Anti-Asthmatic and Cardioprotective Efficacy of Curcumin-A Review

Muhammad Tahir Shahid¹, Syeda Khair-ul-Bariyah²

¹Center for Research in Molecular Medicine (CRIMM), The University of Lahore, Lahore, Pakistan
²Department of Chemistry, Forman Christian College (A Chartered University), Lahore, Pakistan
*Corresponding author’s E-mail: skbariyah@gmail.com

Received 24 February 2014; Accepted 7 April 2014

Abstract. Curcumin is a natural yellow pigment of turmeric. It is used for the treatment of diseases like Alzheimer’s disease, chronic obstructive pulmonary disease, asthma, neuropathic pain, psoriasis, cancer and atherosclerosis. The present review aims to encompass the studies of curcumin as anti-asthmatic and cardioprotective. It has shown antiallergic properties by inhibiting histamine release from mast cells. It has been evidenced to have anti-inflammatory properties through inhibition of the NF-kB pathway. By its good radical scavenging activity, it has proved to be potent in treating cardiovascular diseases. However, its combination with other asthma and cardio medicines needs to be evaluated, especially; combination of herbal medicines or curcumin along with synthetic drugs can lead to positive outcomes. Moreover, derivatives of the drug can also show some promising results and more derivatives, like CNB001, must be synthesized and investigated to control airway epithelial cell function and asthma. Only little work has been done so far showing its effects on the pulmonary functions of smokers, so this area needs to be explored by further clinical trials.

Keywords: Curcumin, antiallergic, asthma, cardioprotective, anti-inflammatory

1. INTRODUCTION

1.1. Asthma

Asthma is a disease of the airways which is chronic in nature. The inflammation of the airways results in increased contractability of the smooth muscles which are surrounding the airways. As a result of this, the airways are narrowed and finally it results in wheezing. Lamina reticularis thickens and eosinophils increase. Moreover, mucous glands increase and the smooth muscles surrounding the airways also increase. Other cell types and components of the immune system involved are T-lymphocytes, macrophages, neutrophils and chemokines, cytokines and histamines, respectively (Murray and Nadel, 2010).

The causes of asthma are both environmental and genetic (Martinez, 2007). Epigenetics as well as the changes occurring in the environment cause asthma (Dietert, 2011). Allergens, air pollution, high ozone levels, traffic pollution, cockroaches, dust mites, animal dander, mold and smoking during and after pregnancy are the factors that result in asthma (Arshad, 2010; Custovic et al., 2012; Gold et al., 2005 and Kelly et al., 2011). Volatile organic compounds like formaldehyde and phthalates in PVC are also linked with asthma causes (McGwin et al., 2010, Jaakkola et al., 2008 and Bomehag et al., 2010). Some respiratory diseases like rhinovirus and respiratory syncytial virus can lead to asthma (Murray and Nadel, 2010). Family histories as well as genetic variations enhanced by environmental exposures are found to be linked to asthma (Martinez, 2007). Twenty five genes were found to be the cause of asthma and over 100 genes according to one study in 2006 (Ober et al., 2006 and Halapi et al., 2009). In patients with history of atopic disease, asthma occurs at a much greater rate (Rapini et al., 2007). The patients with any type of urticaria also face asthma symptoms (Rapini et al., 2007). In obese individuals, buildup of fat leads to decreased respiratory function (Wood et al., 2009). Beta blockers, ASA, NSAIDs and angiotensin-converting enzyme inhibitors are also responsible to trigger the disease in susceptible patients (O’Rourke, 2007; Salpeter et al., 2001; Covar et al., 2005). The exacerbating agents of asthma are animal dander, molds, perfumes, infections of the upper respiratory tract, bacterial and viral infections and psychological stress (Gold et al., 2005; Baxi et al., 2010 and Chen et al., 2007).

