

Airway Inflammation and Asthma Exacerbations: Update on Therapeutic Efficacy of Curcumin

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ABSTRACT

Asthma, a chronic inflammatory respiratory illness, leads to structural alterations in the lungs due to persistent inflammations. Exposure to allergens and variety of environmental triggers, mainly endotoxins and particulate matter (PM10/2.5) exacerbate asthma by enhancing transcription of inflammatory mediators thereby structural alterations and oxidative lung damage. Corticosteroids are effective medications in Th2 mediated asthma with many side effects. Inhaled corticosteroids, the existing therapies, are not advisable in chronic asthmatic cases. Indian system of Ayurvedic medicine is known for therapeutic potential and efficacy, are presently considered as novel strategy against asthma. Curcumin, a phytochemical derived from turmeric, possess wide variety of pharmacological activities with an excellent safety profile. Pre-clinical and clinical studies have shown efficacy of curcumin for targeting transcription factors thereby decreasing inflammatory mediators. Its applications are limited due to rapid metabolization and poor bioavailability through oral route. To overcome bioavailability issue, intranasal route has been selected as a non-invasive route of administration for better absorption with numerous benefits. This article is designed to evaluate possible impacts of intranasal curcumin, as complementary medication to prevent asthma exacerbations induced by various environmental inducers without any side effects.

Index Terms: Air pollution, allergen, asthma, Inflammation, oxidative damage.

I. INTRODUCTION

Asthma, is a chronic, heterogeneous lung disease characterized by airway inflammation, bronchial hyperresponsiveness, and variable airflow obstruction. It is inflammatory and non-communicable disease affecting approximately 300 million people worldwide (Porsbjerg *et al.*, 2023). Inflammation is natural response of our body against injury or infection. It is protective or defence mechanism of body and considered as part of innate immune response. However, prolonged inflammation may be related to diseased condition. Studies suggested central role of inflammation in asthma which stimulates onset and chronicity of the disease (Kudo *et al.*, 2013). Studies suggest that more severe symptoms are reported in countries with low and middle income than those from high income countries due to improper diagnosis, poor health care accessibility, unaffordable therapy, higher exposure to environmental irritants and vulnerability to more severe diseases (Lalloo *et al.*, 2011). As per study in 2019, Global burden of disease (GBD) in India, Uttar Pradesh, Bihar and Odisha are top three states with the highest number of asthmatics

(Vos *et al.*, 2020). In India, asthma prevalence may be associated with age, smoking, household, environmental tobacco smoke exposure etc (Jindal *et al.*, 2012). Asthmatics in India have a high frequency of reported exacerbations (67%) with characteristic features of substantial loss in lung function and emotional limitations resulting in missing work days (Thompson *et al.*, 2013). Highly inflamed airways with inflammatory cell infiltrations have been well described in fatal asthma patients (King *et al.*, 2018; James *et al.*, 2015). In all asthma types, allergic asthma is the most common type affecting a great percentage of population.

II. IMMUNE PATHOGENESIS OF ASTHMA

Inflammation of the airways is the key pathological features and leads to acute and chronic asthma phases which after persistent inflammation leads to airway remodeling. Allergen activated allergic asthma activates T helper 2(Th2) cells to produce cytokines, responsible for airway inflammation (Brusasco *et al.*, 1998; Chung *et al.*, 1999). Inflammation is an essential defence mechanism and the immune system's reaction to stimulations from various sources. Inflammatory stages are divided into two types, acute and chronic, depending on duration of the process and numerous immunological variables (Ward *et al.*, 2010).

Acute inflammation

It is a brief process that lasts a few minutes to a few days where leukocytes translocate into an extravascular area and the release of plasma proteins or fluid, whereas primary inflammatory cells in the tissue, produce inflammatory cytokines, growth factors, and enzymes in chronic inflammation (Arulselvan *et al.*, 2016). The airway epithelium is consistently shed in patches and epithelial cells masses are found in the airway cavity (Barnes *et al.*, 1995, 1996). T helper 2 (TH2) cells mainly influence inflammation by secreting variety of inflammatory cytokines, mainly IL-4, IL-13, IL-5, and IL-9 (Ngoc *et al.*, 2005). IL-4 regulates allergic inflammation and IgE synthesis via Th2 cell stimulations (Borish *et al.*, 1999). IL-13 controls eosinophilic asthma and induce airway remodeling process and acts like IL-4 cytokine (Athari *et al.*, 2019) (Fig.1). IL-5 is vital for eosinophils accumulation, terminal differentiation, and continued survival (Uhm *et al.*, 2012; Cho *et al.*, 2004) and earlier reports have verified a vital role for IL-9 in mucus production (Temann *et al.*, 2002; Steenwinkel *et al.*, 2007; Busse *et al.*, 1992; Wardlaw *et al.*, 1999, Athari *et al.*, 2019).

In addition, various factors like interleukin-5 and 13 (IL-5, IL-13), chemoattractants such as eotaxin, clara cells and chemokine receptor (CCR3) are directly involved in eosinophils recruitments to the lungs in allergic inflammation. After reaching to the site, eosinophils modulate immune response by inducing structural alterations in lungs and activated eosinophils release variety of granules and inflammatory mediators (Possa *et al.*, 2013; Liu *et al.*, 2006). Allergic eosinophilic asthma driven by type 2 inflammation is the predominant endotype (Sugita *et al.*, 2018a; Wenzel *et al.*, 2012). Alveolar macrophages are the main immune effector cells in the lungs (Peters-Golden *et al.*, 2004) responsible for the pro-inflammatory cytokines production, mainly IL-1, TNF- α , IL-6, and GM-CSF, which play an important role in endothelial cell activation, eosinophil survival and other cellular infiltrations. Interleukin-6 and TNF- α may be released by IgE-dependent stimulation (Hamid *et al.*, 2003).

