcumin has a high binding affinity to hemagglutinin (HA), a major capsid glycoprotein of the influenza virus that mediates virus attachment. Curcumin

interacts with hemagglutinin and disturbs the integrity of membrane structure to block virus binding to host cells and prevent IAV entry.<sup>126</sup> In addition, it was found that curcumin directly inactivates various strains of IAV, disturbs their adsorption, and inhibits their replication. Further, curcumin inhibited IAV absorption and replication by activating the Nrf2-hemeoxygenase-1 (HO-1)-axis, a classical anti-inflammatory and antioxidative signaling, which possesses antiviral activity.<sup>127</sup>

Curcumin showed a significant effect on inflammatory markers such as IL-6, IL-10, IFN- $\gamma$ , and MCP-1 in a mouse model of viral-induced acute respiratory distress syndrome. In addition, curcumin significantly inhibited key markers of myofibroblast activation.<sup>128</sup>

The tissue culture infectious dose (TCID<sub>50</sub>) assay showed that the curcumin-modified silver nanoparticles (cAgNPs) have a highly efficient inhibition effect against respiratory syncytial virus infection, giving a decrease of viral titers about two orders of magnitude at the concentration of cAgNPs under which no toxicity was found to the host cells.<sup>129</sup> Finding in vitro demonstrated that curcumin inhibits respiratory syndrome virus by blocking attachment to host cells.<sup>130</sup>

A study on the anti-SARS-CoV activity of 221 phytochemicals revealed that 20  $\mu$ M of curcumin exhibits significant inhibitory effects in a Vero E6 cell-based cytopathogenic effect (CPE) assay. The authors presented evidence for a mild effect of curcumin against SARS-CoV replication and the inhibitory effect of curcumin on SARS-CoV 3CL protease activity, which is essential for the replication of SARS-CoV.<sup>131</sup>

The effect of curcumin on *Klebsiella pneumoniae* B5055-induced lung infection in BALB/c mice showed that curcumin reduced the levels of MPO, MDA, NO, and TNF- $\alpha$  in lung homogenates of mice.<sup>132</sup> Direct delivery of solubilized curcumin into the lungs of C57BL/6 mice inoculated with a lethal dose of *Klebsiella pneumoniae* dramatically diminished pro-inflammatory cytokines IL-1 $\beta$ , IL-6, TNF- $\alpha$  in the BAL cells, the lung and serum of mice with severe pneumonia induced by *Klebsiella*.<sup>133</sup>

In a mouse model of *Staphylococcus aureus*-induced ALI, pretreatment with curcumin markedly attenuated *S. aureus*-induced pneumonia, barrier disruption, lung edema, and vascular leakage. Activation of plasminogen activator inhibitor-1 and infiltration of neutrophils were reduced by curcumin, together with lower levels of proinflammatory cytokines and chemokines.<sup>134</sup> In humanized transgenic mice, expressing either SP-B T or C allele without mouse SP-B gene, bioluminescent labeled *S. aureus* Xen36 (50  $\mu$ L) was injected intratracheally to cause pneumonia. Treatment with curcumin (CMC2.24) significantly reduced mortality, total bacterial flux and lung tissue apoptosis, inflammatory cells, NF- $\kappa$ B expression, and MMPs-2, -9, -12 activities. It is concluded that mice with the SP-B-C allele are more susceptible to *S. aureus* pneumonia than mice with SP-B-T allele; and that CMC2.24 attenuates lung injury, thus reducing mortality.<sup>135</sup>

### **Clinical evidence**

In an open-label nonrandomized clinical trial, the efficacy of nano-curcumin oral formulation (Sinacurcumin soft gel) was evaluated in 21 hospitalized patients with mild to moderate coronavirus disease-19 (COVID-19). After curcumin treatment, most the symptoms, including fever and chills, tachypnea, myalgia, and cough, resolved faster. Moreover, oxygen saturation (SaO<sub>2</sub>) was higher in the treatment group after 2, 4, 7, and 14 days of follow-up and lymphocyte count after 7 and 14 days. Duration of supplemental O<sub>2</sub> use and hospitalization was also meaningfully reduced. In addition, no patient in the treatment group experienced deterioration of infection during the follow-up period.<sup>136</sup>

