Anti-inflammatory Properties of Curcumin, a Major Constituent of *Curcuma longa*: A Review of Preclinical and Clinical Research

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Abstract

Curcuma longa (turmeric) has a long history of use in Ayurvedic medicine as a treatment for inflammatory conditions. Turmeric constituents include the three curcuminoids: curcumin (diferuloylmethane; the primary constituent and the one responsible for its vibrant yellow color), demethoxycurcumin, and bisdemethoxycurcumin, as well as volatile oils (tumerone, atlantone, and zingiberone), sugars, proteins, and resins. While numerous pharmacological activities, including antioxidant and antimicrobial properties, have been attributed to curcumin, this article focuses on curcumin's anti-inflammatory properties and its use for inflammatory conditions. Curcumin's effect on cancer (from an anti-inflammatory perspective) will also be discussed; however, an exhaustive review of its many anticancer mechanisms is outside the scope of this article. Research has shown curcumin to be a highly pleiotropic molecule capable of interacting with numerous molecular targets involved in inflammation. Based on early cell culture and animal research, clinical trials indicate curcumin may have potential as a therapeutic agent in diseases such as inflammatory bowel disease, pancreatitis, arthritis, and chronic anterior uveitis, as well as certain types of cancer. Because of curcumin's rapid plasma clearance and conjugation, its therapeutic usefulness has been somewhat limited, leading researchers to investigate the benefits of complexing curcumin with other substances to increase systemic bioavailability. Numerous in-progress clinical trials should provide an even deeper understanding of the mechanisms and therapeutic potential of curcumin. *(Altern Med Rev* 2009;14(2):141-153)

Introduction

Turmeric (the common name for *Curcuma longa*) is an Indian spice derived from the rhizomes of the plant and has a long history of use in Ayurvedic medicine as a treatment for inflammatory conditions. *C. longa* is a perennial member of the Zingiberaceae family and is cultivated in India and other parts of Southeast Asia.[1] The primary active constituent of turmeric and the one responsible for its vibrant yellow color is curcumin, first identified in 1910 by Lampe and Milobedzka.[2] While curcumin has been attributed numerous pharmacological activities, including antioxidant[3] and antimicrobial properties,[4] this article focuses on one of the best-explored actions, the anti-inflammatory effects of curcumin. Curcumin's effect on cancer (from an anti-inflammatory perspective) is also discussed; however, an exhaustive review of its many anticancer mechanisms is outside the scope of this article. Based on early research conducted with cell cultures and animal models, pilot and clinical trials indicate curcumin may have potential as a therapeutic agent in diseases such as inflammatory bowel disease, pancreatitis, arthritis, and chronic anterior uveitis, as well as certain types of cancer. Numerous clinical trials are currently in progress that, over the next few years, will provide an even deeper understanding of the therapeutic potential of curcumin.

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Active Constituents

Turmeric is comprised of a group of three curcuminoids: curcumin (diferuloylmethane), demethoxycurcumin, and bisdemethoxycurcumin (Figure 1), as well as volatile oils (tumerone, atlantone, and zingiberone), sugars, proteins, and resins. The curcuminoid complex is also known as Indian saffron.[5] Curcumin is a lipophilic polyphenol that is nearly insoluble in water[6] but is quite stable in the acidic pH of the stomach.[7]
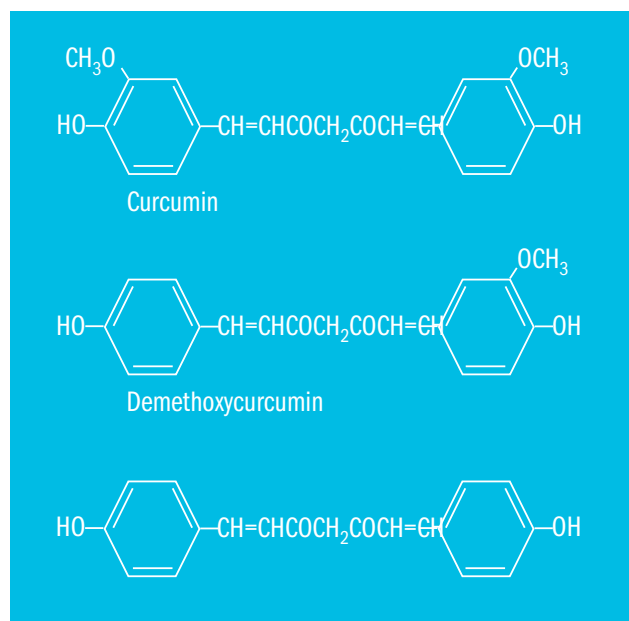
Absorption of Curcumin

Animal studies have shown curcumin is rapidly metabolized, conjugated in the liver, and excreted in the feces, therefore having limited systemic bioavailability. A 40 mg/kg intravenous dose of curcumin given to rats resulted in complete plasma clearance at one hour post-dose. An oral dose of 500 mg/kg given to rats resulted in a peak plasma concentration of only 1.8 ng/mL, with the major metabolites identified being curcumin sulfate and curcumin glucuronide.[8]

