

Curcumin

Summary

- Turmeric is a spice derived from the rhizomes of *Curcuma longa*, a member of the ginger family. Curcuminoids are polyphenolic compounds that give turmeric its yellow color; curcumin is the principal curcuminoid in turmeric.
- The results of phase I clinical trials in colorectal cancer patients suggest that biologically active levels of curcumin can be achieved in the gastrointestinal tract through oral curcumin supplementation. Such trials provide support for further clinical evaluation in people at risk for gastrointestinal cancers. (More Information)
- Until the safety and efficacy of curcumin in individuals with cystic fibrosis has been evaluated in clinical trials, the Cystic Fibrosis Foundation does not recommend the use of curcumin as a therapy for cystic fibrosis. (More Information)
- Although a few preliminary trials suggest that curcumin may have anti-inflammatory activity in humans, larger randomized controlled trials are needed to determine whether oral curcumin supplementation is effective in the treatment of inflammatory diseases. (More Information)
- As a result of promising findings in animal models of Alzheimer's disease, clinical trials of curcumin supplementation in patients with early Alzheimer's disease are under way. (More Information)

Introduction

Turmeric is a spice derived from the rhizomes of *Curcuma longa*, which is a member of the ginger family (*Zingiberaceae*). Rhizomes are horizontal underground stems that send out shoots as well as roots. The bright yellow color of turmeric comes mainly from fat-soluble, polyphenolic pigments known as curcuminoids (Figure 1). Curcumin, the principal curcuminoid found in turmeric, is generally considered its most active constituent (1). Other curcuminoids found in turmeric include demethoxycurcumin and bisdemethoxycurcumin. In addition to its use as a spice and pigment, turmeric has been used in India for medicinal purposes for centuries. More recently, evidence that curcumin may have anti-inflammatory and anticancer activities has renewed scientific interest in its potential to prevent and treat disease.

Metabolism and Bioavailability

Clinical trials in humans indicate that the systemic bioavailability of orally administered curcumin is relatively low (1-3) and that mostly metabolites of curcumin, instead of curcumin itself, are detected in plasma or serum following oral consumption (4, 5). In the intestine and liver, curcumin is readily conjugated to form curcumin glucuronides and curcumin sulfates or, alternately, reduced to hexahydrocurcumin (Figure 2) (6). Curcumin metabolites may not have the same biological activity as the parent compound. In one study, conjugated or reduced metabolites of curcumin were less effective inhibitors of inflammatory enzyme expression in cultured human colon cells than curcumin itself (7). In a clinical trial conducted in Taiwan, serum curcumin concentrations peaked 1-2 hours after an oral dose; peak serum concentrations of curcumin were 0.5, 0.6, and 1.8

micromoles/liter following doses of 4, 6, and 8 g of curcumin, respectively (8). Curcumin could not be detected in serum at lower doses than 4 g/day. More recently, a clinical trial conducted in the UK found that plasma concentrations of curcumin, curcumin sulfate, and curcumin glucuronide were in the range of 10 nanomoles/liter (0.01 micromole/liter) one hour after a 3.6 g oral dose of curcumin (9). Curcumin and its metabolites could not be detected in plasma at doses lower than 3.6 g/day. Curcumin and its glucuronidated and sulfated metabolites were also measured in urine after a dose of 3.6 g/day. There is some evidence that orally administered curcumin accumulates in gastrointestinal tissues. For instance, when colorectal cancer patients took 3.6 g/d of curcumin orally for seven days prior to surgery, curcumin was detected in malignant and normal colorectal tissue (10). In contrast, curcumin was not detected in the liver tissue of patients with liver metastases of colorectal cancer after the same oral dose of curcumin (11), suggesting that oral curcumin administration may not effectively deliver curcumin to tissues outside the gastrointestinal tract.

