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Eddy E. Owaga *
a* School of Nutrition and Health Sciences, Taipei Medical University, No. 250, Wu-Hsing St., Taipei 110, Taiwan.
Email: eowaga@yahoo.co.uk

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Nutrigenomic Approach in Understanding the Antiallergic Effects of Curcumin

Eddy E. Owaga [a]*, John Mponda[b], Rachael A. Nyang'inja[c]
[a]* School of Nutrition and Health Sciences, Taipei Medical University, No. 250, Wu-Hsing St., Taipei 110, Taiwan.
[b]Department of Pharmacy, College of Medicine, University of Malawi, Private Bag 360 Chichiri, Blantyre 3, Malawi.
[c], Department of Mathematics and Computer Studies, Kisumu Polytechnic, P.O. Box 143-40100, Kisumu, Kenya.

Abstract
Curcumin (diferuloyl methane) is a natural yellow polyphenolic pigment isolated from the rhizomes of the plant Curcuma longa L. (turmeric). Several studies have demonstrated curcumin can inhibit antigen-mediated activation of mast cells, IgE production, airway inflammation and passive cutaneous anaphylaxis in allergy animal models. Nutrigenomics, the study of diet-gene interactions in an individual, is the latest emerging area of nutrition research for disease prevention and intervention. The continued increased prevalence of allergic diseases is a matter of public health concern especially in the developed countries. Therefore, this paper attempts to apply the principles and tools of nutrigenomics on how curcumin can be applied as a target intervention in the prevention of allergy diseases. The mechanistic effects of curcumin on proteomic factors include regulation of histamine release during degranulation, cytokines, eosinophils, iNOS (inducible nitric oxide synthase) and mast cells activation events such as, chymase II and Syk kinase. The mechanistic effects of curcumin on post-translation factors include suppression of Syk-dependent phosphorylation of the adaptor proteins linker of activated T cells and Grb2-associated binder 2, Akt, mitogen-activated protein kinases p38, p44/42 (extracellular signal-regulated kinase 1/2), and c-Jun N-terminal kinase. The mechanistic effects of curcumin on transcription factors include inhibition of TNF-α and tryptase mRNA expression. This paper suggests a novel potential of curcumin for utilization in prevention or management of allergic diseases.

Keywords: curcumin, allergy, proteomics, nutrigenomics, mast cells.

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Introduction: Nutrigenomics in health and disease interventions

Nutrigenomics, the study of diet-gene interactions in an individual, is the latest emerging area of nutrition research for disease prevention and intervention [1]. It involves application of technologies such as transcriptomics (RNA molecules, including mRNA, rRNA, tRNA), proteomics (functions, structures, and interactions of proteins) and metabolomics (chemical processes involving metabolites) [2, 3]. Nutrition and genetics both play an important role in human health and development of chronic diseases. With the recent completion of the human genome project, nutrigenomics is increasingly being recognized as a research area with great potential in providing essential information on the interaction between diet, health and diseases [3, 4]. It is anticipated that nutrigenomics will greatly influence how dietary guidelines for populations and recommendations for individuals will be established in future.