Data on the pharmacokinetics, metabolites, and systemic bioavailability of curcumin in humans, mainly conducted on cancer patients, are inconclusive. A phase I clinical trial conducted on 25 patients with various precancerous lesions demonstrated oral doses of 4, 6, and 8 g curcumin daily for three months yielded serum curcumin concentrations of only 0.51 ± 0.11, 0.63 ± 0.06, and 1.77 ± 1.87 µM, respectively, indicating curcumin is poorly absorbed and may have limited systemic bioavailability. Serum levels peaked between one and two hours post-dose and declined rapidly. This study did not identify curcumin metabolites and urinary excretion of curcumin was undetectable.[9]

Another phase I trial, involving 15 patients with advanced colorectal cancer, used curcumin at doses between 0.45 and 3.6 g daily for four months. In three of six patients given the 3.6 g dose, mean plasma curcumin measured after one hour on day 1 was 11.1 ± 0.6 nmol/L. This measurement remained relatively consistent at all time points measured during the first month of curcumin therapy. Curcumin was not detected in the plasma of patients taking lower doses. Glucuronide and sulfate metabolites of curcumin were detected in plasma of all six patients in the high-dose group at all measurement points in the study.[10] Curcumin levels reported in this study are approximately

Figure 1. Structures of Curcumin (Diferuloylmethane), Demethoxycurcumin, and Bisdemethoxycurcumin


1/45 of the levels reported by Cheng et al, who used a similar dose of curcumin (4 g).[9] The reason for the discrepancy is unclear.

While systemic distribution of curcumin tends to be low, Garcea et al demonstrated that 3.6 g curcumin given to 12 patients with varying stages of colorectal cancer for seven days resulted in pharmacologically efficacious levels of curcumin (12.7 ± 5.7 nmol/g) in both malignant colorectal tissue and normal colorectal tissue (7.7 ± 1.8 nmol/g), perhaps accounting for the anti-inflammatory benefits of curcumin observed in diseases of the gastrointestinal tract.[11]

Although research on curcumin pharmacokinetics in healthy subjects is limited, one study using high doses (10 and 12 g in a single oral dose) in 12 healthy subjects measured serum curcumin as well as its sulfate and glucuronide metabolites at various time points up to 72 hours post-dose. As in previous studies, curcumin was rapidly cleared (only one subject had detectable free curcumin in the serum) and subsequently conjugated in the gastrointestinal tract and liver. Area under

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Figure 2. Absorption of Curcumin Phytosome (Meriva) Compared to Non-complex Curcumin in Humans
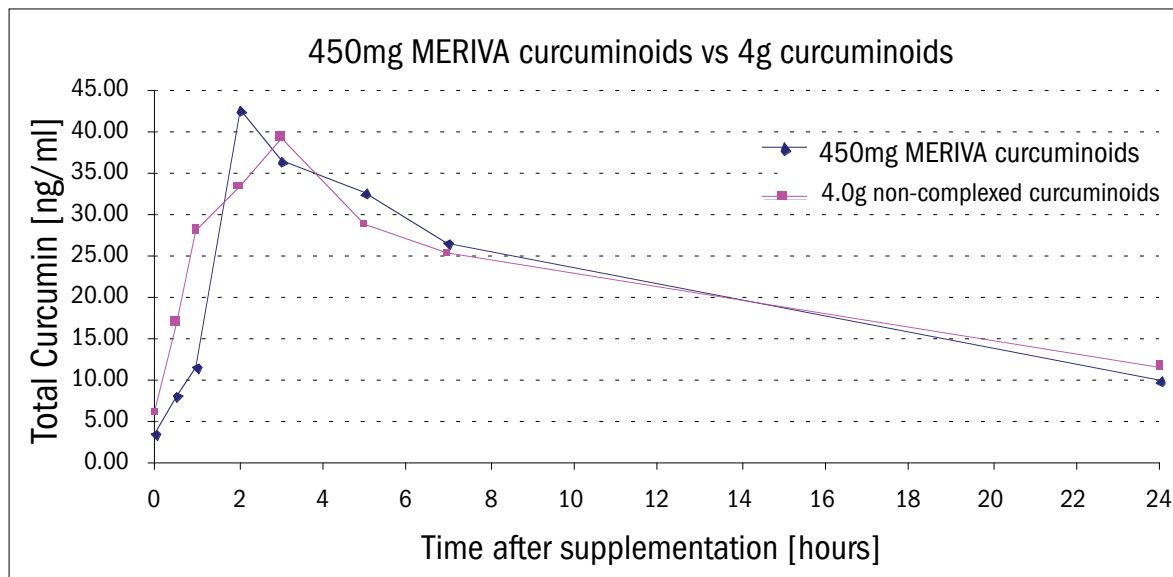
the curve (AUC) for curcumin conjugates was surprisingly higher (35.33 ± 3.78 μg/mL) for the 10-g dose than for the 12-g dose (26.57 ± 2.97 μg/mL), perhaps indicating saturation of the transport mechanism in the gut for free curcumin. Maximum serum concentration (C_{max}) for the 10-g dose was 2.30 ± 0.26 μg/mL compared to 1.73 ± 0.19 μg/mL for the 12-g dose.[12]