The medication for asthma is divided into two classes. First class is quick-relief medication which is for treating severe cases. Second class is for long-term...
control which controls recurrence of the disease and its intensity prevention (NHLBI Guideline, 2007). First class includes beta2-adrenoceptor agonists (SABA), anticholinergic medications and adrenergic agonists (Parsons et al., 2013; Rodrigo et al., 2006 and Schiffman et al., 2009). Second class includes corticosteroids, long-acting beta-adrenoceptor agonists, leukotriene antagonists and mast cell stabilizers (NHLBI Guideline, 2007; Ducharme et al., 2010; Fanta, 2009; Cates et al., 2012; GINA, 2011, Watts et al., 2012; Chauhan et al., 2013, British Guideline, 2009).

1.2. Cardiovascular Diseases

Cardiovascular diseases are the diseases of the heart and related vessels (Maton et al., 1993). There are many reasons for cardiovascular diseases but the most common are atherosclerosis and hypertension. With increase of age, many physical and morphological changes occur that cause risk of the disease. The types of cardiovascular diseases include cardiomyopathy, hypertensive heart disease, cardiac dysrhythmias, endocarditis, cor pulmonale, myocarditis, peripheral arterial disease, congenital heart disease, cerebrovascular disease and rheumatic heart disease. The factors which increase the risk of heart diseases are gender, age, high blood pressure, hyperlipidemia, diabetes mellitus, excessive alcohol and sugar consumption, smoking, air pollution, psychosocial factors, lack of physical activity, obesity and family history (Howard et al., 2002; Finks et al., 2012; Bridge et al., 2010). Intake of low fat and high fiber content food, avoiding tobacco smoking, limiting alcohol consumption, decreasing body fat and daily exercise can lessen the danger (Ignarro et al., 2007; World Heart Federation, 2011, The National Heart, Lung and Blood Institute, 2011; Klatsky, 2009; McIntigue et al., 2006). Mineral and vitamin supplements have not shown any positive results in decreasing the risk of the disease but niacin is a type of vitamin B3 which has shown to reduce the risk factors to some extent. Taking magnesium as a diet supplement reduces high blood pressure (Bhupathiraju et al., 2011; Jee et al., 2002). In those patients who have low risk of heart disease, aspirin has proved to be beneficial. In people having history of cardiovascular disease statins are effective (Berger et al., 2011, Gutierrez et al., 2012).

Some of the medicines used to treat cardiovascular diseases are Zocor, Verapamil, Xarelto (rivaroxaban), Tricor (fenofibrate), Tekturna (aliskiren), Soliris (eculizumab), Rythmol, ReoPro, Posicor, Plavix (clopidogrel bisulfate), Normiflo, Natrexor (nesiritide), Micardis (telmisartan), Lescol (fluvastatin sodium), Kynamro ( mipomersen sodium), Inspira (eplerenone tablets), FenoBrite, Diovon (valsartan), Corlopam, Benicar, Azor (amlodipine besylate), Adcirca (tadalafil), Angiomax (bivalirudin) and many others (Murray and Nadel, 2010).

Curcumin is mostly known for its anti-cancer activities but some work has also been done showing its anti-asthmatic and cardioprotective potential. The present review aims to cover the research done on curcumin disclosing its role in asthma and cardiovascular diseases investigated so far.

2. CURCUMIN

Curcumin is a diarylheptanoid and a natural phenol giving colour to turmeric (Dorland, 2011). It exists in tautomeric forms which can be seen in fig. 1 and fig. 2.