In a double-blind, randomized, controlled trial, the effect of curcumin administered with piperine (to optimize absorption) was assessed in patients with COVID-19. Treated patients with mild, moderate, and severe symptoms showed early symptomatic recovery, less deterioration, fewer red flag signs, better ability to maintain SaO<sub>2</sub> above 94% on room air, and better clinical outcomes. Furthermore, curcumin/piperine treatment appeared to reduce the duration of hospitalization in patients with moderate to severe symptoms, and fewer deaths were observed in the curcumin/piperine treatment group.<sup>137</sup> The antimicrobial and antivirulence activities of curcumin and its ability to synergize with antibiotics against a clinical *Mycobacterium abscessus* strain (29904), isolated from the bronchoaspirate of a 66-year-old woman admitted to hospital for suspected tuberculosis was evaluated. Curcumin was synergic with amikacin, clarithromycin, ciprofloxacin, and linezolid, to which strain 29904 showed resistance/intermediate susceptibility. Curcumin significantly reduced motility and inhibited 4- and 8-day mature biofilms. Synergistic combinations of curcumin and amikacin induced a general reduction in microbial aggregates and substantial loss in cell viability.<sup>138</sup>

The above experimental studies demonstrated that curcumin can be used as an adjunct therapy along with antibiotics as an anti-inflammatory or immunomodulatory agent in the case of acute lung infection. In addition, the data strongly supported a role for curcumin in modulating the pathogenesis of viral-induced ALI/ARDS in a pre-clinical model, potentially manifested through the alteration of inflammation. Several studies have documented that curcumin disrupts the viral infection process via multiple mechanisms, including directly targeting viral proteins, inhibiting particle production and gene expression, and blocking the virus entry, replication, and budding. Therefore, curcumin has promising anti-inflammatory potential in pneumonia and likely other inflammatory lung infections, demonstrating the importance of optimizing the physicochemical properties of active natural products to optimize their clinical application.

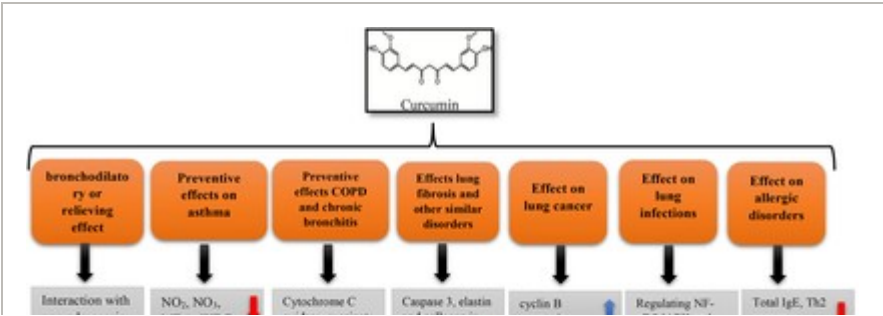
Based on clinical studies, curcumin showed anti-inflammatory, antioxidant, antiviral, anti-thrombotic, and anti-proliferative effects.<sup>137</sup> Therefore, curcumin is proposed as a potential treatment option for COVID-19 by inhibiting the virus entrance, encapsulation and replication, and modulating various cellular signaling pathways. The effects of *C. longa* and curcumin on lung infections (microbial, parasites, and fungi) are summarized in Table 7. Figure 4 also showed preventive effects of *C. longa* and curcumin on respiratory and allergic