Because of curcumin's rapid plasma clearance and conjugation, its therapeutic usefulness has been somewhat limited, leading researchers to investigate the benefits of complexing curcumin with other substances to increase systemic bioavaility. One substance that has been studied is the alkaloid piperine, a constituent from black pepper and long pepper (*Piper nigrum* and *Piper longum*, respectively). In humans 20 mg piperine given concomitantly with 2 g curcumin increased serum curcumin bioavailability 20-fold, which was attributed to piperine's inhibition of hepatic glucuronidation and intestinal metabolism.[13]

Another method currently being investigated is complexing curcumin with a phospholipid, known as a phytosome. The phosphatidylcholine-curcumin complex (Meriva®) is more readily incorporated into lipophilic cell membranes, making it significantly more bioavailable than unbound curcumin. In rats, peak plasma concentration and AUC were five times higher for Meriva than for unbound curcumin.[14] One small unpublished, single-dose trial demonstrated 450 mg of Meriva curcuminoids complexed with phosphatidylcholine was absorbed as efficiently as 4 g unbound *Curcuma longa* (95% curcumin), reflecting a significant increase in bioavailability for Meriva complex (Figure 2).[15]

Anti-inflammatory Mechanisms

Research shows curcumin is a highly pleiotropic molecule capable of interacting with numerous molecular targets involved in inflammation. Curcumin modulates the inflammatory response by down-regulating the activity of cyclooxygenase-2 (COX-2), lipoxygenase, and inducible nitric oxide synthase (iNOS) enzymes; inhibits the production of the inflammatory cytokines tumor necrosis factor-alpha (TNF-α), interleukin (IL) -1, -2, -6, -8, and -12, monocyte chemoattractant protein (MCP), and migration inhibitory protein; and down-regulates mitogen-activated and Janus kinases.[16,17]

COX-2 and iNOS inhibition are likely accomplished via curcumin's suppression of nuclear factor-kappa B (NF-κB) activation.[18] NF-κB, a ubiquitous eukaryotic transcription factor, is involved in regulation of inflammation, cellular proliferation, transformation, and tumorigenesis. Curcumin is thought to suppress NF-κB activation and proinflammatory gene expression by blocking phosphorylation of inhibitory factor I-kappa B kinase (IκB). Suppression of NF-κB activation subsequently down-regulates COX-2 and iNOS expression, inhibiting the inflammatory process and tumorigenesis.[18,19] In an animal model of inflammation, curcumin also inhibited arachidonic acid metabolism and inflammation in mouse skin epidermis via down-regulation of the cyclooxygenase and lipoxygenase pathways.[20]

Curcumin's inhibition of inflammatory cytokines is achieved through a number of mechanisms. *In vitro* studies indicate curcumin regulates activation of certain transcription factors such as activating protein-1 (AP-1) and NF-κB in stimulated monocytes and alveolar macrophages, thereby blocking expression of cytokine gene expression. Down-regulation of intercellular signaling proteins, such as protein kinase C, may be another way in which curcumin inhibits cytokine production.

Curcumin's Anti-inflammatory Properties and Carcinogenesis

It is well understood that proinflammatory states are linked to tumor promotion.[21,22] Consequently, phytochemicals like curcumin that exert a strong anti-inflammatory effect are anticipated to have some degree of chemopreventive activity. Preclinical cancer research using curcumin has shown it inhibits carcinogenesis in a number of cancer types, including colorectal, pancreatic, gastric, prostate, hepatic, breast, and oral cancers, and leukemia, and at various stages of carcinogenesis.[6] Anti-inflammatory mechanisms implicated in the anticarcinogenic potential of curcumin include: (1) inhibition of NF-κB and COX-2 (increased levels of COX-2 are associated with many cancer types);[18,20] (2) inhibition of arachidonic acid metabolism via lipoxygenase and scavenging of free radicals generated in this pathway;[20] (3) decreased expression of inflammatory cytokines IL-1β, IL-6, and TNF-α, resulting in growth inhibition of cancer cell lines;[23] and (4) down-regulation of enzymes, such as protein kinase C, that mediate inflammation and tumor-cell proliferation.[24]