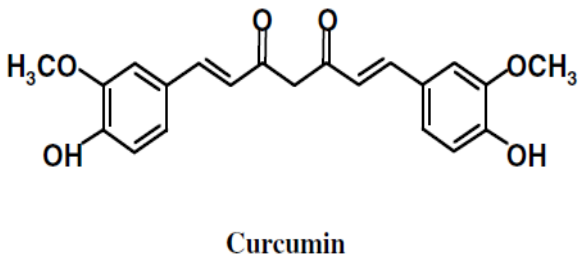
In the recent past, the concept of nutrigenomics has mainly focused on chronic diseases such as obesity, diabetes, cardiovascular diseases, cancer and alcoholism [1, 5-8]. However, the significant increase in type-1 allergic diseases (allergic rhinitis, asthma, atopic eczema) continues to be a serious public health problem, especially in developed countries [9]. School children and adolescents are the most affected as opposed to adults [10]. Though controversial, this increased trend has been attributed to environmental factors namely 'hygiene hypothesis', which suggests that modern methods of hygiene and sanitation have decreased children's exposure to certain microbes, which is thought to lead to less bacteria-derived maturation signals being encountered during early immune development [11]. Apart from the environment and lifestyle concerns, genetic factors have also been implicated in the increased prevalence rates due to the high levels of IgE found in allergic individuals hence predisposing them to allergy response compared to non-allergic persons. Due to the increased trends in allergic diseases, adverse costs, and symptomatic effects of long-term treatment, complementary or alternative dietary methods are necessary in the prevention or improvement of clinical symptoms. Curcumin (diferuloyl methane) is a promising anti-allergic dietary agent that may be useful in the clinical management of allergic disorders [12]. Therefore, this paper attempts to apply the principles and tools of nutrigenomics on how curcumin can be applied as a target intervention in the prevention or management of allergy diseases.

Pathomechanism of type -1 allergy diseases

The pathophysiology of type-1 allergic disorders is associated with elevated production of allergen-specific immunoglobulin E (IgE), which in turn binds high affinity receptor (FcεRI) on the surface of mast cells and sensitizes the mast cells to specific allergens [13]. Subsequent exposures with the allergens result in the cross-linking of the antigen-specific IgE–FcεRI complex, inducing degranulation and rapid release of inflammatory mediators such as histamine, prostaglandins, protease, chemokines and cytokines [11]. These mediators play major roles in causing the allergic-response symptoms, such as mucus secretion, alterations in smooth muscle and blood vessel compartments, airway hyper responsiveness, and recruitment of inflammatory cells [14]. The underlying molecular events include elevated intracellular Ca2+ levels that signal degranulation; increased phospholipase A2 activity in the plasma membrane releasing arachidonic acid-derived prostaglandins and leukotrienes; and enhanced expression of the mitogen-activated protein kinases (MAPK) family and nuclear factor-κB (NF-κB) signalling pathways leading to cytokines secretion [15, 16]. The release of mediators eventually leads to the onset of the allergic symptoms such as sneezing, watery rhinorrhea, itchy nose and nasal obstruction [17]. Due to the increased expenses of drug therapy and side effects of such treatments, there is intense research interest in the role of dietary approach towards the management of allergic disorders.

Source and structure of curcumin

A considerable number of studies suggest curcumin possess potential antiallergic properties. Curcumin (diferuloyl methane) is a natural yellow polyphenolic pigment isolated from the rhizomes of the plant Curcuma longa L. (turmeric) (Fig. 1). It is commonly used as food additive and it has shown a wide spectrum of biological and pharmacological effects such as anti-inflammatory, antioxidant, antimicrobial, antihepatoxic, hypolipidemic, and anticancer properties [12].



Curcumin

Fig. 1. Structure of curcumin (diferuloyl methane), C21H20O6, mwt 368.38

The structure consists of the hydroxyl groups, which largely contributes to the antioxidant and antiallergic activities of curcumin [18]. Due to bioavailability

concerns of curcumin, some studies have explored the potential of derived curcumin analogues towards application of curcumin in various allergy experimental models. For instance, the methoxy-hydroxy analogue was found more potent than curcumin in inhibiting histamine release from rat basophilic leukemia (RBL-2H3) cells but the methyl/ethyl analogues showed less inhibitory effects compared with those of curcumin [19].

