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Safety and Anti-Inflammatory Activity of Curcumin: A Component of Tumeric (*Curcuma longa)*

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ABSTRACT

Introduction: Tumeric is a spice that comes from the root *Curcuma longa,* a member of the ginger family, Zingaberaceae. In Ayurveda (Indian traditional medicine), tumeric has been used for its medicinal properties for various indications and through different routes of administration, including topically, orally, and by inhalation. Curcuminoids are components of tumeric, which include mainly curcumin (diferuloyl methane), demethoxycurcumin, and bisdemethoxycurcmin.

Objectives: The goal of this systematic review of the literature was to summarize the literature on the safety and anti-inflammatory activity of curcumin.

Methods: A search of the computerized database MEDLINE™ (1966 to January 2002), a manual search of bibliographies of papers identified through MEDLINE, and an Internet search using multiple search engines for references on this topic was conducted. The *PDR for Herbal Medicines,* and four textbooks on herbal medicine and their bibliographies were also searched.

Results: A large number of studies on curcumin were identified. These included studies on the antioxidant, anti-inflammatory, antiviral, and antifungal properties of curcuminoids. Studies on the toxicity and anti-inflammatory properties of curcumin have included *in vitro,* animal, and human studies. A phase 1 human trial with 25 subjects using up to 8000 mg of curcumin per day for 3 months found no toxicity from curcumin. Five other human trials using 1125–2500 mg of curcumin per day have also found it to be safe. These human studies have found some evidence of anti-inflammatory activity of curcumin. The laboratory studies have identified a number of different molecules involved in inflammation that are inhibited by curcumin including phospholipase, lipooxygenase, cyclooxygenase 2, leukotrienes, thromboxane, prostaglandins, nitric oxide, collagenase, elastase, hyaluronidase, monocyte chemoattractant protein-1 (MCP-1), interferon-inducible protein, tumor necrosis factor (TNF), and interleukin-12 (IL-12).

Conclusions: Curcumin has been demonstrated to be safe in six human trials and has demonstrated anti-inflammatory activity. It may exert its anti-inflammatory activity by inhibition of a number of different molecules that play a role in inflammation.

INTRODUCTION

Tumeric

Tumeric is a spice that comes from the root *Curcuma longa,* a member of the ginger family, Zingaberaceae (Pierce, 1999). It is bright yellow and has been used as a coloring agent in food in the United States. In India, it has been used for centuries as a spice and a food preservative, and also for its various medicinal properties.

In Ayurveda (Indian traditional medicine),

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tumeric has been used for various purposes and through different routes of administration. It has been used topically on the skin for wounds, blistering diseases such as pemphigus and herpes zoster, for parasitic skin infections, and for acne. It has been used via oral administration for the common cold, liver diseases, urinary tract diseases, and as a blood purifier. For chronic rhinitis and coryza, it has been used via inhalation (Eigner and Scholz, 1999; Majeed et al., 1996)

Curcumin

In the last few decades there has been considerable interest in the active compounds in tumeric called curcuminoids. The major curcuminoid is called curcumin (diferuloyl methane), which makes up approximately 90% of the curcuminoid content in tumeric, followed by demethoxycurcumin and bisdemethoxycurcmin. (Ruby et al., 1995). Hundreds of *in vitro* and animal studies have been published describing the antioxidant, anti-inflammatory, antiviral, and antifungal (Apisariyakul et al., 1995; Roth et al., 1998) properties of curcuminoids (Ammon et al., 1993; Bisset, 1994; Miller and Murray, 1998; White and Foster, 2000; Young-Joon, 1999). The curcuminoids give tumeric its bright yellow color.

OBJECTIVES

The goal of this systematic review of the literature was to summarize the literature on the safety and anti-inflammatory activity of curcumin. There is a great need for safe and effective anti-inflammatory medications, especially those that are effective in the treatment of autoimmune diseases, where long-term therapy is often needed.