Animal Research on Curcumin and Inflammation

Inflammation and Edema

Several animal studies have investigated the anti-inflammatory effects of curcumin. Early work by Srimal et al demonstrated curcumin's anti-inflammatory action in a mouse and rat model of carrageenan-induced paw edema. In mice, curcumin inhibited edema at doses between 50-200 mg/kg. A 50-percent reduction in edema was achieved with a dose of 48 mg/kg body weight, with curcumin nearly as effective as cortisone and phenylbutazone at similar doses. In rats, a lower dose of 20-80 mg/kg decreased paw edema and inflammation. Curcumin also inhibited formaldehyde-induced arthritis in rats at a dose of 40 mg/kg, had a lower ulcerogenic index (0.60) than phenylbutazone (1.70) (an anti-inflammatory drug often used to treat arthritis and gout), and demonstrated no acute toxicity at doses up to 2 g/kg body weight.[25]

Ulcerative Colitis

Curcumin has also been shown to reduce mucosal injury in mice with experimentally-induced colitis. A dose of 50 mg/kg curcumin for 10 days prior to induction of colitis with 1,4,6-trinitrobenzene sulphonic acid resulted in a significant amelioration of diarrhea, improved colonic architecture, and significantly reduced neutrophil infiltration and lipid peroxidation in colonic tissue. Reduced levels of nitric oxide and O_2 radicals and suppressed NF-κB activation in colonic mucosa, all indicators of reduced inflammation and symptom improvement, were also reported.[26]

Rheumatoid Arthritis

In an animal model of streptococcal cell wall-induced rheumatoid arthritis, a turmeric extract devoid of essential oils was given to Wistar female rats. Intraperitoneal injection of an extract containing 4 mg total curcuminoids/kg/day for four days prior to arthritis induction significantly inhibited joint inflammation in both the acute (75%) and chronic (68%) phases. To test efficacy of an oral preparation, a 30-fold

higher dose (to allow for possible low gastrointestinal absorption) of the curcuminoid preparation, given to rats four days prior to arthritis induction, significantly reduced joint inflammation by 48 percent on the third day of administration.[27]

Pancreatitis

In two rat models of experimentally-induced pancreatitis, curcumin decreased inflammation by markedly decreasing activation of NF-κB and AP-1 as well as inhibiting mRNA induction of IL-6, TNF-α, and iNOS in the pancreas. In both cerulein- and ethanol-induced pancreatitis, curcumin's inhibitory effect on inflammatory mediators resulted in improvement in disease severity as measured by histology, serum amylase, pancreatic trypsin, and neutrophil infiltration.[28]

Cancer

Numerous animal studies have explored curcumin's anti-inflammatory mechanisms and their influence on carcinogenesis; however, discussion of these studies in detail is beyond the scope of this paper. Table 1 lists animal studies in which oral or dietary curcumin inhibited carcinogenesis via anti-inflammatory mechanisms.

Clinical Trials Exploring Curcumin's Anti-inflammatory Benefits

Curcumin's potent anti-inflammatory properties have lead to active research on its use for a variety of inflammatory conditions, including postoperative inflammation, arthritis, uveitis, inflammatory pseudotumors, dyspepsia, irritable bowel syndrome, inflammatory bowel disease, pancreatitis, and *Helicobacter pylori* infection. Most studies are promising and further exploration of curcumin's therapeutic value for inflammatory conditions is warranted.

Post-surgery

Satoskar et al examined the effects of curcumin compared to phenylbutazone or placebo for spermatic cord edema after surgery for inguinal hernia or hydrocele. Forty-five patients (ages 15-68) received 400 mg curcumin (Group A), 250 mg lactose powder placebo (Group B), or 100 mg phenylbutazone (Group C) three times daily for six days postoperatively. Parameters measured were spermatic cord edema, spermatic cord tenderness, operative site pain, and operative site tenderness (0: absent, 1: mild, 2: moderate, 3: severe) and reflected by intensity score (TIS) of 0-12. TIS on day 6 decreased in Group A (curcumin) by 84.2 percent, by 61.8 percent in Group B (placebo), and by 86 percent in Group C (phenylbutazone). Although TIS scores for curcumin and phenylbutazone were similar on day 6, curcumin proved to be superior by reducing all four parameters of inflammation. Phenylbutazone did not reduce tenderness at the operative site.[41]

Rheumatoid Arthritis

In a preliminary double-blind, randomized, controlled trial (RCT), curcumin was compared to phenylbutazone in patients with rheumatoid arthritis. Curcumin given at 1200 mg daily was effective in improving joint swelling, morning stiffness, and walking time. Although phenylbutazone provided an even greater benefit, dosages, study size, and details were not available in English full text.[42]

Osteoarthritis

A crossover RCT examined the effect of turmeric extract (50 mg/capsule) in combination with zinc complex (50 mg/capsule) and other botanicals – *Withania somnifera* (450 mg/capsule) and *Boswellia serrata* (100 mg/capsule) in 42 patients with osteoarthritis. Patients were given 2 capsules of test formula or placebo three times daily for three months; then, after a two-week washout period, switched to the opposite treatment for another three months. Assessment every two weeks during the study demonstrated significant improvements in pain severity (p<0.001) and disability scores (p<0.05), but no statistically significant changes in other parameters. Curcumin's role in this improvement cannot be confirmed due to the other botanicals and zinc in the treatment compound.[43]

