

Curcumin

A Contact Allergen

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Abstract

Background: Herbal medicines are used by thousands of patients all over the world. However, they can often cause adverse effects. Turmeric, made from the root of *Curcuma longa*, is a yellow spice used throughout South Asia for its flavor as well as for its medicinal properties. Curcumin is the main ingredient in turmeric. It is known for downregulating the expression of various proinflammatory cytokines and has been studied for its anti-inflammatory mechanism. However, it has also been reported to cause contact dermatitis. Kunkum, a turmeric-based powder applied by Hindu women on their foreheads, has also been found as an allergen.

Objective: The authors have reviewed the anti-inflammatory properties of curcumin and reports of contact dermatitis to understand the possible harmful effects of this commonly used spice, while also

examining its beneficial role in dermatologic conditions. They aim to increase awareness regarding this common herb and its prevalent use not only in South Asia, but also in North America. **Methods:** A thorough literature search of the PubMed database was conducted to identify studies that examined the anti-inflammatory role of curcumin and its role in contact dermatitis. **Results:** Eleven studies demonstrate that although curcumin does have anti-inflammatory properties, it is an allergen. **Conclusion:** Curcumin has many valuable properties that can be exploited to treat dermatologic conditions. However, patients and dermatologists must be keen of possible allergic reactions. Further studies are needed to completely understand this widely used herb and its efficacy in dermatology.

Introduction

The rhizomes of *Curcuma longa* L., from the family Zingiberaceae, are

the source of turmeric, which has been used for centuries as an herbal medicine, a spice in cooking, in cosmetics, and as a dye. The scalded and dried rhizome provides the crude drug *Rhizoma Curcumae Longae*, otherwise known as turmeric root.^{1,2} As an herbal medicine, it has been used to treat inflammatory processes, liver disorders, dyspepsia, peptic ulcer, infections, mycoses, wounds, and skin disorders. The Community herbal monograph³ recognizes only the traditional use of various herbal preparations of turmeric in solid or liquid dosage forms administered orally to increase bile flow for the relief of symptoms of indigestion (such as sensation of fullness, flatulence, and slow digestion). No dermatological uses are recognized. However, turmeric has been recorded as being applied topically for the treatment of acne, wounds, boils, bruises, blistering, ulcers, eczema, insect bites, parasitic infections, hemorrhages, and skin diseases, such as herpes zoster and pemphigus.³ The curcuminoids contained in the rhizome, which confer a yellow color to turmeric, comprise a mixture of curcumin (also known as diferuloylmethane, Natural Yellow 3, and E100), demethoxycurcumin, and bisdemethoxycurcumin. Curcumin makes up about 90 percent of the curcuminoid content. The rhizome also yields volatile oil and oleoresin, comprising zingiberene, aromatic curcumene, aromatic turmerone, α -turmerone, β -turmerone, α -santalene, and other monoterpenes and sesquiterpenes.^{1,4} Chemical reduction of the mixture of curcuminoids found in turmeric produces a colorless

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material comprising a mixture of tetrahydrocurcuminoids. This semi-synthetic material is included in some cosmetic products as an antioxidant ingredient.

Allergic contact dermatitis (ACD) and its animal model, contact hypersensitivity (CHS), are T cell-mediated inflammatory skin diseases induced by contact allergens. Though numerous cellular and molecular players are known, the mechanism of chemical-induced sensitization remains poorly understood. Recent data identify neutrophils to be critically involved in both the sensitization and elicitation phase of CHS.⁵ Tumor necrosis factor (TNF)-alpha and interferon (IFN)-gamma induce expression of interleukin (IL)-33, and IL-33 produced by keratinocytes contributes to ACD.⁶ Blockade of IL-33, TNF-alpha, and IFN-gamma could represent novel and potent strategies to treat ACD.