Chronic inflammation

The chronic airway inflammation is characterized by inflammatory cell infiltrations mainly, T lymphocytes, eosinophils, macrophages/monocytes, mast cells and neutrophils. Neutrophils release cytokines, lipids mediators and proteases that contribute to airway constriction and mucus production. After an allergen challenge, Neutrophil numbers are increased, during the late-phase reaction, and patients with long-standing asthma and with corticosteroid-dependent asthma. IL-8, TNF- α , and leukotriene B4 which are correlated with severity of airway obstruction, neutrophil chemotaxis and duration of disease (Ennis *et al.*, 2003; Ordonez *et al.*, 2000). However, chronic disease progression occurs due to an insufficient immune response, which impairs the body's ability to regulate inflammation (Mukherjee *et al.*, 2018). In asthmatic airways, the epithelium is shed, the ciliated cell layer is lost, the goblet cells swell, and many growth factors, cytokines, and chemokines are upregulated (Bergeron *et al.*, 2010). Airway remodeling is the key structural alterations in asthma, besides airway inflammation where remodeling severity varies in asthmatics. However, as per reports, airway remodeling is not present at birth but some structural features are initiated between 2–4 years of life, often before asthma is diagnosed (Dunnill *et al.*, 1960; Roche *et al.*, 1989). Various external factors are responsible for inflammation and persistent epithelial damage activates the repair mechanisms in lungs (Andersson *et al.*, 2020; Malmberg *et al.*, 2020).

III. ENVIRONMENTAL EXPOSURES AND ASTHMA EXACERBATIONS

Exposures to air pollution is hazardous as it is known to induce exacerbation to inflammatory disorders of the lower airways, such as asthma (Tiotiu *et al.*, 2020). Airborne pollutants including smoke, particulate matters, and bacterial or viral infections are well-established risk factor where biomass burn fumes contains high level of endotoxin (particularly cow dung smoke) and volatile mixtures. Variety of inducible factors contribute in the worsening of the asthma symptoms. So, asthma exacerbations can be defined as aggravations to asthmatic episodes which eventually deteriorate the life expectancy of asthmatics. After inhalation, endotoxin stimulates chain of biochemical interactions triggering lung inflammation and oxidative stress, which play a significant role in asthma advancement. Combinations of environmental and genetic interactions lead to asthma (Youssef *et al.*, 2016), where genetic impact is possibly playing a role that develops before the age of 12, whereas environmental influence develops after the age of 12. Some of the candidate genes predicted to be involved in asthma pathogenesis are genes coding for IL-4, IL-10, G-protein linked receptor, high affinity IgE receptor, Interferon- γ , iNOS, TGF- β 1 (Ober *et al.*, 2011) etc. Endotoxin induced asthma is irreversible, and eventually insensitive to asthma treatments like corticosteroids. Pathogen-associated molecular patterns (PAMPs) are present on pathogens, which are evolutionarily conserved structures and are known by some pattern recognition receptors (PRRs) and passed down from germline (Inouye *et al.*, 2017). Outer cell wall of gram-negative bacteria contain Lipopolysaccharide (LPS), which is well-known PAMP. However, in some circumstances, PRRs also identify host factors as "danger" signals, danger-associated molecular patterns (DAMPs), or abnormal molecular complexes when they are present in unusual locations or due to other types of cellular stress (Roh *et al.*, 2018). PRRs are expressed by many immune cells along with epithelial cells and fibroblasts.

IV. AVAILABLE ASTHMA MEDICATIONS AND LIMITATIONS

For managing severe asthma, long-term management medications are prescribed which help in reducing inflammation, mucous production and swelling of the airways. They include, inhaled long-acting beta-agonists (LABA), often taken along with an inhaled corticosteroid

(combination inhaled medicines) and they open airways by relaxing the smooth muscles. They include vilanterol, salmeterol and formoterol; Inhaled long-acting anticholinergics, relax and enlarge the airways in lungs i.e., Bronchodilators, Cromolyn sodium (Intal), Cromolyn prevents swelling in airways when they come in contact with an asthma trigger and used as an inhaler., Theophylline also helps in smooth muscle relaxation. Oral corticosteroids come in next category which mainly reduces inflammation in airways.

In recent years, corticosteroids administration has upgraded significantly, as inhalation strategy have managed the asthma treatment. These are taken via inhalers therefore effective in treating local inflammation and may control it till longer duration has ability to reduce oral corticosteroids associated side effects. They are often combined with bronchodilators and not suggested for relieving symptomatic relief and for wide-ranging disease management. Due to irreversible narrowing of the airways, some asthma patients do not respond to this remedy (Hirota *et al.*, 2013). Drugs like Leukotriene modifiers help in easing swelling and relax the smooth muscles in airways. Biologic drugs, which work with immune system as they target a cell or protein in our body to prevent inflammation and swelling in airways. They are expensive and given in form of infusions or shots, every few weeks. Monoclonal antibodies, like omalizumab, against IgE and mepolizumab and reslizumab targeting Th2- cytokines, for example IL-5, benralizumab; IL-4 and IL-13 receptor (dupilumab) are presently used biologic drugs (Busse *et al.*, 2001; Fala *et al.*, 2016). Recent studies have reported that neutrophilic inflammation, are responsible for asthma exacerbations as they are insensitive to corticosteroids (Martinez *et al.*, 2009). Commonly used asthmatic drugs are mainly anti-inflammatory in nature and target various signal transduction pathways but are not effective in lung fibrosis (Bourdin *et al.*, 2007). Inhaled corticosteroids (ICS) are well-known for symptomatic control with ability to reduce serious asthma aggravation risks (GINA, 2022). In contrast, ICS relative to long-acting inhaled bronchodilators, i.e. long-acting muscarinic antagonists (LAMAs) and long acting β 2-agonists (LABAs), support chronic obstructive pulmonary disease (COPD) treatment when used in combination (Singh *et al.*, 2021). As per reports, low doses of ICS are extremely supportive in subsiding chronic inflammation in most asthma patients due to eosinophil

infiltrations (Barnes, 2010). However, in COPD, the lung inflammation is predominantly neutrophilic (Barnes, 2019). Basically, different inflammatory conditions are responsible for corticosteroid insensitivity in COPD patients, where only a small improvement in exacerbations are seen (Barnes, 2000; Burge *et al.*, 2013).