Ocular Conditions

Anterior uveitis is a condition characterized by inflammation of the uveal tract of the eye (including the iris) and if untreated can result in blurred vision and permanent damage. Although the exact cause of anterior uveitis is not certain, it has been known to occur

Table 1. Animal Studies Investigating the Anti-inflammatory Effects of Curcumin in Cancer Models[29-40]

Author	Animal Model	Route of Curcumin Administration	Dose
Chan et al 1998[29]	Murine (liver) iNOS production	Oral by gavage, Intravenous	0.5 mL of 10µM solution 0.5 µg/g body weight
Rao et al 1999[30]	Rat colonic aberrant crypt foci	Oral (diet), Subcutaneous	50-2,000 ppm 15 mg/kg body weight
Rao et al 1995[31]	Rat colon cancer	Oral (diet)	2,000 ppm
Perkins et al 2002[32]	Murine familial adenomatous polyposis	Oral (diet), Intraperitoneal	0.1-, 0.2-, 0.5-% diet 100 mg/kg body weight
Shpitz et al 2006[33]	Rat colonic aberrant crypt foci	Oral (diet)	0.6-% diet
Kwon et al 2009[34]	Rat colonic apoptosis	Oral	0.6-% diet
Dujic et al 2009[35]	Murine xenograft tumor	Intraperitoneal	200 µL of 0.2-1.0 µg/mL-curcumin suspension
Garg et al 2008[36]	Murine liver, lung tumor initiation	Oral (diet)	0.01- or 0.0-% diet
Kawamori et al 1999[37]	Rat colonic apoptosis	Oral	0.2- or 0.6-% diet
Huang et al 1998[38]	Murine lymphomas/leukemias	Oral (diet)	2-% diet
Aggarwal et al 2005[39]	Murine breast cancer with lung metastasis	Oral (diet)	2-% diet
Tomita et al 2006[40]	Murine T-cell leukemia	Oral (gavage)	300 mg/kg body weight

with trauma to the eye, other eye diseases, tuberculosis, rheumatoid arthritis, measles, or mumps. Treatment is usually aimed at decreasing inflammation.[44]

In a clinical trial involving 32 patients (ages 19-70) with anterior uveitis, 375 mg curcumin was administered alone or with antitubercular therapy (to those patients demonstrating a positive PPD skin prick test) three times daily for 12 weeks. Of those in the curcumin-only group (n=18), 100 percent reported marked improvement after two weeks of therapy,

compared to 86 percent in the curcumin/antitubercular therapy group (n=14). Improvements were observed in visual acuity and aqueous flare and were accompanied by a decrease in keratic precipitates.[45]

Curcumin has been used for idiopathic orbital inflammatory pseudotumors (IOIP). Orbital pseudotumors include ocular lesions that are non-neoplastic in nature for which there is no clearly defined cause. The condition is an immunological inflammatory condition characterized by a hard mass in the orbit, inflammation of the conjunctiva, and decreased visual acuity.

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Conventional treatment consisting of corticosteroids is often ineffective.[46] In a small study of eight patients with IOIP, 375 mg curcumin three times daily was given for 6-22 months, until complete regression of symptomology was achieved. Patients were followed for two years and assessed at three-month intervals. Only five patients completed the study, but four completely recovered on curcumin therapy. One patient was asymptomatic but continued to have some restriction of ocular movement.[47]

Gastrointestinal Conditions

Curcumin's anti-inflammatory properties and therapeutic benefit have been demonstrated for a variety of gastrointestinal conditions, including dyspepsia, *Helicobacter pylori* infection, peptic ulcer, irritable bowel syndrome, Crohn's disease, and ulcerative colitis.

Dyspepsia and Gastric Ulcer

In a phase II clinical trial involving 45 subjects (24 males, 21 females, ages 16-60 years), 25 with endoscopically diagnosed peptic ulcers were given 600 mg curcumin five times daily 30-60 minutes before meals, at 4:00 pm, and at bedtime for 12 weeks. Ulcers were absent in 12 patients (48%) after four weeks, in 18 patients after eight weeks, and in 19 patients (76%) after 12 weeks. The remaining 20 patients, also given curcumin, had no detectable ulcerations at the start of the study, but were symptomatic – erosions, gastritis, and dyspepsia. Within 1-2 weeks abdominal pain and other symptoms had decreased significantly.[48]

Irritable Bowel Syndrome

In patients with irritable bowel syndrome (IBS) the most common symptoms are abdominal pain, bloating, altered bowel habits, and increased stool frequency.[49] It is thought that low-grade inflammation of the intestinal mucosa is responsible for some symptomology.[50] In an eight-week pilot study of IBS patients, either 72 mg or 144 mg of a standardized turmeric extract was administered to a group of 102 or 105 subjects, respectively. After four weeks, those in the 72-mg group experienced a 53-percent reduction in IBS prevalence, while the 144-mg group experienced a 60-percent decrease. In post-study analysis, abdominal pain and discomfort scores were reduced by 22 percent in the 72-mg group and 25 percent in the 144-mg group.[51]