Antiallergic effects of curcumin

Several studies, both in vitro and in vivo, have provided strong evidence for the immunomodulatory and antiallergic activities of curcumin by providing more information on the potential underlying cellular and molecular mechanisms. Passive cutaneous anaphylaxis (PCA) model is widely used to simulate allergy conditions in animal studies in order to evaluate the therapeutic potential of various dietary and pharmaceutical agents. Baek et al. studied the antiallergic activity of curcumin in vivo and found curcumin inhibited antigen-mediated activation of mast cells and passive cutaneous anaphylaxis in mice [20]. Choi et al. found curcumin dose-dependently reduced the vascular permeability changes triggered by compound 48/80 in the anaphylaxis response model [21]. Lee et al. also reported that curcumin suppressed the passive cutaneous anaphylaxis reaction in a dose-dependent manner [22]. Other studies showed intranasal curcumin suppressed airway inflammations in mouse model of asthma [23]. In the guinea pig model induced with allergic rhinitis, curcumin reduced the allergy-related symptoms such as sneezing, rubbing frequencies, lacrimation and nasal congestion, and reduced the inflammatory cells infiltration of nasal mucosa [24].

As earlier highlighted in the pathomechanism section, elevated IgE levels is one of the key factors involved in the pathogenesis of allergy. It has been reported that oral administration of curcumin (50 mg/kg) suppressed the mast cell dependent IgE and antigen-induced local passive cutaneous anaphylaxis [12]. Further evaluation of anti-inflammatory properties of curcumin using an asthmatic mice model found serum IgE was significantly decreased by curcumin [25]. Other studies in guinea pig allergy model showed curcumin treatment prevented significantly elevation of serum IgE in nasal lavage [24]. Nishikawa et al. investigated the anti- inflammatory effect of curcumin in compound 48/80 stimulated canine cutaneous mastocytoma mast cells and found reduced degranulation and immunoglobulin IgG cells [26]. Taken together, curcumin may have inhibitory effects on the various allergy models through suppression of transcription, proteomic, and/or metabolomics factors involved in the inflammatory cells such as mast cell-mediated degranulation and cytokine release as deliberated below:

a) Mechanistic effects of curcumin on proteomic factors

Histamine is mainly released from the mast cells granule resulting in increased vascular permeability causes fluid to escape from capillaries into the tissues, and symptoms of an allergic reaction, namely a runny nose and watery eyes. In a study by Choi et al. , pretreatment of rat peritoneal mast cells (RPMCs) with curcumin inhibited degranulation and histamine release in a dose-dependent manner (50 – 100 μM) [21]. Calcium uptake into RPMCs was also inhibited in a concentration-dependent manner, while intracellular cyclic adenosine monophosphate (cAMP) was increased. Lee et al., studied the antiallergic activity of curcumin and its mechanism of action in Bone-marrow derived mast cells (BMMC) and RBL-2H3 cell lines and found that curcumin suppressed antigen-induced degranulation in a dose-dependent manner , however, this effect of curcumin was found to be reversible [22]. It has also been shown that methyl/ethyl and methoxy-hydroxy curcumin analogues can inhibit histamine release in RBL-2H3 cells through blockade of Ca2+ signaling events [19].

Cytokines are key players in the induction and development of allergy-related symptoms. Baek et al. studied the effect of curcumin on protease-activated receptors (PAR2)- and PAR4-mediated HMC-1 mast cell activation and found curcumin (10 and 100 μmol/l) inhibited TNF-α secretion from trypsin or activating peptide-stimulated HMC-1 mast cells [20]. The suppression of degranulation and secretion of TNF- α and IL-4 by curcumin (3 μmol/l) has also been demonstrated in mast cell cultures and the passive cutaneous anaphylaxis model [22]. Moreover, Thakare et al. indicated suppressed IL-4 levels in nasal lavage in guinea pig allergy model after curcumin treatment [24]. Other studies have shown curcumin inhibited OVA-induced increases in interleukin (IL)-17 level in bronchoalveolar lavage fluid and increased IL-10 (T regulatory cells) level in a mouse model of allergic asthma [27]. Curcumin also inhibited house dust mites -induced lymphocyte proliferation and IL-2, IL-5, granulocyte macrophage-colony stimulating factor (GM-CSF), and IL-4 production in vivo [28]. Using a mouse model of allergic asthma, Ma et al observed that curcumin inhibited OVA-induced increases in eosinophil count [27]. In a related study, Srivastava et al., found curcumin (i.p. 10 or 20 mg/kg bw) decreased the frequency of eosinophils and the inflammatory cells, in bronchoalveolar lavage fluid In a murine model of asthma [12]. Thakare et al. also reported that curcumin treatment prevented significantly elevation of eosinophil peroxidase in nasal homogenate of guinea

pig allergy model [24].