V. HERBAL DRUGS DERIVED FROM MEDICINAL PLANTS FOR ASTHMA TREATMENT

Currently prescribed drugs are associated with several side effects which vary depending on the dose, administration and the class of the drug (Tompson *et al.*, 2021). Since available asthma medications only provide symptomatic relief, herbal compounds are suggested to improve asthma treatment. Most of the world population use plant-derived medications, which possess various properties, like immunomodulatory, anti-histamine, cellular co-receptor expression, lymphocyte expression, phagocytosis etc. Several studies have shown immunomodulatory activities like immunostimulatory and immunosuppressive activities in the medicinal plant products (Nagarathna *et al.*, 2013; Mukherjee *et al.*, 2014; Sethi *et al.*, 2015; Agrawal *et al.*, 1999). Immunomodulatory potential is being used for health benefits. Some modern medicines are derived from the traditional herbal medicine (Nagarathna *et al.*, 2013) (Table.1). It has been reported that tribal communities have used many plant species in respiratory disease particularly asthma in many forms, like decoction, juice and dry powder (Ignacimuthu *et al.*, 2006; Savithramma, *et al.*, 2007).

VI. CURCUMIN AS AN ALTERNATIVE AND COMPLEMENTARY MEDICATION

Turmeric displays anti-inflammatory, anti-oxidant, antiviral, antibacterial, antifungal, and anticancer properties (Aggarwal, 2006). Curcumin derived from *Curcuma longa* is regularly used throughout India as a spice and food colorant and in other Asian countries and the western world. Curcumin constitutes 5% of turmeric which gives its characteristic yellow colour. Molecular weight of curcumin is 368.38 g/mol and chemical formula is C₂₁H₂₀O₆. It is a polyphenolic, lipid-soluble compound which can be only dissolved in organic solvents like, DMSO, acetone, methanol, and ethanol. It is sparingly soluble in water at both neutral and acidic pH levels,

although it dissolves in alkaline pH. Curcumin is not stable at neutral basic pH conditions as more than 90% of curcumin decomposes rapidly in buffer systems (Pan *et al.*, 1999). Several modified forms like curcumin nanoparticles, liposomal encapsulations and cyclodextrin formulation has been used to enhance its bioavailability, solubility, absorption, and dispersibility and delivery efficacy to the body. These formulations have shown some promises to improvement in use of curcumin as efficient therapeutic agent (Jager *et al.*, 2014; Purura *et al.*, 2017). Curcumin has been extensively used in Indian ayurvedic system to treat allergies and asthma (Memarzia *et al.*, 2022). Several reports suggested therapeutic benefits of curcumin and described it as an effective "drug" for various types of lung illnesses treatments. They exhibit a beneficial role on inflammation, histopathological changes in lungs, airway responsiveness, and immunoregulatory actions in an animal model of lung diseases (Table.2). A study reported that consuming powdered roots of *Curcuma longa* L. (containing curcumin) for six months showed better disease control in children and adolescents with persistent asthma (Manarin *et al.*, 2019), but they have not investigated immunomodulatory properties (Kim *et al.*, 2011).

Table.1 List of medicinal plants with immunomodulatory properties

S.no	Medicinal plant	Hindi name	English name	Biological effect/immunomodulatory properties	Reference
1	Aloe vera (family - Liliaceae)	Ghrita Kumari	<i>Aloe</i>	Anti-inflammatory properties, ability to inhibit cytokines, ROS production, and JAK1-STAT1/3 signaling pathway	Ma et al., 2018
2.	<i>Glycyrrhiza glabra</i>	Mulethi	<i>Licorice root</i>	Reduced levels of TNF- α , in BALF and IL-6, COX-2, NOS-II and TNF- α mRNA expression in the lung tissue. Inhibition of neutrophilic airway inflammation by blocking IL-17/STAT3 pathway. Prevents in the decrease of IFN- γ and the increase of IL-4, IL-5, IL-13 in BALF, reduced serum immunoglobulin IgE and OVA-specific IgE levels.	Kim et al., 2020; Wu et al., 2016
3	<i>Allium sativum</i> (family-	Lasun	<i>Garlic</i>	It has long been used to treat cancers such as colon, rectal, stomach,	Alam et al., 2016

	Liliaceae)			breast, prostate, and bladder cancers, as well as lung cancer	
4	<i>Piper longum</i> (Family- Piperaceae)	Pippali	<i>Long pepper</i>	increased macrophage migration index and phagocytic index, indicating immunostimulatory activity	Tripathi et al, 1999
5.	<i>Piper nigrum</i> (Family- Piperaceae)			Attenuates the expression of GATA3, IL-4, IL-6, IL-1 β , ROR γ t, IL-17A, TNF- α and increased the secretion of IL-10, INF γ in BALF and lung homogenate. Suppressed the level of total IgE, anti-OVA IgE, anti-OVA IgG1 and histamine release in serum.	Bui et al., 2017
6	<i>Phyllanthus emblica</i> (Family- Euphorbiaceae)	Amla	<i>Gooseberry</i>	Antioxidant activity; enhanced GSH, catalase	Ghosh et al., 2013; Saini et al. (2022)
7	<i>Tinospora cordifolia</i> (Family- Menispermaceae)	Giloe/guduchi	<i>Gulanchar tinospora</i>	Immunomodulatory and cytotoxic effects	Sharma et al., 2012; Kapil et al., 1997; Subramanian 2002.
8	<i>Withania somnifera</i> (Family- Solanaceae) Withaferin A	Ashwagandha	<i>Winter Cherry</i>	Inhibits lung injury and pulmonary fibrosis through downstream TGF- β 1 signals and hydroxyproline (OH-proline) in mice. Blocks the activation of the NLRP3 signaling pathway.	Zhao et al., 2019
9.	<i>Zingiber officinale</i> (Family Zingiberaceae)	Adrak	<i>Ginger</i>	Inhibits NF- κ B signaling, IL-2, IL-4, TNF- α PDE inhibition Reduces Lung IL-4, IL-5 expression And Serum IgE level	Khan et al., 2015
10.	Quercetin (flavonoid found in many plants)	<i>Quercus oak</i>	<i>Quercetine</i>	Inhibits BALF eosinophil count, IL-4, IL-5, eotaxin, Lung and BALF IL-25, IL-33, Lung P-selectin, GATA3, MMP-9 expression; Enhances BALF, IFN- γ	Ravikum ar et al., 2020
11.	<i>Berberis aristata</i> (Family Berberidaceae)		<i>Berberine</i>	Inhibition of COX pathways mast cell-mediated allergic responses; suppression of Fc γ RI-mediated and MAPK signaling regulation, IL-4, TNF- α ; IL-5, IL-6, IL-13, IL-17, IL-1; IgE NF-	Ma et al., 2020