Inflammatory Bowel Disease

Crohn's disease (CD) and ulcerative colitis (UC) are the two primary forms of inflammatory bowel disease (IBD). The primary difference between the two is nature and location of inflammatory changes in the gastrointestinal tract. CD can affect any part of the gastrointestinal tract and affects the entire bowel wall. In contrast, UC is restricted to the colon and the rectum and disease is confined to the intestinal epithelium. Although very different in scope, both diseases may present with abdominal pain, vomiting, diarrhea, bloody stools, weight loss, and secondary sequelae such as arthritis, pyoderma gangrenosum, and primary sclerosing cholangitis.[52]

Holt et al conducted a pilot study to examine the effect of curcumin therapy in 10 patients with IBD (five with CD and five with UC, ages 28-54) who had previously received standard UC or CD therapy. Five patients with proctitis (UC of the rectal area) received 550 mg curcumin twice daily for one month and then were given the same dose three times daily for an additional month. Hematological and biochemical blood analysis, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) (the latter two inflammatory indicators), sigmoidoscopy, and biopsy were all performed at baseline and at the study end. Symptoms were assessed by questionnaire and daily symptom diary. The other five patients, with Crohn's disease, received 360 mg three times daily for one month and then four times daily for a second month. Crohn's Disease Activity Index (CDAI), CRP, ESR, hematological blood analysis, and kidney function was assessed in all patients at baseline and end of study. In the proctitis group all five patients improved by study's end as indicated by a global score, two eliminated prestudy medications, two decreased their medications, and all five subjects demonstrated normal ESR, CRP, and serologic indices of inflammation after two months. In the CD group, CDAI scores decreased by an average of 55 points, and CRP and ESR decreased in four of five patients.[53]

Another clinical trial was conducted to assess the efficacy of curcumin as a maintenance therapy in 82 patients with quiescent UC. Subjects were randomized to receive 1 g curcumin twice daily plus sulfasalazine or mesalamine (n=43), or placebo plus sulfasalazine or mesalamine (n=39) for six months. Subjects were assessed at baseline, every two months for six months,

and again at the end of a six-month follow-up period via the Clinical Activity Index (CAI) and Endoscopic Index (EI). Only two of 43 patients (4.7%) receiving curcumin plus sulfasalazine/mesalamine experienced a relapse during the six-month study, compared to eight of 39 subjects (20.5%) in the placebo plus sulfasalazine/mesalamine group. Subjects in the curcumin group also demonstrated significant improvement in CAI (p=0.038) and EI scores (p=0.001), indicating a decrease in UC-associated morbidity. Interestingly, at the end of the six-month follow-up period, during which all patients took only sulfasalazine or mesalamine, eight additional patients from the curcumin group relapsed (total of 23.3%) compared to six additional patients in the placebo group (total of 35.9%). The authors concluded that curcumin plus standard therapy was more effective in maintaining remission than placebo plus standard UC treatment.[54]

Pancreatitis

Clinical research on curcumin's therapeutic benefit for pancreatitis is limited and has primarily focused on its antioxidant properties. However, research indicates the inflammatory response plays a critical role in development of pancreatitis and subsequent tissue damage.[28,55] For this reason, it seems likely an anti-inflammatory agent like curcumin, effective against a variety of inflammatory molecular targets and shown to decrease inflammatory markers in an animal model of pancreatitis,[28] might prove to be effective in humans.

One pilot study examined the effect of curcumin for tropical pancreatitis in 15 patients. Subjects received 500 mg curcumin with 5 mg of piperine to enhance absorption (n=8) or placebo (n=7) for six weeks. Treatment effect on pain patterns as well as erythrocyte malonylaldehyde (MDA; an indicator of lipid peroxidation) and glutathione (GSH) were assessed at baseline and after six weeks. In the curcumin group there was a significant reduction in MDA levels (from 14.80 ± 1.19 to 6.02 ± 0.95). There was no significant change in either GSH or pain value scores between the curcumin and placebo groups. Further research is needed to determine the role of lipid peroxidation in pain and other symptomology associated with pancreatitis.[56]

Renal Graft Rejection

An RCT investigated the effect of a combination of 480 mg curcumin and 20 mg quercetin (per capsule) on delayed graft rejection (DGR) in 43 kidney transplant patients. Subjects were randomized to low-dose (one capsule), high-dose (two capsules), or placebo (one capsule twice daily) groups for one month post-surgery. Of 39 participants who completed the study, two of 14 in the control group experienced DGR compared to zero in either treatment group. Early function (significantly decreased serum creatinine 48 hours post-transplant) was achieved in 43 percent of subjects in the control group, 71 percent of those in the low-dose treatment group, and 93 percent in the high-dose group. Since the amount of quercetin in the compound was minimal, the majority of benefit is thought to be due to curcumin's anti-inflammatory and antioxidant activity.[57]

Likely mechanisms for improved early function of transplanted kidneys include induction of the hemeoxygenase enzyme, inhibition of NF-κB and pro-inflammatory cytokines, and scavenging of free radicals associated with tissue damage.[57]

In addition to the research presented here, there are a number of ongoing clinical trials exploring the effects of curcumin in various inflammatory conditions (Table 2).