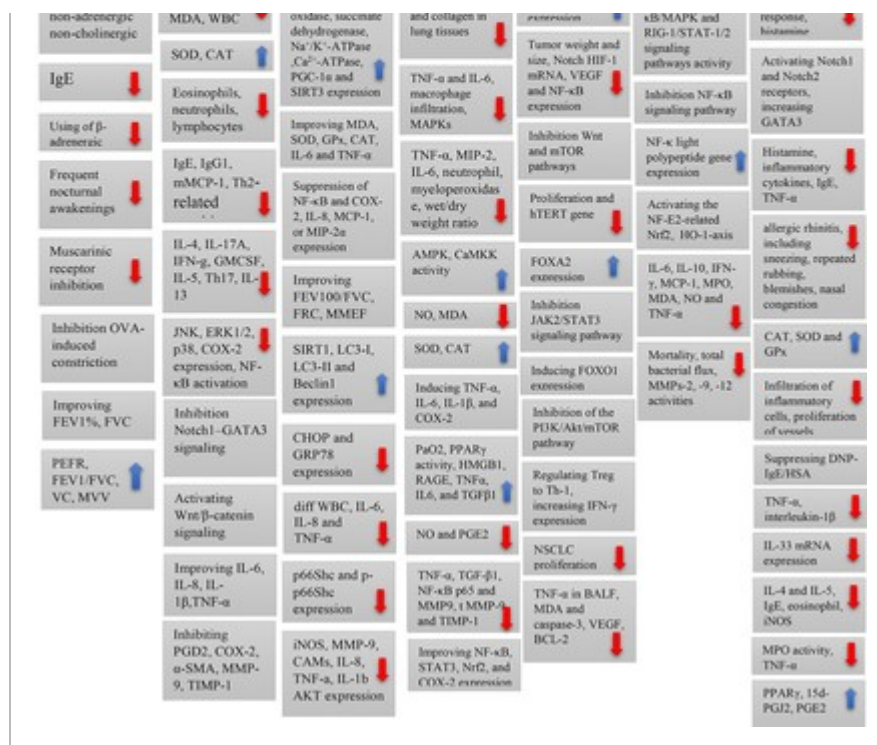
disorders.

TABLE 7. The effects of *Curcuma longa* and curcumin on lung infections

| Study type | Study design           | Preparations                     | Dose    | Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | References |
|------------|------------------------|----------------------------------|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Exp.       | H1N1-induced infection | Bisabolane-type sesquiterpenoids | —       | Inhibited A/PR/8/34 (H1N1) replication in MDCK cells by compounds 2, 11 and 14, A/PR/8/34 (H1N1) replication in A549 cells by compound 2, reduced TNF-α, IL-6, IL-8, and IP-10 production at the mRNA and protein levels in A549 cells by compounds 4, 8, 9, 13 and 17, regulated steroid biosynthesis, oxidative phosphorylation and protein processing in the endoplasmic reticulum by compound 4, inhibited p-NF-κB p65, NF-κB p65, IκBα, p-p38 MAPK, p-IκBα, RIG-1, STAT-1/2 and p-STAT-1/2 expression in the signaling pathways | 123        |
|            | IAV-infected           | Curcumin                         | 0–10 μM | Inhibited IAV in vitro, alleviated                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 124        |

Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; BID, 2 times/day; Clin., clinical; Exp., experimental; IAV, influenza A virus; IκBα, nuclear factor of kappa light polypeptide gene; enhancer in B-cells inhibitor-alpha; NWSCF, Novel water-soluble curcumin formulation; PAI-1, plasminogen activator inhibitor-1; s.c., subcutaneously; SARS-CoV, severe acute respiratory syndrome associated coronavirus.