The mast cell degranulation is a key step in the pathogenesis of IgE-mediated allergies [29]. Lyn/Syk tyrosine kinases have been directly implicated in FcεRI signalling and activation of mast cell leading to release of the vasoamines and pro-inflammatory mediators [30]. Therefore, Lyn/Syk tyrosine signaling pathway is a potential target for therapeutic intervention in IgE-mediated allergies. Lee et al. determined the antiallergic activity of curcumin in vivo and its mechanism of action in mast cells and found that curcumin did not inhibit the phosphorylation of Syk itself, but it directly inhibited Syk kinase activity in vitro [22]. iNOS (inducible nitric oxide synthase) is involved in immune response and produces large quantities of nitric oxide as an immune defense mechanism. Due to the free radical nature on nitric oxide, it may be involved in inflammation. Srivastava et al. reported that curcumin inhibited iNOS (inducible nitric oxide synthase) expression in lungs in a murine model of asthma [12]. Besides, Thakare et al. also indicated that curcumin treatment prevented elevation of NO in nasal lavage in vivo [24]. Chymases are the major proteins stored and secreted by mast cells. Ju et al. studied Brown rats primed intraperitoneally with β-lactoglobulin then fed on curcumin (0.5%) with 10% coconut oil or safflower oil and observed reduced release of chymase II (RChy II), an indicator of degranulation of mucosal mast cell in intestine [31].

(b)Mechanistic effects of curcumin on post-translation factors

Lee et al. studied the antiallergic activity of curcumin in mast cell cultures and found curcumin suppressed Syk-dependent phosphorylation of the adaptor proteins linker of activated T cells and Grb2-associated binder 2, which are critical molecular events in mast cell activation [22]. In addition, Lee et al. found that phosphorylation of Akt and the mitogen-activated protein kinases p38, p44/42 (extracellular signal-regulated kinase 1/2), and c-Jun N-terminal kinase, which are critical for the production of inflammatory cytokines, were also inhibited by curcumin. Besides, Nishikawa et al. also reported that curcumin inhibited the protein tyrosine- and threonine-phosphorylation in canine cutaneous us mastocytoma mast cells [26]. Furthermore, curcumin inhibited trypsin-induced extracellular signal-regulated kinase (ERK) phosphorylation in protease-activated receptors (PAR2) - and PAR4-mediated HMC-1 mast cells activation [20].

(c) Mechanistic effects of curcumin on transcription factors

Using mast cell knock-in mice, Yu et al. demonstrated that mast cell and FcεRI-dependent mechanisms of mast cell activation are required for optimal expression of enhanced airway responses, airway inflammation, and mucin gene expression in chronic asthma model [32]. Other studies have shown curcumin (10 and 100 μmol/l) inhibited TNF-α and tryptase mRNA expression in trypsin-stimulated HMC-1 mast cells [20]. Ammar et al. studied anti-inflammatory properties of curcumin using an asthmatic murine model and found suppressed TNF-α mRNA expression level [25]. Other studies on the potential anti-inflammatory effects of curcumin showed decreased costimulatory molecule expression (CD80, CD86, and OX40L) on antigen-presenting cells and attenuated expression of MMP-9, OAT, and TSLP genes [28].

Conclusion

This paper suggests a novel potential of curcumin for utilization in prevention or management of allergic diseases via nutrigenomics tools approaches which include the modulatory effects of curcumin on proteomic, post-translation and transcription factors involved in the pathogenesis of allergy. Although most information were mainly derived from in vitro and in vivo models, further trials targeting clinical subjects and ascertaining the cellular and molecular mechanisms of the antiallergic effect could enlarge the utilization area of curcumin as a functional food in prevention or management of type-1 allergy diseases such as allergic rhinitis and asthma.

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