Cancer Chemoprevention and Treatment with Curcumin

The impact of curcumin's anti-inflammatory effects on carcinogenesis in humans remains to be determined. However, animal research demonstrates inhibition at all three stages of carcinogenesis – initiation, promotion, and progression. During initiation and promotion, curcumin modulates transcription factors controlling phase I and II detoxification of carcinogens;[36] down-regulates proinflammatory cytokines, free radical-activated transcription factors, and arachidonic acid metabolism via cyclooxygenase and lipoxygenase pathways; and scavenges free radicals.[59-61] In the promotion and progression stages of carcinogenesis curcumin decreases frequency and size of tumors and induces apoptosis via suppression of NF-κB and AP-1 in several cancer types.[20,37]

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Table 2. Ongoing Clinical Trials Exploring Curcumin's Benefits in Inflammatory Conditions[58]

Clinic Trial Identifier	Condition	Trial Site	Intervention	Trial Phase	Completion Date
NCT00752154	Rheumatoid arthritis	University of California, Los Angeles	Curcumin, 4-12 g daily	Pilot Study	September 2009
NCT00792818	Knee osteoarthritis	Mahidol University, National Research Council of Thailand	*Curcuma longa* extracts, Ibuprofen	Phase III	November 2009
NCT00793130	Ulcerative colitis	Tel-Aviv Sourasky Medical Center	Coltect – (curcumin 1 g daily, green tea, selenium)	Unknown	November 2009
NCT00779493	Irritable bowel syndrome	Kaiser Permanente	Curcumin, 900 mg twice daily	Phase IV	November 2009
NCT00528151	Leber's hereditary optical neuropathy	Mahidol University	Curcumin, 250 mg twice daily	Phase III	Unknown
NCT00595582	Mild cognitive impairment	Louisiana State University	Curcumin + Bioperine, 5.4 g daily	Unknown	January 2009

Clinical trials published in peer-reviewed literature utilizing curcumin for chemoprevention or as a cancer therapy are somewhat limited. A phase I clinical trial investigated the use of curcumin as a chemopreventive agent in 25 patients with various types of high-risk or pre-malignant lesions. After an initial dose of 500 mg curcumin daily, the dose was increased to as much as 8 g daily for three months. Histological improvement of precancerous lesions was observed in one of four patients with cervical intraepithelial neoplasm (significant decreases in hyperkeratosis, parakeratosis), one of six patients with intestinal metaplasia of the stomach (fewer goblet cells), one of two patients with recently resected bladder cancer (decreased dysplasia and inflammation), two of seven patients with oral leukoplakia, and two of six patients with Bowen's disease.[9]

Three other clinical trials have investigated the use of curcumin therapy in patients with established colorectal cancer. Sharma et al conducted two separate clinical trials exploring curcumin's effect on malignancies and tumor marker levels.[10,62] In one trial, 15 patients with advanced colorectal cancer were given a low-dose (440-2,200 mg daily) Curcuma extract

(equivalent to 36-180 mg curcumin) for up to four months. In one patient, measurement of serum tumor marker levels revealed a decrease of carcinoembryonic antigen levels from 310 ± 15 μg/L to 175 ± 9 μg/L after two months of treatment with 440 mg Curcuma extract. Stable disease via CT scan was observed in five of 15 patients – one taking 440 mg extract, one taking 880 mg, and one taking 1,760 mg for three months, and in one taking 880 mg and one taking 1,320 mg for four months.[62]

In the second trial, researchers used a higher potency curcuminoid preparation, each capsule containing 450 mg curcumin, 40 mg demethoxycurcumin, and 10 mg bisdemethoxycurcumin. Fifteen patients with advanced colorectal cancer were given curcuminoid doses of 450-3,600 mg daily for up to four months. Blood and imaging tests were performed at baseline and various points throughout the trial. In six patients given the 3,600-mg dose, mean prostaglandin E_2 (PGE_2) levels measured after 29 days of treatment decreased by 46 percent compared to baseline.[10] PGE_2 is an end product of cyclooxygenase that has been shown to stimulate growth of human colorectal cancer cells.[63] In addition,

Table 3. Clinical Trials Investigating the Use of Curcumin in Cancer[58]