METHODS

A search of the computerized database MEDLINE™ (1966 to January 2002), and a manual search of bibliographies of papers identified through MEDLINE was conducted. An Internet search using multiple search engines including Yahoo, Google, Vivisimo, and the keywords "curcumin" and "tumeric" for references on this topic was also conducted. The *Physicians Desk Reference (PDR) for Herbal Medicines* (2000) and four textbooks on herbal medicine (Majeed et al., 1995; Miller and Murray, 1998; Peirce, 1999; White and Foster, 2000) and their bibliographies were also searched.

RESULTS

A large number of studies on curcumin were identified. A search of MEDLINE™ using the keyword "curcumin" yielded 666 citations. These included studies on the toxicity, antioxidant, anti-inflammatory, antiviral, and antifungal properties of curcuminoids. Studies on the safety and the anti-inflammatory properties of curcumin have included *in vitro* studies, animal studies, and human studies.

Toxicity: turmeric, tumeric extracts, and curcumin

The average intake of tumeric in the diet in India is approximately 2–2.5 g in a 60-kg individual. This corresponds to an intake of approximately 60–100 mg of curcumin daily (Shah, 1999). The Food and Drug Administration has classified tumeric among substances Generally Recognized as Safe (GRAS).

Toxicity studies on animals have been conducted and curcumin has been found to be safe even at high doses in most studies in rats, guinea pigs, and monkeys (Shankar et al., 1980). However, some species (e.g., mice; and in rats with prolonged high-dose intake) are susceptible to hepatotoxicity on ingesting tumeric.

Ames test

- Turmeric extracts and curcumin have been tested for mutagenicity using the Ames test. They were found to be nonmutagenic (Nagabhushan and Bhide, 1986).

Animal studies

- In rats, a single feeding of a 30% tumeric diet produced no toxic effects (Majeed et al., 1996).

- Addition of turmeric (0.5%) or curcumin (0.015%) to the diet of mice did not have a significant effect on the incidence of chromosomal damage, pregnancy rate, number of live and dead embryos, total implants, and mutagenic index (Vijayalaxmi, 1980).
- A study in which rats were fed curcumin 1.8 g/kg per day for 90 days and monkeys were fed 0.8 mg/kg per day for 90 days showed no adverse effects (Majeed et al., 1995).
- A study was performed using Wistar rats and female Swiss mice who were fed tumeric (0%, 1%, and 5%) and ethanolic tumeric extract (0%, 0.05%, and 0.25%) in their diet for 14 and/or 90 days. The rats did not show any adverse effects at 14 days at any dose of tumeric, while the mice showed some evidence of hepatotoxicity at all the above doses at 14 days. The rats fed the high dose of 5% tumeric for a longer period of 90 days showed a reduction in body weight gain, alterations in liver weights, and hepatotoxicity (Deshpande et al., 1998).
- Hepatotoxicity was seen in mice fed whole turmeric (0.2%, 1%, 5%) or ethanolic tumeric extract (ETE; 0.05%, 0.25%) for 14 days (Kandarkar et al., 1998).

Human studies

- A phase 1 study with 25 subjects found no toxic effects of curcumin even with administration of 8000 mg of curcumin per day. Serum concentration was highest 1–2 hours after oral administration and gradually declined within 12 hours (Cheng et al., 2001).
- Eighteen (18) patients with rheumatoid arthritis (ages 22–48 years) were given 1200 mg/d of curcumin for 2 weeks. No side-effects were reported by the patients and no significant changes in blood pressure, pulse, erythrocyte sedimentation rate (ESR), renal or hepatic function were seen (Deodhar et al., 1980).
- In a controlled trial of 5-day duration with 45 postsurgical patients and three groups—placebo, curcumin (1200 mg/d), and phenylbu-tazone (300 mg/d)—1 patient in the curcumin group complained of mild transient giddiness on the third postoperative day, while 1 patient in the placebo group complained of nausea on the first postoperative day. There was no change in blood tests carried out before and after drug administration (Satoskar et al., 1986).
- A study was conducted on 19 patients with acquired immune deficiency syndrome (AIDS) who were given 2500 mg of curcumin per day. Two patients had some gastric irritation, one of whom had a past history of peptic ulcers. No other adverse reactions were reported, and blood tests (a complete blood count with differential, chemistry panel, amylase) showed no adverse effects (James, 1994).
- Other clinical studies (Lal et al., 1999, 2000) using doses of 1125 mg/d have not found any side effects in humans at these doses.