Irritant contact dermatitis (ICD) is an eczematous reaction to toxic chemicals contacting the skin and is the most common form of contact dermatitis. It is recognized that irritancy does not represent a single monomorphous entity, but rather a complex biologic syndrome with diverse pathophysiology and clinical manifestations. The clinical presentation is highly variable depending on several factors, including properties and strength of the irritant, dose, duration and frequency of exposure, environmental factors, and skin susceptibility. The pathophysiological mechanism depends on activation of the innate immune system and involves skin barrier disruption, cellular changes, and release of proinflammatory mediators that directly recruit and activate T lymphocytes. The diagnosis of ICD is often clinical and involves a

comprehensive history and examination as well as the exclusion of ACD with patch testing.

Methods

A thorough literature search of the PubMed database was conducted to identify studies that examined the anti-inflammatory role of curcumin and its role in contact dermatitis. No limitations were placed on year or type of study. Only articles in English were included. Search terms used were Ayurveda contact dermatitis, turmeric contact dermatitis, and curcumin contact dermatitis. This revealed a total of 89 articles. After duplicates were removed, 35 articles remained. Titles and abstracts were screened for those articles with studies pertaining to contact dermatitis, while those that examined only the molecular mechanisms were excluded. The final analysis included 11 studies.

Results

Curcumin suppresses pro-inflammatory pathways.^{7,8} It inhibits the expression of TNF-alpha induced IL-1beta, IL-6, TNF-alpha, cyclin E, mitogen-activated protein kinases (JNK, p38 MAPK, and ERK), and NF-kappaB in HaCaT cells.⁹ It can also reverse the anti-apoptotic function of TNF-alpha in skin cells. Curcumin also inhibits phosphorylase kinase activity.^{10,11} PhK integrates multiple signaling pathways and couples these pathways to glycogenolysis and adenosine triphosphate (ATP)-dependent phosphorylation to ensure a continuous energy supply for cell function. It is activated by glycogen phosphorylase and inhibited by glycogen synthase in glycogenolysis; it provides essential energy for producing high-energy phosphate bonds in reactions involving proteins

as well as transferring phosphate bonds from ATP to activate phosphorylase-b. Although it is known to be abundant mostly in muscle, this enzyme is also involved in regulating calcium-dependent phosphorylation events in the epidermis.⁷

Many cases of contact dermatitis caused by curcumin have previously been reported (Table 1). Goh et al¹² described a spice miller who developed dermatitis on the hands caused by curry powder and *Curcuma longa*; he had a positive patch test to *Curcuma longa* 25% in petrolatum.¹² Hata et al¹³ described a woman who developed erythema, papules, and vesicles on the dorsa of her hands after applying a medicament containing *Curcuma longa* on the skin. She had positive patch tests to curcumin 1%, 0.5%, and 0.1% in petrolatum. Kiec-Swierczynska et al¹⁴ described a pasta worker who developed acute contact dermatitis of the hands and forearms due to the yellow color, curcumin, in the pasta that she handled. She had positive patch tests to curcumin 1%, 0.1%, 0.01%, and 0.001% in petrolatum. Two cases of contact urticaria caused by turmeric have also been reported, again in an occupational exposure context.¹⁵ One case appeared to have a nonimmunological etiology and the other an immunological etiology.

Chemical reduction of the mixture of curcuminoids found in turmeric produces a colorless material comprising a mixture of tetrahydrocurcuminoids. This semi-synthetic material is included in some cosmetic products as an antioxidant ingredient. Two cases of contact allergy to this material in the United Kingdom following the use of a sunblock cream have been confirmed by patch testing.^{16,17}