**FIGURE 4**[Open in figure viewer](#) | [PowerPoint](#)

Preventive effects of *Curcuma longa* and curcumin on respiratory and allergic disorders. AKT, protein kinase B; CAT, catalase; COX-2, cyclooxygenase-2; FEV1, first second of forced expiration; GPx, glutathione peroxidase; GSH, glutathione; IgE, immunoglobulin E; iNOS, nitric oxide synthase; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MMEF, mid-maximum expiratory flow; MMP-9, matrix metalloproteinase 9; NF- $\kappa$ B, nuclear factor kappa-light-chain-enhancer of activated B cells; PEFr, peak expiratory flow; PGD2, prostaglandin D2; PPAR $\gamma$ , peroxisome proliferator-activated receptor gamma; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF- $\alpha$ , tumor necrosis factor; VC, vital capacity; VEGF, vascular endothelial growth factor; WBC, white blood cells

## 3.7 Preventive effects on allergic disorders

### 3.7.1 *C. longa* extracts and essential oil

#### Experimental evidence

The anti-allergic activity of turmeric extract is due to its anti-inflammatory, anti-histamine, and immune system regulating activities. There is a report regarding the therapeutic effect of *C. longa* in treating allergic and inflammatory diseases such as arthritis, bronchitis, and dermatitis. In addition, this plant is effective in improving immune disorders, including allergies.<sup>45</sup>

In a study performed on mice and rats, the anti-allergic activity of *C. longa* at a dose of 500 g was investigated. Release of histamine-induced by compound 48/80 from mast cells significantly inhibited by n-Hexane (Hex), benzene (Benz), ethyl acetate (AcOEt), n-butanol (BuOH), and water extracts of the crude plant. As a result, the suppressive activity of the *C. longa* extract on type I and IV allergies and the strong effects of AcOEt extract has been

observed. Therefore, the anti-allergic activity of *C. longa* may be related to the curcuminoids component of the plant.<sup>139</sup>

### 3.7.2 Curcumin

#### *Experimental evidence*

In an allergy model produced in mice using the fungal allergen *A. fumigatus*, administration of curcumin at a dose of 200 g significantly inhibited the allergic response and suppressed total IgE response. In addition, curcumin reduced the overall Th2 response and inflammatory responses in mice exposed to *A. fumigatus*.<sup>140</sup> Administration of curcumin (20 mg/kg) also reduced allergen-induced airway contraction and histamine hyperactivity in OVA-sensitized guinea pigs.<sup>35</sup>

The anti-allergic properties of curcumin and tetrahydro curcumin (THC) significantly reduced histamine secretion from rat basophilic cells. In addition, anti-allergic activity was mediated by mechanisms related to the antioxidant activity of curcumin compounds.<sup>141</sup>

The protective effect of curcumin (200 mg/kg) on acute airway inflammation in rats with allergic asthma improved the penetration of inflammatory cells in the airways and regulated the levels of Notch1 and Notch2 receptors along with increased GATA3 expression. Prevention of the development and deterioration of allergic airway inflammation following curcumin treatment was associated with inhibition of the Notch1-GATA3 signaling pathway.<sup>51</sup>

A mice model of allergic asthma was treated with two different doses of curcumin (20 and 100 mg/kg) and methylprednisolone from day 21 to day 28. The results showed that administration of curcumin reduced the number of total and differential leukocytes both in the BALF and blood.<sup>142</sup> Administration of curcumin (100 and 200 mg/kg) in allergic responses of OVA-induced allergic rhinitis in mice reduced the releasing of allergic inflammatory mediators such as histamine, inflammatory cytokines, OVA-specific IgE and TNF- $\alpha$ . Curcumin also inhibited histopathological changes in the nasal mucosa and improved the symptoms of rhinitis.<sup>143</sup>

Oral administration of curcumin (100 and 200 mg/kg) in OVA-induced allergic rhinitis in the guinea pig was evaluated. Curcumin reduced the penetration of inflammatory cells and improved the histopathological changes of the nasal mucosa. In addition, the symptoms of allergic rhinitis, including sneezing, repeated rubbing, blemishes, and nasal congestion, are reduced.<sup>144</sup> Treatment with curcumin dissolved in distilled water (200 mg/ml; 20  $\mu$ L per nostril) in a rat model of allergic rhinitis, increased antioxidant activity such as glutathione, CAT, SOD, and GPx in both inferior turbinate tissue and serum leading to reduce oxidative stress and increased oxidative enzyme.<sup>145</sup>