In summary, tumeric extracts and curcuminoids have been shown to be safe at even high doses. However, it has been shown to cause some gastric irritation in humans, hepatotoxicity in mice, and at high doses, hepatotoxicity in rats.

Humans appear to be able to tolerate high doses of curcumin without significant side-effects. This may be because of differences in metabolism of curcumin in humans as compared to susceptible species such as rats.

A study of curcumin metabolism (Ireson et al., 2002) in subcellular fractions of human and rat intestinal tissue, in the corresponding hepatic fractions as well as *in situ* in intact rat intestinal sacs, found differences between the two species. Curcumin conjugation was found to be much greater in intestinal fractions from humans than in those from rats, whereas curcumin conjugation was less extensive in hepatic fractions from humans as compared to those from rats. Cytosol from human intestinal and liver tissue exhibited 18 and 5 times, respectively, the curcumin-reducing ability as that observed with the corresponding rat tissue. Thus, it was concluded that in humans, extensive metabolic conjugation and reduction of curcumin occurs in the gastrointestinal tract, and that there is more metabolism in human than in rat intestinal tissue.

Because of an inhibitory effect on platelet aggregation, there is a potential for curcumin to interact with antiplatelet and anticoagulant

medications (Shah et al., 1999). In addition, curcumin should be used with caution in patients with gallstones, because it can stimulate gallbladder contractions (Rasyid and Lelo, 1999).

Evidence of anti-inflammatory activity

A large number of *in vitro* and animal studies have been conducted to evaluate the effect of curcumin on inflammation. It has been found to act at various different levels of the arachadonic acid inflammatory cascade and through effects on various enzymes and cytokines. Based on the findings of the following studies, the anti-inflammatory effect of curcumin may be via the following different mechanisms.

In vitro studies

- By decreasing the catalytic activities of phospholipase A_2 and phospholipase C γ_1, thereby decreasing arachadonic acid release from cellullar phosphoilipid (Rao et al., 1995).
- Inhibitory effect on phospholipase D activity (Yamamoto et al., 1997).
- Inhibition of cyclo-oxygenase-2 (COX-2) expression (Goel et al., 2001; Plummer et al., 1999; Ramsewak et al., 2000; Zhang et al., 1999)
- Inhibition of lipopolysaccharide (LPS) and interferon-γ–induced production of nitric oxide in macrophages (Brouet and Ohshima, 1995) and nitrite in peritoneal cells (Chan et al., 1995b).
- Downregulation of chemokine expression (monocyte chemoattractant protein-1 [MCP-1, and interferon-inducible protein) in bone marrow stromal cells (Xu et al., 1997).
- Inhibition of lipooxygenase (Ammon et al., 1993; Began et al., 1998; Skrzypczak-Jankun et al., 2000).
- Inhibition of tumor necrosis factor (Chan, 1995a).
- Blockade of the interleukin 1a and TNFa-induced activation of ubiquitous transcription factors AP-1 and NF-kB in bone marrow stromal cells. (Xu et al., 1997–1998)
- Inhibitory effect on platelet-activating factor and arachadonic acid mediated platelet aggregation through inhibition of thromboxane formation and Ca^{2+} signaling (Shah et al., 1999).
- Inhibition of T_H1 cytokine profile in $CD4^+$ T cells by suppressing interleukin-12 production in macrophages (Kang et al., 1999a, 1999b).
- Inhibition of incorporation of arachadonic acid into membrane lipids, inhibition of prostaglandin E_2, leukotriene B_4, leukotriene C_4, inhibition of secretion of collagenase, elastase, hyaluronidase by macrophages (Joe and Lokesh, 1997).
- Blockade of cyclosporin A-resistant CD28 costimulatory pathway of human T-cell proliferation (Ranjan et al., 1998).

Figure 1 summarizes the information from these studies with a diagrammatic representation of the sites of action of circumin along the pathway of inflammation.