TABLE 1. Evidence of curcumin as an allergen

REFERENCE	PARTICIPANTS (n)	METHODS	RESULTS
Fischer et al²⁸	2 A) 53-year-old man with chlorhexidine solution (0.05% curcumin) for skin disinfection prior to surgery B) 56-year-old woman with chlorhexidine solution to disinfect jugular-venous catheter for hemodialysis	Patch tested with European standard series, supplementary standard series, curcumin in petroleum at 1% and in ethanol at 0.05%	A) Positive for curcumin (++), <i>Myroxylon pereirae</i> (balsam of Peru), and isoeugenol B) Positive for curcumin (+ for 1% in petroleum and +++ for 0.05% in ethanol)
Futrell et al²⁹	55	Patch testing at 25% in petrolatum	2 positive for allergen (3.63%)
Goh et al¹²	1 64-year-old man, miller in spice shop with dermatitis on hands, forearms, and dorsa of feet	Positive patch test at 25% in petroleum	Positive for turmeric powder—sensitization through airborne dust created by milling
Hata et al¹³	1 31-year-old woman sensitized to Chinese herbal ointment, Chuu-ou-kou	Initial Turmeric patch testing at 2.5%, 1.25%, and 0.25% petroleum Additional patch tests for curry powder and ginger at 2.5%, 12.5%, 25% petroleum separately, cinnamic aldehyde at 1.0%, 0.5%, 0.1% petroleum, cinnamic alcohol at 1.0% lanolin, and vanilla essence at 10.0% petroleum	Positive for curcumin, kankyo of ginger family, cinnamic aldehyde and cinnamic alcohol. Negative for vanilla essence—common benzene ring Aryl group connecting to benzene ring is antigenic
Kiec-Swierczynska et al¹⁴	1 – 59 year old female in pasta factory with curcumin as food color	Patch testing of curcumin at 1%, 0.1%, 0.01%, and 0.001%; curcuma at 10%, 1%, 0.1%; curry powder 10% and 1%; ginger powder 10% and 1%; cinnamic alcohol 2%; cinnamic aldehyde 1%; isoeugenol 2%	Positive to very low concentrations of curcumin (0.001%), curcuma, curry spice blend containing <i>Curcuma longa</i> , and powdered ginger, which belongs to the same family of plants as <i>Curcuma longa</i> . Positive patch tests to cinnamic alcohol and cinnamic aldehyde Reacted to isoeugenol (shares structure with curcumin, cinnamic alcohol, aldehyde) without being positive to eugenol
Kumar et al²¹	20	Patch testing of Kum-kum vs. European standard series of allergans vs. brilliant lake red R, sudan I, aminoazobenzene and canaga oil	20 positive for kum-kum, Brilliant Lake Red R, sudan I, amino-azobenzene and canaga oil (100%) 0 positive for European standard series of allergans
Lamb et al¹⁷	1 54-year-old woman with eczematous reaction to Avon Age Block Environmental Protection Cream® (Corby, UK)	Patch testing of British standard series and facial series and sunblock cream	Positive for tetrahydrocurcuminoid (1% petroleum)

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TABLE 1 continued. Evidence of curcumin as an allergen

REFERENCE	PARTICIPANTS (n)	METHODS	RESULTS
Liddle et al ¹⁵	2 A) 44-year-old woman mixing ingredients at nutritional supplement company B) 20-year-old woman with pruritus and urticarial lesions that responded to intramuscular diphenhydramine	A) Patch testing with North American Contact Dermatitis Group screening tray—negative; prick testing with curcumin—positive B) Prick testing with curcumin—positive	A) Nonimmunological etiology (histamine, prostaglandins, leukotrienes, and substance P) B) Immunological etiology (IgE mediated)
Nath et al ²³	46 30 women (65.2%) and 16 (34.8%) men with kum-kum induced dermatitis Pigmented contact dermatitis (35/46) in 76.1% Allergic contact dermatitis (11/46) in 23.9%	Patch testing using cosmetic battery and Indian Standard series of allergens done on 25 patients Patch testing with patient's own kumkum was performed only on 13 patients	Positive allergic reactions were seen to thimerosal (18/25; 72%), gallate mix (12/25; 48%), and one each (1/25; 4%) to paraphenylenediamine (PPD), Kathon CG (methylchloroisothiazolinone and methylisothiazolinone; Supelco Inc., State College, PA), benzotriazol, tertbutyl hydroquinone and parabens. Positive for kum-kum in 7/13 patients patch tested; allergic CD to kum-kum was seen in 11 out of 46 patients (23.9%).
Sundaram et al ³⁰	1 18-year-old woman with hypopigmented patch on front of neck	Clinical examination	Gradual repigmentation started after she stopped application of vermilion. Complete repigmentation occurred after topical moderately potent steroid application. Sweat retention in the anterior hollow of neck may be a factor.
Thompson et al ¹⁶	1 53-year-old woman with application of Avon Age Block cream® (Avon Cosmetics Limited, Northampton, UK)	Patch testing to European Standard Series, Avon Age Block cream, and 26 individual ingredients of the product	Positive for tetrahydracurcumin (1% petroleum)