The effects of 4 mg distilled water-soluble curcumin (200 mg/ml solution; 20  $\mu$ L per nostril) on experimental allergic rhinitis showed that the scores of allergy symptoms included

sneezing, nasal rubbing, eye staining, and nasal congestion were significantly reduced compared to the control group. In addition, curcumin reduced the infiltration of inflammatory cells, the proliferation of vessels in the lamina propria, and decreased cup cell metaplasia in the epithelium. As a result, curcumin can be considered as an effective treatment for allergic rhinitis in rats.<sup>146</sup>

Administration of curcumin (100 mg/kg) and bisdemethoxycurcumin (BDMC) (50, 100, and 200 mg/kg) in OVA-sensitive allergic rhinitis mice showed an inhibitory effect on the increased IgE and histamine levels and suppressed the occurrence of nasal rubbing. In addition, BDMC stimulated the release of  $\beta$ -hexosaminidase and granules and suppressed membrane ruffling in monoclonal anti-2,4,6-dinitrophenyl IgE/human serum albumin (DNP-IgE/HSA). The degree of degranulation of intoxicants is also regulated by BDMC.<sup>147</sup>

In adjuvant-induced arthritis (AIA) in rats, the oral administration of curcumin (CM) and CM-loaded Ns (CM-Ns) (50 mg/kg/day for 14 days) decreased the levels of TNF- $\alpha$  and interleukin-1 $\beta$  in both synovial fluid and blood serum.<sup>148</sup>

The obtained data showed that following the placement of inflammatory cells in skin areas and normalization of epidermal thickness, significant regeneration of skin tissue structure occurs. In addition, curcumin regulated cytokine expression in atopic dermatitis in mice and reduced the regulation of IL-33 mRNA expression. Also, treatment with curcumin resulted in redox balance, and the phosphorylation status of P65-NF-kB was restored.<sup>149</sup> The effect of curcumin was evaluated in mice with OVA-induced allergic conjunctivitis. Administration of curcumin (10 or 20 mg/kg) significantly suppressed IgE, eosinophil-mediated inflammation of the conjunctiva, and production of IL-4 and IL-5 in the conjunctiva, spleen, and cervical lymph nodes. In addition, curcumin inhibited the production of activated iNOS following the OVA challenge.<sup>150</sup> These results showed that curcumin suppresses allergic conjunctiva.

Administration of curcumin (50–100 mg/kg) in a rat model of chronic colitis significantly reduced the progression of myeloperoxidase (MPO) activity and TNF- $\alpha$ .<sup>151</sup> Intraperitoneal administration of curcumin (30 mg/kg) for 2 weeks in a rat model of colitis induced by trinitrobenzene sulfonic acid (TNBS) improved the survival rate of rats with colitis and reduced the macroscopic scores of colitis. In addition, curcumin increased the expression levels of PPAR $\gamma$ , 15-deoxy-D12,14-prostaglandin J2 (15d-PGJ2), and PGE2.<sup>152</sup>

In experimental autoimmune encephalomyelitis (EAE) models, which is an animal model of multiple sclerosis (MS), curcumin (100–200 mg/kg) reduced EAE and the number of inflammatory cells penetrating the spinal cord. Curcumin also decreased the lymphocyte proliferation of the myelin basic protein MBP reaction and the expression of IL-17, TGF- $\beta$ , IL-6, IL-21, STAT3, and ROR $\gamma$ t.<sup>153</sup> In addition, the polymeric form of nano-curcumin (PNC) decreased disease score, improved myelination, increased progenitor cell markers, and reduced oxidative stress.<sup>154</sup>