Clinical Trial Identifier	Condition	Site	Intervention	Trial Phase	Completion Date
NCT00365209	Colon cancer prevention	Chao Family Comprehensive Cancer Center	Curcumin	Phase II	Unknown
NCT00118989	Colon cancer prevention	University of Pennsylvania	Curcuminoid complex, 4 g daily	Phase II	June 2009
NCT00641147	Familial adenomatous polyposis	Johns Hopkins University	Curcumin, 700 mg twice daily	Phase II	March 2013
NCT00745134	Rectal cancer	MD Anderson Cancer Center	Curcumin, 4 g daily, Capecitabine	Phase II	July 2010
NCT00486460	Pancreatic cancer	Tel-Aviv Sourasky Medical Center	Gemcitabine, Curcumin, Celebrex (doses unknown)	Phase III	Unknown
NCT00094445	Pancreatic cancer	MD Anderson Cancer Center	Curcumin, 8 g daily	Phase II	December 2009
NCT00113841	Multiple myeloma	MD Anderson Cancer Center	Curcumin + Bioperine, 2 g twice daily	Pilot Study	December 2008
NCT00689195	Osteosarcoma	Tata Memorial Hospital	Curcumin and Ashwagandha (doses unknown)	Phase I and II	May 2012
NCT00475683	Oral mucositis – children on chemotherapy	Hadassah Medical Organization	Curcumin liquid extract, 10-30 drops 3 times daily	Phase III	December 2009

two patients (one taking 900 mg, the other taking 1,800 mg) demonstrated stable disease (determined via CT scan or MRI) after two months. The patient taking the higher dose remained stable for four months but withdrew due to diarrhea thought to be treatment related.[10]

Another clinical trial investigated curcumin's effects in patients with colorectal cancer at doses of 450, 1,800, or 3,600 mg daily for seven days.[11] The aim of this study was to determine if these doses resulted in pharmacologically active levels of curcumin in colorectal tissue or had any effect on tissue levels of the oxidative DNA adduct pyrimido(1,2-a)purin-10(3H)-one (M_1G) (a mutagenic byproduct of lipid peroxidation) or COX-2 – markers of DNA damage and inflammation. The highest dose (3,600 mg) resulted in a significant decrease in M_1G adducts from 4.8 ± 2.9 to 2.0 ± 1.8 per 107 nucleotides. No curcumin dose had an effect on tissue levels of COX-2 protein.

In another clinical trial, curcumin stabilized disease progression in patients with advanced pancreatic cancer. Twenty-one patients received 8 g curcumin daily until disease progression. Serum cytokine levels as well as NF-κB and COX-2 levels in peripheral blood mononuclear cells were monitored. One patient achieved disease stabilization for 18 months. Interestingly, a second patient experienced significant increases in serum cytokine levels (4- to 35-fold) accompanied by a brief, but marked tumor regression (73%). Down-regulation of NF-κB and COX-2 were also observed.[64]

Currently there are nine ongoing clinical trials investigating the benefits of curcumin as a therapy for various cancers. Of these, three are preventive trials on subjects with adenomatous polyps at risk for colorectal cancer. The remaining seven trials are investigating the effects of curcumin (both alone and with conventional

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medications) in patients with established cancer of various types. Table 3 lists ongoing clinical trials investigating the anticancer potential of curcumin. It is hoped the completion of these trials over the next few years will provide a better understanding of curcumin's efficacy for chemoprevention and treatment of active cancer.

Cautionary Information

In every published clinical trial, curcumin appears to be extremely safe, even at doses up to 8 g daily. Of less importance are *in vitro* and animal trials that in select settings have demonstrated potentially adverse effects. *In vitro*, in the presence of copper and cytochrome p450 isoenzymes, curcumin induced DNA fragmentation and base damage.[65] In a rat model of liver cancer curcumin did not prevent spontaneous hepatic tumor formation and in fact, shortened life span from 88.7 to 78.1 weeks (p=0.002).[66]

There is also some evidence that curcumin inhibits the activity of certain chemotherapy drugs. Research reveals curcumin decreased camptothecin-induced death of cultured breast cancer cells and prevented cyclophosphamide-induced breast tumor regression in mice.[67] Curcumin might also interfere with the absorption and efficacy of the chemotherapy drug irinotecan, which is used to treat colon cancer.[68]

On the other hand, curcumin may enhance the effects of some chemotherapy drugs. In a mouse xenograft model of human breast cancer, curcumin in conjunction with paclitaxel (Taxol) significantly inhibited breast cancer metastasis to the lung to a greater degree than either curcumin or paclitaxel alone. Prevention of breast cancer metastasis in this study appeared to be via curcumin's inhibition of NF-κB.[39]

Conclusion

Curcumin's diverse array of molecular targets affords it great potential as a therapeutic agent for a variety of inflammatory conditions and cancer types. Consequently, there is extensive interest in its therapeutic potential as evidenced by the number of ongoing phase II and III clinical trials. The primary obstacle to utilizing curcumin therapeutically has been its limited systemic bioavailability, but researchers are actively investigating a number of different curcumin compounds and analogs that may be more effective and better absorbed. Results from completed clinical trials are encouraging and trials currently being conducted for both inflammatory conditions and cancer should clarify curcumin's value as a therapeutic agent and confirm some of the mechanisms responsible for its efficacy.

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