It is considered to interact with the molecules involved in inflammation by down-regulating cyclooxygenase-2, lipooxygenase and nitric oxide synthase activity (Gupta, 2011; Abe et al., 1999; Goel et al., 2008). Curcumin has proved to be effective in pancreatic cancer, colon cancer, psoriasis, arthritis, Alzheimer’s disease and multiple myeloma (Hatcher et al., 2009; Yan et al., 2009; Zhao et al., 2012). In colon cancer, it serves as vitamin D receptor ligand (Bartik et al., 2010).
3. CURCUMIN AND RESPIRATORY DISORDERS

Curcumin has been reported to treat Acute Respiratory Distress Syndrome in a model of female rats by alteration of inflammation and myofibroblast differentiation (Avasarala et al., 2013). Some of the lung injuries are induced by aspirating gastrointestinal decontamination agents. Curcumin has also been evidenced to show preventive effect against these injuries because of its anti-inflammatory potential (Gunaydin et al., 2012). Congenital Central Hypoventilation Syndrome (CCHS) has been reported to be due to duplications of the PHOX2B gene. It is suggested that 17-AAG and curcumin are effective in vitro in rescuing the nuclear localization and transactivation activity of PHOX2B carrying the largest expansion of polyAla and promoting the clearance of aggregates of these mutant proteins (Di Zanni et al., 2012). In acute lung injury, curcumin was evidenced to be a good therapeutic agent (Guzel et al., 2009). Curcumin has been found to be an alternative therapy for injury of lung transplantation. It is due to suppression of nuclear factor-kappa B-mediated expression (Sun et al., 2008). Curcumin can be used successfully in the hyperactive states of the gut and airways (Gilani et al., 2005). Curcumin has been reported to inhibit pro-inflammatory cytokine production by lung inflammatory cells ex vivo (Literat et al., 2001). In paraquat lung injury, curcumin has been found to have protective effect (Venkatesan, 2000).

4. ANTI-ASTHMATIC POTENCY OF CURCUMIN

Curcumin is not water-soluble. In one study, its dry emulsion (DE-CUR) was prepared to deliver it orally and checked its anti-asthmatic efficacy by using murine asthma model. Levels of T-helper cytokines (interleukin-4, interleukin-5, interleukin-13) and airway hyperresponsiveness was evidenced to suppress showing effectiveness of DE-CUR as a component of functional foods and asthma medicines (Jang et al., 2014). Intestinal absorption as well as anti-asthmatic potential of curcumin was found to increase by fabricating solid dispersion granules containing curcumin(SDG-CUR), hence, proving it to be a potent oral formulation (Jang et al., 2014). The nasal epithelium serves as a defense during respiratory infections like those caused by respiratory syncytial virus (RSV). Curcumin inhibited the replication and budding of RSV as well as the epithelial responses to it. Moreover, the upregulation of the epithelial barrier function was enhanced. It showed inhibition of NF-kB, eIF-2α dephosphorylation, proteasome and COX2. Without cytotoxicity, it proved to treat lower respiratory tract diseases in young children and infants (Obata et al., 2013).

The evaluation of intranasal curcumin in mouse blood plasma and lung tissue was carried out by HPLC. Detection of the drug was done after every 15 min-3h at a dosage of 5 mg/kg. This dosage showed potency against asthma by bronchoconstriction inhibition and recruitment of inflammatory cells in the lungs. By HPLC, retention of curcumin absorption was reported for up to 3 h. This study evidenced the possibility of curcumin to be used in nasal drops. Curcumin serves to retain breathing after asthma attack (Glickman et al., 2013). In vitro and in vivo experiments were performed to explore the effects of curcumin in asthma on the proliferation of airway smooth muscle cells (ASMCs). As compared to model group, reduction of the airway wall thickness, the number of ASMCs and the expression of extracellular signal-regulated kinase (ERK) were reported in the curcumin treated group. Platelet-derived growth factor (PDGF) which causes cell proliferation is inhibited by curcumin. Moreover, PDGF-induced phosphorylation of ERK ½ was also found to decrease in rats. Protein expression of Caveolin-1 and mRNA was also upregulated by curcumin (Zeng et al., 2013).