### **Clinical evidence**

Patients with allergic rhinitis received oral curcumin (500 mg daily) for 2 months in a clinical study. The results showed a reduction in sneezing, rhinorrhea, nasal congestion, and airflow resistance in the nose.<sup>65</sup>

In a randomized, double-blind, controlled trial; the effect of curcumin nanomicelle (40 mg) was evaluated in 65 patients with rheumatoid arthritis. Administration of curcumin improved the tender joint count (TJC) and swollen joint count (SJC)<sup>155</sup> and prevented the production and function of TNF.<sup>156, 157</sup> The inhibitory effects of curcumin on human synovial fibroblast growth occurred through induction of apoptosis and inhibition of PGE2 production in rheumatoid arthritis patients.<sup>155</sup> Treatment with curcumin (500 mg) resulted in the highest percentage of improvement in overall Disease Activity Score (DAS) and American College of Rheumatology (ACR) scores in patients with rheumatoid arthritis.<sup>158</sup>

Based on findings above, curcumin showed antihistamine effects by inhibiting histamine secreted by mast cells and basophil leukemia cells. On the other hand, the penetration of inflammatory cells, including plasma cells, lymphocytes, macrophages, and neutrophils were reduced by curcumin, indicating the anti-allergic properties of this agent. The level adjustment of Notch1 and Notch2 receptors were improved by curcumin. It can be stated that the anti-allergic effects of curcumin are related to the antioxidant activity of curcumin compounds. The effects of *C. longa* and curcumin on allergic disorders are summarized in Table 8. The molecular mechanisms of curcumin on respiratory, allergic, and immunologic disorders are shown in Table 9.

**TABLE 8.** The effects of *Curcuma longa* and curcumin on allergic and immunologic disorders

| Study type | Study design                         | Preparations        | Dose             | Effects                                                                 | References |
|------------|--------------------------------------|---------------------|------------------|-------------------------------------------------------------------------|------------|
| Exp.       | Rats                                 | Crude plant extract | 500 g            | Inhibited the histamine secretion from rat peritoneal mast cells        | 139        |
|            | Fumigatus-induced Mice allergy model | Curcumin            | 200 g            | Reduced Th2 and inflammatory responses, total IgE                       | 140        |
|            | OVA-sensitized guinea pigs           | Curcumin            | 20 mg/kg, orally | Reduced allergen-induced airway contraction and histamine hyperactivity | 35         |
|            | Rats                                 | Curcumin            | 100 mg/ml        | Inhibited histamine secretion from rat basophilic leukemia cells        | 141        |

| Study type | Study design                 | Preparations | Dose      | Effects                                                                             | References |
|------------|------------------------------|--------------|-----------|-------------------------------------------------------------------------------------|------------|
|            | Rat model of allergic asthma | Curcumin     | 200 mg/kg | Prevented airway inflammation development, inhibited Notch1-GATA3 signaling pathway | 51         |

Abbreviations: *A. fumigatus*, *Aspergillus fumigatus*; ACR, American College of Rheumatology; AD, atopic dermatitis; AR, allergic rhinitis; BDMC, bisdemethoxycurcumin; Benzene, Benz; *C. longa*, *Curcuma longa*; Clin., clinical; DAS, Disease Activity Score; EAE, encephalomyelitis; Ethyl acetate, AcOEt; Exp., experimental; i.p, intraperitoneally; IgE, Immunoglobulin E; IL, interleukin; iNOS, nitric oxide synthase; iv, intravenous; MPO, myeloperoxidase; MS, multiple sclerosis; n-Buthanol, BuOH; n-Hexane, Hex; OVA, ovalbumin; PGE2, prostaglandin E2; PNC, polymerized nano-curcumin; PPAR $\gamma$ , peroxisome proliferator-activated receptor gamma; RA, rheumatoid arthritis; RDCT, randomized, double-blind, controlled trial; SJC, swollen joint count; Th2, T helper 2; TJC, tender joint count; TNBS, trinitrobenzene sulphonic acid; TNF, tumor necrosis factor.