				κ B signaling pathway inhibition, CCL11 production STAT6 pathway modulation	
12	<i>Polygonum cuspidatum</i> (Family Polygonaceae)	Japanese knotweed	<i>Resveratrol</i>	Reduces BALF IL-4, IL-5, IL-6, IL-17, TNF α , TGF- β ; Inflammatory cells, Serum IgE, IgG, inhibition of PI3K-Akt signaling pathway, Lung TGF- β expression	Lee et al., 2017
13	<i>Mangifera indica</i> L. (Family Anacardiaceae)	Mango	<i>Mangiferin</i>	Serum and BALF OVA-specific IgE, IL-4, and IL-5	Rivera et al., 2011
14	<i>Nigella sativa</i> (Family Ranunculaceae)	Kalonji seeds	<i>Thymoquinone (TQ)</i>	Reduces BALF IL-2, IL-6, IL-4, IL-5, IL-13, Serum IgE, OVA-specific IgE, IgG, BALF eosinophils, PGE2 Enhances BALF IFN- γ	Ikhsan et al., 2018
15.	<i>Ocimum basilicum</i> (Family Lamiaceae)	tulsi	<i>Basil</i>	Reduces BALF IL-4, IgE, TP, PLA2; Serum NO2, NO3, MDA; Increases BALF IFN- γ	Eftekhari et al., 2018
16.	<i>Sesamum indicum</i> (Family Pedaliaceae)		<i>Sesame</i>	Reduces Lung IL-6, IL-1 and Serum IgE level	Hsu et al., 2013

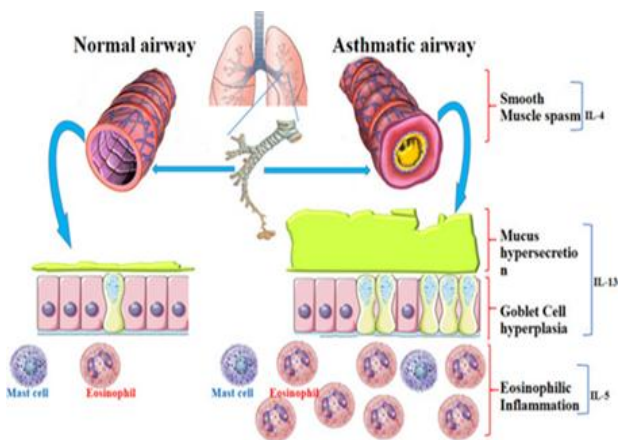


Fig.1 Asthma, chronic respiratory disease (Athari, 2019)

Later, another study reported improvement in FEV1 and hematologic parameters in 60 patients with mild to moderate bronchial asthma after curcumin administration but there was no improvement in the asthma symptoms (Abidi *et al.*, 2014). Curcumin has a well-known safety record. As per JECFA (The Joint United Nations and World Health Organization Expert Committee on Food Additives) and EFSA (European Food Safety Authority) reports, the Allowable Daily Intake (ADI) value of curcumin is 0–3 mg/kg body weight

(Kocaadam *et al.*, 2017). Some side effects have also been reported despite well-established safety profile. As per reports, in a dose response study, after receiving 500–12,000 mg for 72 h, some side effects were experienced (Lao, *et al.*, 2006; Sharma *et al.*, 2004). In a trial, using standardized oral *Curcuma* extract, 180 mg of curcumin per day were given to advanced colorectal cancer patients for up to 4 months without evident toxicity or measurable bioavailability systemically (Sharma *et al.*, 2001). A follow up study has suggested that up to 8 g could be given daily to patients for few months without obvious toxicity (Cheng *et al.*, 2001) (Table.3 & 4). Intranasal route has been selected for curcumin administration for better absorption as nasal mucosa is highly vascular and has low pH 3-5, which helps in enhanced bioavailability. Intranasal Curcumin (2.5 mg/kg and 5mg/kg) was found protective against acute and chronic asthmatic models (Chauhan *et al.*, 2014; Subhashini *et al.*, 2013 Curcumin absorption in blood plasma (1.5µg/ml) was noted after 3 hours of intranasal administration (5mg/kg) (Subhashini *et al.*, 2013). In chronic asthma model group, 40% mortality was noted in dexamethasone treated mice, whereas mice with curcumin treatment were normal without any side effects (Chauhan *et al.*, 2014).

Another study has reported enhanced both MMP-2 and MMP-9 levels in the sputum and BAL fluid of chronic asthma patients (Maisi *et al.*, 2002). Reduced collagen deposition, MMP-9 activity and expression in asthmatic mice lungs were shown after intranasal curcumin treatment (Chauhan *et al.*, 2017). Recently, another method was used for increasing its solubility and protecting it from degradation, micelle's shield was incorporated (Chawla *et al.*, 2021). Commonly used asthmatic drugs are mainly anti-inflammatory in nature and target various signal transduction pathways but that are not effective in lung fibrosis (Bourdin *et al.*, 2007). Structural alterations in lungs were reported in OVA-induced acute and chronic asthmatic mice where persistent inflammation led to airway remodeling (Subhashini *et al.*, 2016). Epithelial and smooth muscle thickening of lung tissue in acute asthmatic mice was enhanced in chronic condition (Chauhan *et al.*, 2014). Various inflammatory cytokines, interleukin (IL)-4, IL-5, IL-9, and IL-13 are involved in chronic airway inflammation which is mediated by T helper type 2 (Th2) cells. Apart from inflammation, these cytokines induce mucus cell hyperplasia, smooth muscle contraction, and airway remodeling. Moreover, Th17 cells also participate in the airway inflammation and secrete IL-17A and IL-17F (Papi *et al.*, 2018).

