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Review

Curcumin use in pulmonary diseases: State of the art and future perspectives

Diana Lelli[a,*], Amirhossein Sahebkar[b], Thomas P. Johnston[c], Claudio Pedone[a]

[a] Area di Geriatria, Università Campus Bio-Medico di Roma, via Alvaro del Portillo 21, 00128 Roma, Italy
[b] Biotechnology Research Center, Mashhad University of Medical Sciences, BuAli Square, Mashhad, 9196773117 Iran
[c] Division of Pharmaceutical Sciences, School of Pharmacy, University of Missouri-Kansas City, 2464 Charlotte Street, Kansas City, MO, 64108,USA

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ABSTRACT

Curcumin (diferuloylmethane) is a yellow pigment present in the spice turmeric (*Curcuma longa*). It has been used for centuries in Ayurveda (Indian traditional medicine) for the treatment of several diseases. Over the last several decades, the therapeutic properties of curcumin have slowly been elucidated.

It has been shown that curcumin has pleiotropic effects, regulating transcription factors (e.g., NF-kB), cytokines (e.g., IL6, TNF-alpha), adhesion molecules (e.g., ICAM-1), and enzymes (e.g., MMPs) that play a major role in inflammation and cancerogenesis.

These effects may be relevant for several pulmonary diseases that are characterized by abnormal inflammatory responses, such as asthma or chronic obstructive pulmonary disease, acute respiratory distress syndrome, pulmonary fibrosis, and acute lung injury. Furthermore, some preliminary evidence suggests that curcumin may have a role in the treatment of lung cancer.

The evidence for the use of curcumin in pulmonary disease is still sparse and has mostly been obtained using either in vitro or animal models. The most important issue with the use of curcumin in humans is its poor bioavailability, which makes it necessary to use adjuvants or curcumin nanoparticles or liposomes.

The aim of this review is to summarize the available evidence on curcumin's effectiveness in pulmonary diseases, including lung cancer, and to provide our perspective on future research with curcumin so as to improve its pharmacological effects, as well as provide additional evidence of curcumin's efficacy in the treatment of pulmonary diseases.

Contents

Abbreviations: AP-1, activator protein 1; BALF, bronchoalveolar lavage fluid; BCL, B-cell lymphoma; CFTR, cystic fibrosis transmembrane conductance regulator; CXCL, chemokine CXC motif ligand; EGR-1, early growth protein 1; FOXO1, forkhead box protein O1; HDAC2, histone deacetylase; HIF-1α, hypoxia-inducible factor 1α; HO-1, haeme oxygenase-1; ICAM, intracellular adhesion molecule; iNOS, inducible nitric oxide synthase; JAK/STAT3, janus kinase/signal transducer and activator of transcription 3; LOX, lipoxygenase; miRNAs, microRNAs; MMPs, matrix metalloproteinases; NF-κB, nuclear factor kappa B; Nrf-2, nuclear factor erythroid 2-related factor 2; TGF-β1, transforming growth factor beta 1; Th-17, T helper 17; TIMPs, tissue inhibitor of matrix metalloproteinases; TNF, tumor necrosis factor; Treg, T regulator; VEGF, vascular endothelial growth factor.

* Corresponding author at: via Alvaro del Portillo 21, 00128 Roma, Italy.
E-mail addresses: d.lelli@unicampus.it (D. Lelli), amir_saheb@yahoo.com (A. Sahebkar), JonstonT@umkc.edu (T.P. Johnston), c.pedone@unicampus.it (C. Pedone).

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1. Introduction

Curcumin is a component of turmeric, which is derived from Curcuma longa and used as a dietary spice and coloring agent. It has been used for centuries in Ayurveda (Indian traditional medicine) and in traditional Chinese medicine to treat several illnesses such as anorexia, hepatic disorders, and arthritis [1].

The biological effects of curcumin are mediated by modulation of several molecular targets through its action on multiple signalling pathways and by its regulation of the expression of several transcription factors, inflammatory cytokines, enzymes, growth factors, receptors, adhesion molecules, antiapoptotic proteins, and cell cycle proteins and their associated anti-inflammatory, antioxidant, and anticancer activity [2]. Furthermore, curcumin is well tolerated in humans [3].