Animal studies

- Oral administration of curcumin to rats decreased levels of Gp A 72 (a glycoprotein found in increased levels in rats with adjuvant-induced arthritis) by 73%, with concomitant lowering of paw inflammation. (Joe et al., 1997).
- In carrageenin-induced paw edema in rats and mice, the ED_{50} (dose effective in reducing edema by 50%) in mice was 48 mg/kg curcumin, and 45 mg/kg cortisone. In rats it

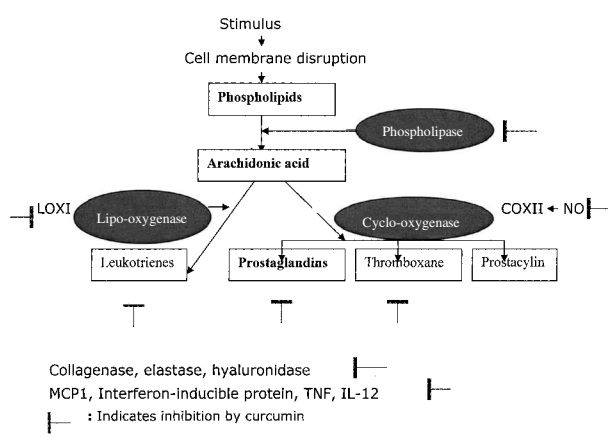

FIG. 1. Sites of action of curcumin along the pathway of inflammation. MCP-1, monocyte chemoattractant protein-1; COX-II, cyclo-oxygenase-II; TNF, tumor necrosis factor; IL-12, interleukin-12.

was 100.2 mg/kg curcumin and 78 mg/kg cortisone (Srimal and Dhawan, 1973).

Human studies

- A double-blinded crossover trial was performed on 18 patients with rheumatoid arthritis. All patients received 1200 mg/d of curcumin for 2 weeks and 300 mg/d of phenylbutazone for another 2 weeks. The sequence of administration of the two medications was randomly allocated. Statistically significant improvement in morning stiffness, walking time, and joint swelling were seen at the end of both treatment regimens as compared to baseline, however the magnitude of the improvement was higher after the phenylbutazone regimen (Deodhar et al., 1980).
- A randomized placebo-controlled double-blinded trial was conducted on 45 postsurgical patients (hernia or hydrocele). Patients were randomly assigned to receive curcumin (1200 mg/d), phenylbutazone (300 mg/d), or placebo for 5 days. Four clinical parameters of inflammation and pain were evaluated: spermatic cord edema, spermatic cord tenderness, pain at operative site, and tenderness at operative site. These were evaluated using a semiquantitative scale of 0, absent; 1, mild; 2, moderate; and 3, severe. Addition of these gave a total intensity scale ranging from 0 to 12. Mean reduction in total intensity score at day 6 for curcumin was 2.38 (standard error [SE] 0.59, $p < 0.01$), for phenylbutazone was 1.57 (SE: 0.55, $p < 0.05$), and for placebo was 1.0 (SE: 0.79, not significant [NS]). Curcumin was demonstrated to be efficacious in reducing these parameters of postoperative inflammation (Satoskar, et al., 1986).
- An open-label trial enrolled 53 patients with chronic anterior uveitis, of whom 32 patients completed a 12-week course of treatment. Of these, 18 patients were given 1125 mg of curcumin per day for 12 weeks, and an improvement in all patients on curcumin alone was noted. The remaining 14 patients had a strong purified protein derivitive (PPD) reaction and were given antitubercular treatment as well as 1125 mg of curcumin daily for 12 weeks. In this group 12 patients (86%) showed improvement in response to the treatment. This study did not have a control group and was not blinded. Curcumin was discontinued after 12 weeks. Over the next 3 years, biweekly follow-up examinations were conducted and 55% of patients in the first group and 36% in the second group had a recurrence (Lal et al., 1999).
- A case series included 5 patients with idiopathic inflammatory orbital tumors (infiltration of orbital fat by lymphocytes, eosinophils and plasma cells). All five patients were given curcumin 375 mg three times per day (1125 mg each day), for 6–22 months. Four patients recovered completely, while in one patient the swelling regressed completely but some limitation of movement persisted.