Asthma severity is related to airway smooth muscle thickening, a symbol of structural alterations in asthmatic

airways (James *et al.*, 2009). These changes include epithelial denudation, goblet cell metaplasia, increased airway smooth muscle mass, and increased subepithelial thickening from increased deposition of extracellular matrix proteins (ECMs) like collagen, proteoglycans, and glycoproteins, and angiogenesis (Shifren *et al.*, 2012). Several products of the Th2 pathway can control remodeling changes (Nelson *et al.*, 2020; McBrien *et al.*, 2017). Variety of cytokines, including IL4, IL5, and IL13, vascular endothelial growth factor (VEGF), etc. have been demonstrated to stimulate different aspects of airway remodeling (Hirst *et al.*, 1996; Panettieri *et al.*, 1996; Cohen *et al.*, 2000; Chen *et al.*, 2006) (Fig 2).

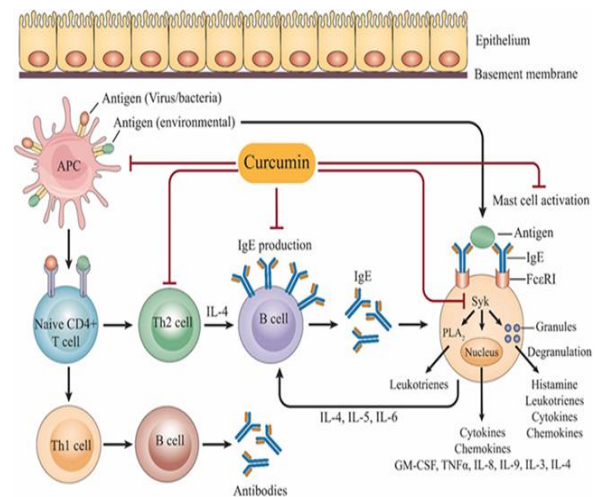


Fig 2. Schematic view of the modulatory effects of curcumin on allergic responses and mast cell activation. Basophils and mainly mast cells are critical players in allergic diseases (Haftcheshmeh *et al.*, 2022).

Table.2 Immunomodulatory effects and therapeutic efficacy of curcumin in allergic diseases investigated in human (Haftcheshmeh *et al.*, 2022).

Disease	Population size	Dose Curcumin	Duration of treatment	Results	References
Dermatitis		1 g/day	4 weeks	Reduced pruritus severity Reduced the level of substance P.	Panahi <i>et al.</i> , 2012
Allergic rhinitis	241	500 mg/day	2 month	-Increased production of IL-10.- Decreased the production TNF-α, IL-8, and IL-4	Wu., 2016

Asthma	34	30mg/kg/day	6 months	Better control of the disease	Manarin et al., 2019
Asthma	15	2000mg/day	-	Had no significant effects on the total white blood cell count, blood eosinophils, and serum IgE	Kim et al., 2011
Asthma	60	500 mg/day	4 weeks	Decreased the total blood leukocyte count. Reduced the neutrophils, eosinophil count	Abidi et al., 2014
Asthma	30	3000 mg/day	12 weeks	Ongoing	Quan et al., 2021
Eczema	150		4 weeks	Improve the clinical symptoms of the disease including, erythema, scaling, thickening and itching	Rawal et al., 2009
Dermatitis	30	6g/day		reduce the severity of radiation dermatitis	Ryan et al., 2013

Table.3 Clinical trial of active Curcuminoid Compounds

S.no.	Dose and route of curcumin administration	Time in minutes	Absorption in blood plasma/serum in µg/mL	Absorption in lungs µg/mL	References
1	2 g/kg, p.o in rats	50	1.35	-	Shoba et al., 1998
2	2g, p.o. in human	60	0.006		Shoba et al., 1998
3	4–8g, p.o. in humans	60	0.41–1.75		Cheng et al., 2001
4	3.6 g/day, p.o. in human	60	11.1		Sharma et al., 2004
5	2mg/kg in rat tail vein	60	6.6		Sun et al., 2013
6	500 mg/kg to rats	60	490.3		Suresh et al., 2010
7	5mg/kg, i.n. to mice	60	1.38	2.5	Subhashini et al., 2013
8.	5 mg/kg, i.n. to mice	180	1.55	3.6	Singh et al., 2023

VII. BACTERIAL ENDOTOXIN AND ASTHMA EXACERBATIONS

Environmental endotoxins have been linked to asthma exacerbations in both non-atopic and atopic individuals (Liu et al., 2002). According to hygiene hypothesis, microbial exposure in infancy helps in the healthy lung development and reduces the likelihood of asthma and other atopy-related

conditions. Recent research, however, clearly suggests that exposure to particular pathogenic bacteria that can cause pneumonia, bronchiolitis, and wheezing during infancy can be the trigger for asthma and aberrant lung development. Systemic entry of bacteria into the body results in major vital organ damage. Multiple organ failures and sepsis induced lung inflammation are responsible for millions of deaths worldwide each year. The invading organisms are recognized by immune cells mostly alveolar macrophages and epithelial cells present in the lungs, which further mediates pathogen associated molecular pattern (PAMPs) for chemokine secretion and recruiting inflammatory cells. LPS induces lung damage by releasing potent inflammatory cytokines (like TNF- α , and IL-1 β), intravascular coagulation, bleeding, shock, initiation of the complement cascade, and release of histamine, followed by inflammation. In 1998, gram-negative bacteria are recognized by TLR4 via the lipid A moiety of LPS by the group of Bruce Beutler (Poltorak et al., 1998). Alveolar macrophages not only recruit other cells but also secrete huge number of proteases, ROS, arachidonic acid derived mediators and cytokines that augments inflammation (Aggarwal et al., 2014). After treatment, curcumin had been shown to block the phosphorylation of Phospholipases A2, expression of Cox-2 and catalytic activities of Lox-5 in LPS-stimulated murine macrophages (RAW264.7) and in HT-29 human colon cancer cells (Hong et al., 2004). Efficacy of intranasal curcumin was thoroughly evaluated in LPS induced asthma exacerbations in OVA-induced asthma, where dose and timings of LPS exposure was thoroughly investigated (Kumari et al., 2015). Asthmatic exacerbations induced by LPS following OVA aerosol led to NLRP3 activation which was reduced in intranasal curcumin treatment groups. Furthermore, inflammatory cell infiltrations, mRNA and protein expressions of TLR-4, NLRP3, NF- κ B, Caspase-1, IL-1 β , MMP-9, IL-5, and IL-17 were ameliorated while lung structural abnormalities were brought back to normal (Jaiswal et al., 2022). Interestingly, additive anti-inflammatory and anti-asthmatic effects were observed in combination therapy of curcumin with corticosteroid, Dexamethasone (Jaiswal et al., 2022). Curcumin also inhibited IL-5 and IL-4 release (Th2-associated cytokines), while lowered histamine and IgE levels in allergic asthma after LPS exposure (Kumari et al., 2015). Curcumin has been shown to prevent redox-active oxygen and nitrogen species, lipid peroxidation, and the activation of many antioxidant enzymes including catalase, superoxide dismutase (SOD), and glutathione peroxidase (GPx). Anti-allergic and immunomodulatory effects of curcumin have been reported by various investigators (Kurup