In the last decades the role of curcumin in several diseases, such as inflammatory bowel disease, rheumatoid arthritis, psoriasis, and cancer, has been elucidated [4]. Curcumin may also have a role in respiratory diseases such as chronic obstructive pulmonary disease (COPD) [5], asthma [6], pulmonary fibrosis [7], and acute lung injury [8,9], which are characterized by either chronic inflammation or abnormal inflammatory responses. Additionally, curcumin has been studied in lung cancer.

The aim of this review is to summarize the available evidence on curcumin's effectiveness in pulmonary diseases (see Table 1), including lung cancer, and to provide our perspective on future research on curcumin so as to improve its pharmacological effects, and to provide additional evidence of curcumin's efficacy in the treatment of pulmonary diseases.

2. Biological effects of curcumin

The most important biological effects of curcumin are anti-inflammatory, anti-oxidant, and anti-neoplastic, which are mediated by modulation of several molecular targets such as transcription factors, inflammatory cytokines, and proteins involved in cell replication and survival [2].

In vitro and *in vivo* models show that curcumin's anti-inflammatory effect is mediated by the modulation of several targets; one of the most important is nuclear factor kappa B (NF-κB), a transcription factor that regulates the expression of many genes that are involved in innate and adaptive immunity, and in inflammation [10]. The action on this pathway is of particular importance because NF-κB also regulates the expression of genes involved in cell survival and proliferation, angiogenesis, and, consequently, invasion and metastasis, which play an important role in carcinogenesis [10] (Fig. 1). Downregulation of NF-κB by curcumin is mediated by inhibition of IκBα kinase and AKT, which are needed for NF-κB activation [11]. NF-κB downregulation leads to reduced levels of COX-2 and 5-LOX, which are implicated in prostaglandin synthesis from arachidonic acid (a key feature of inflammation) [12], and to downregulation of inflammatory cytokines such as IL-5 and IL-8 (produced by monocytes, macrophages and lymphatic cells) [13]. Furthermore, curcumin has effects both *in vitro* and in animal models many inflammatory cells; for example, it inhibits the proliferation of lymphocyte T helper (Th) 1 and Th2 cells, with a consequent reduction in IgG secretion [14]. Curcumin also inhibits mast cells, blocks histamine release [15], and acts on neutrophils by downregulating IL-8, which inhibits their migration due to a direct cytotoxic effect. Moreover, curcumin acts on macrophages, with subsequent downregulation of IL-1, IL-6, and TNF-α [4] and

Table 1
Summary of main biological targets of curcumin in pulmonary disease and of available studies on this topic in humans.

Disease	Main targets	Studies in humans
COPD	NF-κB (−)	Yes
	AP-1	n: 2
	Oxidants (−)	
	HO-1 (+)	
	Inflammatory cells in BALF (−)	
	HDAC2 (+)	
Asthma	NF-κB (−)	Yes
	Nrf2/HO-1 pathway (+)	n: 2
	Inflammatory cells (−)	
	Th17 cells (−)	
	Treg cells (+)	
	iNOS (−)	
Pulmonary fibrosis	TGF-β1 (−)	No
	Inflammatory cells (−)	
	iNOS (−)	
	1-OH (+)	
	NF-κB (−)	
	AP-1 (−)	
	Cathepsins (+)	
Cystic fibrosis	CFTR (+)	No
Acute lung injury	Inflammatory cells in BALF (−)	No
	TNF-α, IL-1β, IL-8, IL-6 (−)	
	iNOS (−)	
	NF-κB (−)	
Lung cancer	miRNAs (+/−)	No
	DNA repair proteins (−)	
	JAK/STAT3 (−)	
	FOXO1 (+)	
	EGR-1 (−)	
	MMPs (−)	
	NF- κB (−)	
	HIF-1α (−)	

Abbreviations: +: stimulates; −: inhibits; NF-κB: nuclear factor kappa B; HO-1: haeme oxygenase-1; BALF: bronchoalveolar lavage fluid; HDAC2: histone deacetylase; Nrf-2: nuclear factor erythroid 2-related factor 2; Th-17: T helper 17; Treg: T regulator; iNOS: inducible nitric oxide synthase; TGF-β1: transforming growth factor beta 1; AP-1: activator protein 1; CFTR: cystic fibrosis transmembrane conductance regulator; miRNAs: microRNAs; JAK/STAT3: janus kinase/signal transducer and activator of transcription 3; FOXO1: forkhead box protein O1; EGR-1: early growth protein 1; MMPs: matrix metalloproteinases; HIF-1α: hypoxia-inducible factor 1α