The inhibition of the mRNA expression and production of thymic stromal lymphopoietin (TSLP) in the human mast cell line, HMC-1 cells was investigated. The assays used were caspase-1, luciferase, immunosorbent and reverse transcription-polymerase chain reaction. The expression and production of TSLP was evidenced to decrease with the maximum inhibition rate to be 59.16±4.20% at 50µM of curcumin. The luciferase and caspase-1 activity was found to decrease. Hence, the role of curcumin in the treatment of atopic and inflammatory diseases was proved (Moon et al., 2013). In a mouse model of allergic asthma, the mechanism of curcumin on ovalbumin (OVA)-induced allergic inflammation was investigated. Eosinophil count was noted to be increased and OVA-induced eosinophilia in lung tissue was inhibited. Inhibition of Th 17 cells and increase of Treg cells was expressed by flow cytometry (FCM). The use of curcumin in allergic asthma became clear with this study (Ma et al., 2013).

The potential of curcumin to modulate CD4+ Tcells-mediated autoimmune disease was investigated. This treatment resulted in the induction of unfolded protein response (UPR) signaling pathway. Furthermore, increase in the expression of ER stress associated transcriptional factors XBP-1 and cleavage of p50ATF6α and C/EBP homologous protein in CD4+ and Jurkat T cells was also reported(Zheng et al., 2013). The link between curry intake and pulmonary function among smokers and...
non-smokers was studied taking 2,478 Chinese older adults who aged 55 yrs and above in the Singapore Longitudinal Studies. Curry intake was found to be significantly linked with better FEV(1) and large differences in FEV (1) and FEV (1)/FVC% between curry and non-curry intake were recorded among current and past smokers. Mean adjusted FEV (1) for current smokers was 9.2% higher, for past smokers it was 10.3% higher and for non-smokers 1.5% higher (Ng et al., 2012).

Matrix metalloproteinases (MMPs) are found to be involved in asthma. The expression and secretion of various MMPs are reported to be regulated by curcumin (Kumar et al., 2012). Curcumin-solitd lipid nanoparticles (curcumin-SLNs) were studied in an ovalbumin (OVA)-induced allergic rat model of asthma. The tissue concentrations were found to increase followed by suppression of airway hyperresponsiveness. The expression of T-helper-2-type cytokines (interleukin-4 and interleukin-13) were evidenced to be inhibited, thus, proving curcumin-SLNs to be positive in asthma treatment. The role of curcumin in allergic conjunctivitis (AC) in an experimental AC model was investigated. Curcumin was found to suppress allergic conjunctival inflammation (Chung et al., 2012).

A curcumin derivative, CNB001, was checked to control airway epithelial cell function and asthma. Synthetic double-stranded RNA stimulated normal human bronchial epithelial (NHBE) cells. IL-6, TNF-α and GM-CSF production by NHBE cells was suppressed by the derivative of curcumin more effectively than curcumin. It also significantly inhibited the decrease of E-cadherin and vimentin mRNA expression was reported to increase. Overall, the derivative CNB001, treated neurophilic airway inflammation in asthma (Narumoto et al., 2012). In another study, curcumin was found to alleviate the pathological changes of chronic asthma (Karaman et al., 2012).

The inhibitory effects of thymoquinone (TQ) and curcumin on the biological changes linked with asthma were studied. Inflammatory cells’ aggregation was inhibited more by thymoquinone (TQ) in bronchoalveolar lavage (BAL) fluid and lung tissues. More significant decrease of serum IgE was seen by TQ along with greater inhibitory effects on iNOS and TGF-β1. Inhibition of mRNA expression of TNF-α was greater by curcumin (Ammar et al., 2011). Oral administration of curcumin on lung histopathology, serum nitric oxide levels and fungal burden in a murine model of asthma and oropharyngeal candidiasis (OPC) was reported. Improvement of all histological parameters was seen in curcumin treated group and curcumin along with its combination with dexamethasone decreased nitric oxide levels. Decrease in fungal burden was also noted. Hence, treatment of chronic asthma with curcumin was evidenced to be effective along with decrease in OPC frequency (Karaman et al., 2011).