et al., 2006; Jang et al., 2014). Curcumin also prevented MAPK/NF-κB activation and inflammation thereby asthma exacerbations after LPS exposure.

Table 4. Dose and route of Curcumin administration and absorption

Active Compound	Test animal group	Dose	Measured parameters	References
Curcumin	32 adult male Wistar rats (200-250gm)	100 mg/kg/day for 28 days orally.	↓ALP, ↓ASP, ↓ALT	Ghoreshi et al., 2017
Curcumin and Curcumin Phytosome	50 male mice (25-30 g)	100-200 mg/kg body weight orally.	Groups III and IV ↑MDA, ↓SOD, ↓CAT and ↓GPx. Group V ↓MDA, ↑SOD, ↑CAT and ↑GPx.	Tung et al., 2017
Curcumin + dimethylnitrosamine	32 Adult male Wistar rats (260-280 gm)	100 mg/kg body weight orally.	Group III ↓AST, ↓ALT, and ↓ALB Group IV ↓AST, ↓ALT, and ↓ALB	Kyung et al., 2018
Curcumin	66 Adult male Wistar rats (180-200 g).	100-200mg/kg body weight orally.	Group III ↓ALT, ↓AST, ↓AFP, ↓albumin concentration, ↓MDA and ↑SOD Group IV ↓ALT, ↓AST, ↓AFP, ↑albumin concentration, ↔ MDA and ↔ SOD, ↑hepatic lobule physique	Elmansiet et al., 2017
Curcumin + BPA	36 Adult male Wistar rats (220-250 g)	100-130 mg/kg body weight orally.	Group III ↓MDA, ↑SOD, ↑CAT, ↑GPx and ↑GST Group IV ↓MDA, ↑SOD, ↑CAT, ↑GPx and ↑GST Group V ↑MDA, ↓SOD, ↓CAT, ↓GPx and ↓GST Group VI ↓MDA, ↑SOD, ↑CAT, ↑GPx and ↑GST Group VII ↓MDA, ↑SOD, ↑CAT, ↑GPx and ↑GST	Uzunhisar cikli et al., 2019
Curcumin + Paraquat (PQ)	36 adult male Wistar rats (220-250 g)	100 mg/kg body weight orally.	Group V ↓ALT, ↓AST, ↓ALP and ↓MDA Group VI ↓ALT, ↓AST,	Kheiripour et al., 2021

Curcumin	24 adult male Wistar rats	Curcumin 50 mg/kg body weight for 12 weeks orally.	↓ALP and ↓MDA Group IV (first phase) and Group III (second phase) ↓fibrosis, ↓liver biomarkers, ↑CAT, ↑SOD, ↑GSH, ↑electrolyte homeostasis	Zaidi, 2020
Curcumin	25 adult male Wistar rats (250-280 grams)	10-50 mg/kg body weight, intraperitoneally for 5 weeks.	↓NLRP3, IL-1β, IL-6, IL-18, TNF-α ↑BDNF/TrkB, PI3K/Akt signaling pathways	Sun et al., 2020
Curcumin	30 adult male Wistar rats (180-200 grams)	300 mg/kg body weight orally for 4 weeks.	↓Serum creatinine, ↓urine albumen, and ↓urea nitrogen enhanced Ecadherin, ↓LC3 proteins expression, ↓p62, ↓phosphorylated levels of Akt, ↓mTOR, and ↓PI3K levels	Tu et al., 2019
Curcumin	30 adult male Wistar rats (200-220 grams)	15-60 mg/kg body weight, through oral gavage	Reduced Inflammation via up-regulating miR-200a-mediated TXNIP and ↓NLRP3 inflammasome pathway	Ding et al., 2018
Curcumin	48 adult male Wistar rats (230-250 grams)	200 mg/kg body weight	Reduced Inflammation by downregulation of TNFα, IL1β, and JIL6 Blocked TLR4 /MyD88/NFκB signal pathways	Zhang et al., 2019

[↓significantly decreased, ↑ significantly increased, ↔ showed no effect (still)]

VIII. NLRP3 INFLAMMASOME ACTIVATION IN ASTHMA

A wide range of triggers activate NLRP3 inflammasome (Pellegrini et al., 2017). The first stage of the process is a reaction involved activation of certain cytokine or TLR4 receptors (after binding to LPS), which can increase the NF-κB mediated transcription of NLRP3, pro-IL-1 and pro-IL-18 (Fusco et al., 2020). An increasing data suggested that inflammasomes are responsible for the heightened inflammatory response, which has been associated to respiratory infections and asthma exacerbations (Lee et al.,

2014; Jaiswal et al., 2022). Investigations on animals and human subjects showed that NLRP3 inflammasome protein was up-regulated in asthma patients (Rossios et al., 2018) and in OVA-induced asthma which demonstrated NLRP3 inflammasome performed a significant role in asthma development (Kim et al., 2017). Decrease in plasma secretion of TNF- α and IL-6 was reported in mice model of sepsis after curcumin treatment. These findings support the idea that curcumin is a well-known molecule to effectively control sepsis due to its anti-inflammatory potential (Zhao et al., 2012). Another report has shown that curcumin administration has reduced NLRP3 inflammasome activation and IL-1 β production in mouse model of colitis (Gong et al., 2018). Furthermore, another study reported that curcumin has prevented NF- κ B-mediated proinflammatory pathway and NLRP3-facilitated innate immune response. In another study, curcumin analogue has been shown to prevent colitis by inhibiting JNK/NF- κ B activation (Hu et al., 2022).