DISCUSSION

Tumeric extracts have been demonstrated to be safe in animal studies in a number of species, although some species have been found to be susceptible to hepatotoxicity after ingesting large amounts of turmeric or tumeric extracts. This has been hypothesized to be caused by differences in metabolism between different species. A difference in curcumin metabolism between humans and rats, a species susceptible to hepatotoxicity with high doses, was demonstrated in a study by Ireson et al. (2002). Humans appear to be able to tolerate high doses of curcumin without significant side-effects. A phase 1 study by Cheng et al. (2001), found no adverse effects of curcumin ingestion for 3 months of doses upto 8000 mg/d. Other human studies of curcumin include the following: a double-blinded, crossover trial in 18 patients with rheumatoid arthritis (Deodhar et al., 1980), a randomized, placebo-controlled trial with 45 postsurgical patients (Satoskar et al., 1986), a study on 19 patients with AIDS (James, 1994), an open-label trial of 32 patients with chronic anterior uveitis (Lal et al., 1999), and a case series of 5 patients with idiopathic inflammatory orbital tumors (Lal et al., 2000). The doses of curcumin in these studies ranged

from 1125 mg/d to 2500 mg/d. Two (2) patients with AIDS reported gastric irritation, of whom 1 had a past history of peptic ulcers. One (1) postsurgical patient reported mild transient giddiness. No other adverse reactions were reported, including changes in blood reports. Thus curcumin appears to be safe in humans even at high doses.

Various *in vitro* and animal studies point to the possible mechanisms of the anti-inflammatory activity of curcumin. Curcumin has been shown to inhibit a number of different molecules involved in inflammation including phospholipase, lipooxygenase, COX-2, leukotrienes, thromboxane, prostaglandins, nitric oxide, collagenase, elastase, hyaluronidase, MCP-1, interferon-inducible protein, tumor necrosis factor, and interleukin-12.

The four published human reports on the anti-inflammatory activity of curcumin have all reported some anti-inflammatory activity. The first study was a double-blinded crossover trial (Deodhar et al., 1980) of 18 patients with rheumatoid arthritis receiving curcumin and phenylbutazone each for 2 weeks. Improvement in morning stiffness, walking time, and joint swelling was seen at the end of both treatment regimens compared to baseline, however, the magnitude of improvement was greater in the phenylbutazone group. There was no washout period between the two treatment regimens, and some carry-over effect between the two regimens is likely. Furthermore, because of the lack of a placebo group the efficacy of curcumin cannot be adequately assessed (Deodhar et al., 1980). The second study was a randomized, double-blinded, placebo-controlled trial by Satoskar et al. (1986) conducted on 45 postsurgical patients (hernia or hydrocele). Four clinical parameters of inflammation and pain were evaluated: spermatic cord edema, spermatic cord tenderness, pain at operative site, and tenderness at operative site. Curcumin was demonstrated to be efficacious in reducing these parameters of postoperative inflammation. The third (Lal et al., 1999) was an open-label, nonrandomized study of patients with chronic anterior uveitis, comparing two groups: one group ($n = 18$) received curcumin alone and the second group comprised patients who had a strong PPD reaction ($n = 14$) received curcumin plus antitubercular medication. Both groups showed improvement. However, because both groups received curcumin, the efficacy of curcumin cannot be adequately assessed. The fourth report (Lal et al., 2000) was a case series that reported on the experience of a small sample of five patients with idiopathic inflammatory orbital pseudotumors, where all five patients showed improvement after treatment with curcumin. In summary, there are some clinical data suggestive of anti-inflammatory activity of curcumin, including one randomized, double-blinded, placebo-controlled trial. However, more randomized, blinded, controlled human studies are needed to evaluate the efficacy of curcumin as an anti-inflammatory medication for different indications.

CONCLUSIONS

Curcumin has been demonstrated to be safe in six human trials and has demonstrated anti-inflammatory activity. Laboratory studies have identified a number of different molecules involved in inflammation that are inhibited by curcumin including, phospholipase, lipooxygenase, COX-2, leukotrienes, thromboxane, prostaglandins, nitric oxide, collagenase, elastase, hyaluronidase, MCP-1, interferon-inducible protein, tumor necrosis factor, and interleukin-12.

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