**TABLE 9.** The molecular mechanisms of curcumin on respiratory, allergic, and immunologic disorders

| Study design | Molecular mechanisms                                                                                                                        | References |
|--------------|---------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Exp.         | Phosphorylation of JNK, ERK1/2, p38, COX-2 expression, NF- $\kappa$ B activation                                                            | 50         |
|              | Inhibited Notch1–GATA3 signaling pathway                                                                                                    | 51         |
|              | Balanced Treg/Th17 I ratio                                                                                                                  | 32         |
|              | Improved the expression of IL-6, IL-8, IL-1 $\beta$ , TNF- $\alpha$                                                                         | 55         |
|              | Increased mRNA expression level of M1 macrophage, IL-6, iNOS, IL-1 $\beta$                                                                  | 57         |
|              | Inhibited sPLA2 activity, PGD2 releasing, COX-2 expression                                                                                  | 58         |
|              | Decreasing $\alpha$ -SMA, MMP-9 and TIMP-1 expression                                                                                       | 59         |
|              | Regulated MCP-1, MUC5AC, PPAR $\gamma$ expression, NF- $\kappa$ B phosphorylation, p65 and NF- $\kappa$ B p65 DNA-binding                   | 60         |
|              | Enhanced CCOSD activities, Na <sup>+</sup> /K <sup>+</sup> + -ATPase, Ca <sup>2+</sup> + -ATPase, mRNA, PGC-1 $\alpha$ and SIRT3 expression | 67         |
|              | Increased SIRT1, LC3-I, LC3-II and Beclin1 expression, reducing CHOP and GRP78 expression                                                   | 71         |

| Study design | Molecular mechanisms | References |
|--------------|----------------------|------------|
|--------------|----------------------|------------|

Abbreviations: AKT, protein kinase B; BCL-2, B-cell lymphoma 2; CCOSD, cytochrome C oxidase, succinate dehydrogenase; Clin., clinical; CSHM, cell surface adhesion molecules; Exp., experimental; FOXO1, forkhead box protein O1; Foxp3, forkhead protein-3; IFN- $\gamma$ , interferon- $\gamma$ ; IL-6, interleukin 6; iNOS, nitric oxide synthase; JNK, c-Jun N-terminal kinases; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MMP-9, Matrix metalloproteinase 9; MPO, myeloperoxidase; NF- $\kappa$ B, nuclear factor kappa B; NF- $\kappa$ B, nuclear factor kappa-light-chain-enhancer of activated B cells; Nrf2, nuclear factor (erythroid-derived 2)-like 2; PGC-1 $\alpha$ , Pparg coactivator 1 alpha; PLA2, phospholipase A2; PPAR $\gamma$ , peroxisome proliferator-activated receptor gamma; TGF- $\beta$ , transforming growth factor-beta; Th1, T helper type 1; TNF- $\alpha$ , factor alpha; UCA1, urothelial cancer associated 1; VCAM-1, vascular cell adhesion protein 1; VEGF, vascular endothelial growth factor;  $\alpha$ -SMA,  $\alpha$ -smooth muscle actin.

## 4 CONCLUSION

This review article shows the potential therapeutic effects of *C. longa* and curcumin on various respiratory disorders, including asthma, COPD, chronic bronchitis, fibrosis, lung cancer, lung infections, and allergic disorders based on experimental and clinical findings. Both experimental and clinical studies suggested that *C. longa* and curcumin could be used as a bronchodilator agent in the treatment of obstructive pulmonary disorders. The preventive or prophylactic effects of *C. longa* and curcumin on various respiratory and allergic disorders were mediated by anti-inflammatory, antioxidant, and immunomodulatory properties. However, further clinical studies of the plant and curcumin on respiratory and allergic disorders are needed to justify their use in clinical practice for the treatment of these diseases.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest in this article.

Open Research



## DATA AVAILABILITY STATEMENT

Data are available by corresponding author in request.

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