IX. MICROBIAL DYSBIOSIS AND ALLERGIC ASTHMA

Microbial Dysbiosis may develop in two conditions, either due to a damage of beneficial microorganisms and expansion of pathological microbes or loss of microbial diversity which may affect immunology of mucosal tissue and provoke greater susceptibility to asthma (Peterson et al., 2014). In recent years, it was reported that the fermentation of dietary fibre by Lactobacillaceae and Bifidobacteriaceae in the intestine increases the level of short chain fatty acids (SCFAs), leading to a reduction in inflammation associated with the Th2 response (Kaur et al., 2020; Schenzel et al., 2024). Moreover, butyrate, propionate, and acetate have been reported to alleviate allergic airway inflammation via Tregs (Angurana et al., 2018). Lactobacillus and Bifidobacterium increase the interleukin IL-10 secretion thereby inhibited atopic immune response which is IgE-dependent. Some reports suggested a steady increase in the identification of Proteobacteria in the airways of asthma patients as compared to subjects without asthma (Zhang et al., 2016). Dysbiotic communities considerably contribute to progression of asthma and related severity, where a connection is detected between microbial dysbiosis and, asthma exacerbations and response to disease therapeutics (Hufnagl et al., 2020). A recent report has shown gut dysbiosis and its impact on host health and its modulation by curcumin where it has ameliorated various diseases caused microbial disturbances (Zhu et al., 2024).

X. PARTICULATE MATTER (PM10/2.5) INDUCED AIRWAY INFLAMMATION

As per reports, air pollution exposure (particulate matter and other exhausts) has also been implicated in aggravating asthmatic symptoms (Tiotiu et al., 2020; Guarnieri et al., 2014; Zu et al., 2017). The air pollution impacts accumulate over time and appear during sensitive phases of life. Long-term exposure to elevated PM levels has been linked to reduced lung function, increased incidence of respiratory infections, development of chronic respiratory conditions, and even lung cancer (Johnston., 2019; Sun., 2020). Based on thorough investigations on asthma and associated molecular mechanisms, which have revealed its aggravated impacts on both, adaptive and innate immune responses (Bronte-Moreno et al., 2023; Lu et al., 2021). Oxidative stress was also induced after exposure to air pollutants and enhanced ROS release in HBECs lead to direct oxidative damage and enhance intracellular calcium concentrations lead to release of IL-33. Recent study revealed curcumin attenuated PM-induced lung damage and inflammation by regulating MAPK/NF- κ B signaling via Nrf2/HO axis thereby ROS generation (Lee et al., 2023). Short term exposure to PM10/2.5 collected from Varanasi, India revealed lung inflammation and early fibrotic changes in lungs of asthmatic mice which were significantly reduced by intranasal curcumin in mice model. This study reported reduced apoptotic changes in A549 cells in vitro after intranasal curcumin administration (Sharma et al., 2025).

XI. MECHANISTIC PATHWAY INVOLVING OXIDATIVE STRESS AND Nrf2

ROS has been reported to play a crucial physiological role in cellular homeostasis as well as various human diseases (Pazzino et al., 2017). Oxidative stress due to excess ROS produced by immune cells in asthma patients are noted due to simultaneous reduction of antioxidant response (Martin et al., 2014). The oxidants/antioxidants balance is maintained in normal condition (Kisaoglu et al., 2013); nevertheless, inflammatory damages can disturb this balance, and disease progresses (Victoni et al., 2021). In mammalian cells, cytoprotective mechanisms has been developed that abrogate ROS production via nuclear factor erythroid 2-related factor (Nrf2)/Kelch-like ECH-associated protein (Keap1) pathway signaling. Nuclear factor erythroid 2-related factor (Nrf2) is a transcriptional activator that binds to the antioxidant response element (ARE). Therefore, Nrf2 acts in the protection of cells and tissues from oxidative stress (Ahn et al., 2017). In-vitro and in-vivo studies have reported that curcumin has enhanced glutathione (GSH) synthesis as an important intracellular antioxidant and reduced airway inflammation via Nrf2/HO-1 activation and reduced reactive oxygen species (ROS) and reactive nitrogen species being its scavenger (Sussan et al., 2015; Zheng et al., 2017; Liu et al., 2015). Another study

reported that curcumin has regulated pulmonary oedema by preventing Nrf2 and HIF1- α up-regulation (Matthew et al., 2018). Alteration in Keap-1/Nrf-2 pathway may be protective for the activation of Nrf2 antioxidant pathway against external oxidative stress. Ramasamy et al., reported that sensitivity of Nrf2-directed antioxidant pathways may be a key factor in determining susceptibility to allergen-mediated asthma (Rangasamy et al., 2005). Studies have also reported di butyl phthalate (DBP) induced allergic airway inflammation (Maestre-Battle et al., 2020) where curcumin activates Nrf2-mediated mast cell activation, deteriorating allergic airway inflammation (Wang et al., 2021).

XII. CURCUMIN AND EPIGENETIC MODIFICATIONS

Environmental factors are considered as initiator signals for epigenetic modifications and a major contributor in asthma (Huerta-Yepez et al., 2011). Allergen sensitization has been reported to enhance the HDAC 1 expression in asthmatic mice lungs. Enhanced expression of and MMP-9 and NF- κ B suppressed expression of H3acK9 along with HDAC 1, suggested possible connection among these factors in allergic asthma pathogenesis (Efraim et al., 2014). Studies in asthmatic and rhinitis patients have shown increased HIF-1 α expression which proposed direct participation of HIF-1 α in pulmonary inflammation (Bian et al., 2018). Curcumin has inhibited HDAC activation in allergic asthma which was equivalent to known HDAC inhibitors (HDACi) with anti-proliferative, anti-inflammatory, anti-angiogenic and anti-fibrotic properties (Balasubramanian et al., 2008; Soflaei et al., 2018; Islam et al., 2023), so widely being investigated for various diseases. Higher HDAC 8 expressions in allergic asthma were significantly reduced after curcumin treatment thereby decreased bronchoconstriction via MAP kinase pathway (Fang et al; 2020). PCI is a potent and specific HDAC8 inhibitor with >200-fold selectivity over other class I HDACs whereas curcumin is also known as a pan HDACi (Liu et al., 2020).