The treatment of stable, persistent atopic asthma with oral curcumin was investigated. Adult patients were selected for the study and they were given 1000 mg of curcumin twice a day or placebo. For a period of six months spirometry was performed followed by asthma control test (ACT) scoring and measurements for fractional excretion of nitric oxide (NO), serum eosinophil count, total IgE and leukocyte count. In the treatment arm, 9 patients were subjected and six were in the placebo group. The given dosage of curcumin was not reported to significantly affect postbronchodilator FEV (1) and ACT scores along with other parameters studied (Kim et al., 2011). Curcumin was evidenced to inhibit allergic airway inflammation and hyperresponsiveness through NF-kB inhibition with an IC(50) of 21.50±1.25µM. Amelioration of mucus occlusion in lung tissues was found to be significant (Oh et al., 2011).

The extract of curcumin (60%) inhibited bacterial infections which result in exacerbation of asthma (Nilani et al., 2010). Curcumin was found to inhibit inflammatory genes in inflammatory lung diseases (Barnes, 2009). Curcumin extract (60%) was reported to scavenge nitric oxide as an alternate anti-asthmatic therapy (Nilani et al., 2009). Curcumin has been evidenced to show anti-inflammatory activity in murine asthma model and lung epithelial cells A549 by suppressing nitric oxide (NO) and iNOS, thus, proving itself to be an adjuvant therapy for airway inflammation (Moon et al., 2008). Curcumin was found to reverse steroid resistance in asthma patients (Meja et al., 2008). Curcumin was also reported to have antiallergic properties as it has inhibitory effects on histamine from mast cells (Kurup et al., 2008).

The role of curcumin as an immunomodulator was investigated by using murine model of latex allergy taking BALB/c mice that were exposed to allergens. As a result, the mice developed latex allergy with a Th2 type of immune response. After treatment with curcumin the allergic responses were controlled (Kurup et al., 2007). Curcumin was found to enhance antibody responses at low doses and can also downregulate the expression of various proinflammatory cytokines (TNF, IL-1, IL-2, IL-6, IL-8, IL-12) and chemokines (Jagetia et al., 2007). Curcumin was reported to be an inhibitor of JNK kinase (Wuyts et al., 2003). Features of asthma, like, airway hyperreactivity to histamine and airway constriction, were induced in guinea pigs by sensitizing them with ovalbumin (OVA). The pigs were treated with curcumin (20 mg/kg body weight) both before and after sensitization. Specific airway
Conductance (SGaw) determined airway constriction and hyperreactivity. Both airway constriction and hyperreactivity were seen to be inhibited significantly, thus, proving curcumin’s effectiveness in OVA-sensitized guinea pigs. Curcumin also inhibited Dermatophagoides farinae (Df)-induced lymphocyte proliferation and production of IL-2. Hence, by inhibition of cytokines’ production, curcumin controls allergic diseases.

5. CARDIOPROTECTIVE POTENCY OF CURCUMIN

Curcumin has been reported to induce autophagy in human umbilical vein endothelial cells (HUVECs) which serves as a therapeutic avenue for the treatment of oxidative stress-related cardiovascular diseases (Han et al., 2012). Curcumin was evidenced to induce cardioprotective effect against catecholamine-induced cardiotoxicity via preservation of mitochondrial function. Male Wistar rats received subcutaneous injection of isoproterenol for a period of 2 days consecutively with or without pretreatment with curcumin 60 mg·kg(-1)·day(-1). Isoproterenol induced apoptosis and cell death which was found to be protected by curcumin. Moreover, mitochondrial swelling and respiration were prevented by curcumin and it prevented the ISO-induced increase in mPTP calcium susceptibility in isolated cardiomyocytes (Izem-Meziac et al., 2012). The turmeric extract has been found to have therapeutic activities that block the cardiac, renal and hepatic toxicities induced by doxorubicin. This is due to its free radical scavenging activity (Mohamad et al., 2009). Curcumin was reported to decrease serum cholesterol level and hence it protects against the pathological changes occurring with atherosclerosis. Curcumin has p300-HAT inhibitory effects and because of this it prevents the development of cardiac hypertrophy and heart failure. It also prevents atrial arrhythmias and ventricular arrhythmias (Wongcharoen et al., 2009). Oral pretreatment with curcumin (200 mg/kg) on isoproterenol-induced myocardial injury in rats was found to increase antioxidant activity of curcumin, hence, showing cardioprotective property (Nazam et al., 2007). Curcumin enhances the activities of detoxifying enzymes like glutathione-S-transferase and inhibits free-radical generation in myocardial ischemia in rats (Miriyala et al., 2007).