Discussion

Typically, kumkum is used by women of Hindu Indian origin as a mark of their marital status.^{18–21} Interestingly, however, men formed a significant proportion (16/46; 34.8%)

of cases with kumkum-induced dermatitis in a study by Nath et al.²³ CD to kumkum is typically localized to the site of application; however, the surrounding skin may be involved if the kumkum trickles down the skin in

sweat.^{18,20–22} Kumkum can produce both allergic and pigmented CD. In a study by Nath et al, allergic CD to kumkum was seen in 11 out of 46 patients (23.9%).²³ The term “pigmented contact dermatitis” was

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introduced by Osmundsen in 1970 to explain the pigmentation that followed CD; however, the dermatitis may not be clinically overt and hyper- or hypo-pigmentation may be the only visible symptom of a contact allergy.²⁴

Kumkum is emerging as an important cause of pigmented CD, with several recent reports.^{1,4} It appears that only “red kumkum” can sensitize and cause pigmented CD.¹⁸ The reason might be that red kumkum is more commonly used than other colored kumkum formulations, and that probably only red kumkum contains a high percentage of the sensitizers that cause pigmented CD.¹⁸ Commercially prepared kumkum is colored with azo dyes, and this can cause pigmented CD.²⁰ Kumkum is also known to contain the dye Brilliant Lake Red R,1,3 which has been implicated in pigmented CD.²⁵ In south Indian states, kumkum is prepared at home by alkalizing pure turmeric powder, but commercial kumkum is used more often nowadays.¹⁹ The exact composition of commercially available kumkum is not known, but it contains starch or chalk powder colored with various azo dyes.^{18,20} Other known components in commercial kumkum include various other dyes (coal tar dyes, toluidine red, erythrosine, and lithol red calcium salt), eight fragrances, groundnut oil, tragacanth gum, tumeric powder, parabens, and canaga oil.^{18,21} Goh et al¹⁸ reported positive reactions with Brilliant Lake Red R, Sudan I, and aminoazobenzene and canaga oil in patients with kumkum-induced dermatitis. Laxmisha et al²⁶ reported positive patch test reactions to thimerosal and gallate mix in kumkum-induced dermatitis. Thimerosal is widely used as a preservative in vaccines, eye medications, contact-lens solutions, solutions for intracutaneous skin

testing, immunoglobulin preparations, and cosmetics.²⁷ Sensitization can occur in childhood due to vaccination.²⁷ Hence, a positive patch test reaction should be evaluated with care.²⁷ In a study by Nath et al,²³ patients with kumkum-induced dermatoses showed positive allergic reactions to thimerosal (18/25 patients), gallate mix (12/25), and PPD, Kathon CG, benzotriazol, tert-butyl hydroquinone, and parabens [one patient (4%) each].²¹ The positive reaction to PPD can be explained by cross reactivity to azo dyes, which may be present in commercial kumkum.

Conclusion

Hypersensitivity, type 1 allergy, to spices is common but type 4 allergy is rare. Curcumin has many valuable properties that have been exploited to treat dermatologic conditions. However, it can serve as a contact allergen. Further studies are needed to completely understand this widely used herb, its mechanism of action, efficacy in dermatology, and possible allergic reactions.

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