XIII. CURCUMIN AND PIPERINE COMBINATION STRATEGY

Piperine, an alkaloid, is the chief constituent of *Piper longum* Linn. with a well-known therapeutic value. It is well-known for variety of effective properties including anti-pyretic, anti-depressant, hepatoprotective, anti-metastatic, anti-thyroid, immunomodulatory and anti-tumor (Sunila et al., 2004; Parmar et al., 1997; Lee et al, 2005; Pradeep et al., 2002; Panda et al., 2003). It has been reported that due to increased absorption and reduced metabolism might have improved the bioavailability of curcumin and its serum concentration in rats and human (Shobha et al. 1998; Damanhoury et al., 2014; Basnet et al., 2011; Kurup et al., 2004). Bioavailability of drugs has been reported to get enhanced by

piperine by affecting their glucuronidation in the liver and small intestine. Curcumin and piperine are well-known phytochemicals with anti-inflammatory and immunomodulatory potential (Bishnoi et al., 2011; Chauhan et al, 2018; Cowan et al., 2010).

XIV. CURCUMIN AND DEXAMETHASONE COMBINATION

Corticosteroids and other medications may be effective in asthma facilitated by Th2 cells but are associated with multiple side effects. Dexamethasone, a glucocorticosteroid has been reported to reduce eosinophilic symptoms and aggravated asthmatic along with several anti-inflammatory effects symptoms (Zhu et al., 2019). However, the mtROS was inefficient to stimulate the NLRP3 inflammasome activation (Camargo et al., 2018). Earlier study has reported that curcumin stimulate ligand-dependent and independent TLR4 dimerization thereby TLR4-mediated signaling (Hynes et al., 2020) which activate the NLRP3 to initiate inflammasome assembly, cleavage of caspase 1, and release of IL-1 β via transcription factor NF- κ B (Yang et al., 2015). Intranasal curcumin and dexamethasone additive effects were better in IL-17 response after combined exposure of allergen with LPS making lungs more functional (Alizadeh et al., 2017). It has been found that IL-17 release contributes in eosinophil recruitment and lung inflammation responsible for TGF- β production, collagen deposition and pulmonary fibrosis (Gomex et al., 2020; Islam et al., 2022).

XV. CURCUMIN NANOFORMULTIONS

The use of nanocurcumin formulation through pulmonary route have given better results, particularly in lung diseases including COPD, asthma, pulmonary fibrosis and lung cancer (Lelli et al., 2017). It was reported that overall hydroxyproline content was reduced in bleomycin-induced rat model of pulmonary fibrosis after curcumin nano formulation administration where inflammatory cytokines were significantly reduced (Hemmati et al., 2021). In another study, curcumin solid lipid nanoparticles (curcumin-SLNs) have significantly decreased airway hyper-responsiveness and inflammatory cell infiltrations along with inflammatory cytokines, IL-4 and IL-13 as compared to non-treated asthma group (Wang et al., 2012). Curcumin has low aqueous solubility, and therefore nanosuspension may prove to be suitable formulation. Nanosuspensions have a strong adhesiveness with the mucosal surfaces, resulting into extended residence time

with the target site, thus improving absorbance and maximum reduction of drug loss.

XVI. LIMITATIONS AND FUTURE ASPECTS

Curcumin has been comprehensively suggested in traditional Indian medicine as therapeutic strategy for allergy and asthma treatment (Memarzia et al., 2022). In spite of the high therapeutic potential, reports from In vitro and In vivo studies have constantly suggested its low absorption, rapid metabolism, short half-life, and low tissue distributions contributing to its poor bioavailability as the major limitation (Anand et al., 2007). Since there is no specific receptor or target organ, Curcumin along with many other dietary polyphenols, can paradoxically target many organs or cell lineages. Furthermore, despite being high oral dose uptake, only a minute amount of curcumin was reported to get absorbed in the blood as it was quickly metabolized and excreted out via faeces and urine (Niu et al., 2016). Using many formulations (amorphous), solubility and bioavailability problems of curcumin have been widely investigated which showed that nanoparticles supplementations with active ingredients or nano formulations had increased stability and bioavailability of curcumin (Sunagawa et al., 2021). It can also be used as adjunct medication with corticosteroids to minimize the side effects to long term use in near future. Apart from many therapeutic roles of curcumin including anti-asthmatic, anti-cancer property of curcumin is very well studied in many cancers where curcumin has strongly inhibited NF- κ B activity which may lead to cellular apoptosis (Gupta et al., 2012). Hence, the ways to increase bioavailability of curcumin and thereby pharmacological efficacy nowadays is the major concern which may be helpful to treat cancer along with other inflammatory conditions.

CONCLUSION

Numerous reports from both earlier investigations suggested medicinal benefits of curcumin and described it as an effective "drug" for the various types of lung illnesses treatments. They exhibit a beneficial role on lungs pathologies, airway responsiveness, and immunoregulatory actions in an animal model of lung diseases. Due to various medicinal properties and promising efficacies, curcumin has got much attention as a complementary and an alternative medication. Due to bioavailability issues, various routes of administration have been utilized where

intranasal route of administration was found better effective at lower doses. Curcumin has been effective in inhibiting pro-inflammatory transcription factors such as NF- κ B and AP-1, reduce the proinflammatory cytokines such as IL-1 β , IL-2, TNF- α , IL-6, IL MIP-1 α , MCP-1 and PGE2, down-regulate enzymes such as COX-2 and -5, 5-lipoxygenase as well as inhibit the mitogen activated protein kinases (MAPK) and pathways involved in nitric oxide synthase (NOS) enzyme synthesis. New aspects and targets of curcumin is also under investigation where various formulations are in the process of development. Comprehensive, well-designed cohort clinical trials are still awaited to finally validate the clinical benefits of intranasal curcumin. Further, hydrophilic curcumin may be better option for asthma treatment with better efficacy without any degradation.

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