6. CONCLUSION

Curcumin is a natural polyphenolic antioxidant compound that exerts anti-inflammatory and immunomodulatory effects influencing the activation of T cells (immune cells). It can also inhibit pro-inflammatory cytokines and chemokines expression by suppressing NF-kB signaling pathway. It is due to its immunomodulatory potential that proves its usefulness in diseases like arthritis, allergy, asthma, atherosclerosis, diabetes and cancer. The article covers the anti-asthmatic and cardioprotective potential of curcumin, yet, its protective role in pulmonary function of smokers needs to be investigated further. Moreover, its synergic effect with other asthma and cardioprotective medicines needs to be checked. New analogs of curcumin to selectively inhibit different MMPs can also be designed. So far, curcumin has shown promising results in asthma and cardiac treatment and further combinatorial studies with synthetic and herbal medicines can open new horizons for research and treatment.

REFERENCES

Arshad SH (2010). Does exposure to indoor allergens contribute to the development of asthma and allergy?. Current allergy and asthma reports, 10: 49-55.
Shahid and Khair-ul-Bariyah

Anti-Asthmatic and Cardioprotective Efficacy of Curcumin - A Review


Dorland (2011). Dorland’s Illustrated Medical Dictionary, 32.


Han J, Pan XY, Xu Y (2012). Curcumin induces autophagy to protect vascular endothelial cell survival from oxidative stress. Autophagy, 8: 812-25.


Watts K, Chavasse RJ (2012). Leukotriene receptor antagonists in addition to usual care for acute asthma in adults and children. Cochrane Database of Systematic Reviews, 5.


Muhammad Tahman Shahid did his BS (Hons) (Biochemistry) from IMBB (Institute of Molecular Biology and Biotechnology), The University of Lahore, Lahore, Pakistan in the year 2010. He did his M.Phil (Biochemistry) from CRIMM (Center for Research in Molecular Medicine), The University of Lahore, Lahore, Pakistan in the year 2014. His areas of research and interest are chemotherapy, molecular biology, enzymology and pathology. He has publications in both national and international journals covering areas of nuclear extract preparation from stem cells, analgesia and cancer medicines. He has expertise in the areas of cell culturing (stem cells), MTT Assay, PCR, ELISA, PAGE, Western Blotting and all blood tests. He is working in partnership as a biochemist in Invitro Diagnostic Centre, Lahore since 2008 and is running his own pathology lab in Gujranwala, Pakistan by the name of Al Asmar Diagnostic Lab.

Syeda Khair-ul-Bariyah did her M.Sc. (Organic Chemistry) from Government College University, Lahore, Pakistan in the year 2007 and completed her M.Phil (Organic/Biochemistry) from Forman Christian College (A Chartered University), Lahore, Pakistan in the year 2011. She has publications in both national and international journals covering areas of effect of essential oils on diabetes and their anti-urease activity, nuclear extract preparation, mineral content, nutritional value and analysis of physical characteristics of essential oils, analgesia and cancer medicines and reviews on medicinal plants. Her main areas of research and interest are medicinal plants, drug discovery and modification. She also has expertise in the areas of stain removal synthesis and synthesis of perfumes. She is also a graduate in science education and currently a masters student of science education with main focus on effective teaching methodologies.