Biological Activities

Antioxidant Activity

Curcumin is an effective scavenger of reactive oxygen species and reactive nitrogen species in the test tube (in vitro) (12, 13). However, it is not clear whether curcumin acts directly as an antioxidant in vivo. Due to its limited oral bioavailability in humans (see Metabolism and Bioavailability above), plasma and tissue curcumin concentrations are likely to be much lower than that of other fat-soluble antioxidants, such as alpha-tocopherol (vitamin E). However, the finding that oral curcumin supplementation (3.6 g/day) for seven days decreased the number of oxidative DNA adducts in malignant colorectal tissue suggests that curcumin taken orally may reach sufficient concentrations in the gastrointestinal tract to inhibit oxidative DNA damage (11). In addition to direct antioxidant activity, curcumin may function indirectly as an antioxidant by inhibiting the activity of inflammatory enzymes or by enhancing the synthesis of glutathione, an important intracellular antioxidant (see below).

Anti-inflammatory Activity

The metabolism of arachidonic acid in cell membranes plays an important role in the inflammatory response by generating potent chemical messengers known as eicosanoids (14). Membrane phospholipids are hydrolyzed by phospholipase A2 (PLA2), releasing arachidonic acid, which may be metabolized by cyclooxygenases (COX) to form prostaglandins and thromboxanes, or by lipoxygenases (LOX) to form leukotrienes. Curcumin has been found to inhibit PLA2, COX-2, and 5-LOX activities in cultured cells (15). Although curcumin inhibited the catalytic activity of 5-LOX directly, it inhibited PLA2 by preventing its phosphorylation and COX-2 mainly by inhibiting its transcription. Nuclear factor-kappa B (NF-kB) is a transcription factor that binds DNA and enhances the transcription of the COX-2 gene as well as other pro-inflammatory genes, such as inducible nitric oxide synthase (iNOS). In inflammatory cells, such as macrophages, iNOS catalyzes the synthesis of nitric oxide, which can react with superoxide to form peroxynitrite, a reactive nitrogen species that can damage proteins and DNA. Curcumin has been found to inhibit NF-kB-dependent gene transcription (16), and the induction of COX-2 and iNOS in cell culture and animal studies (17, 18).

Glutathione Synthesis

Glutathione is an important intracellular antioxidant that plays a critical role in cellular adaptation to stress (19). Stress-related increases in cellular glutathione levels result from increased expression of glutamate cysteine ligase (GCL), the rate-limiting enzyme in glutathione synthesis. Studies in cell culture suggest that curcumin can increase cellular glutathione levels by enhancing the transcription of genes that encode GCL (20, 21).

Effects on Biotransformation Enzymes Involved in Carcinogen Metabolism

Biotransformation enzymes play important roles in the metabolism and elimination of a variety of biologically active compounds, including drugs and carcinogens. In general, phase I biotransformation enzymes, including those of the cytochrome P450 (CYP) family, catalyze reactions that increase the reactivity of hydrophobic (fat-soluble) compounds, preparing them for reactions catalyzed by phase II biotransformation enzymes. Reactions catalyzed by phase II enzymes generally increase water solubility and promote the elimination of these compounds (22). Although increasing biotransformation enzyme activity may enhance the elimination of potential carcinogens, some carcinogen precursors (procarcinogens) are metabolized to active carcinogens by phase I enzymes (23). CYP1A1 is involved in the metabolic activation of several chemical carcinogens. In cell culture and animal studies, curcumin has been found to inhibit procarcinogen bioactivation or measures of CYP1A1 activity (24-27). Increasing phase II biotransformation enzyme activity is generally thought to enhance the elimination of potential carcinogens. Several studies in animals have found that dietary curcumin increased the activity of phase II enzymes, such as glutathione S-transferases (GSTs) (26, 28, 29). However, curcumin intakes ranging from 0.45-3.6 g/day for up to four months did not increase leukocyte GST activity in humans (9).

Induction of Cell Cycle Arrest and Apoptosis

After a cell divides, it passes through a sequence of stages—collectively known as the cell cycle—before it can divide again. Following DNA damage, the cell cycle can be transiently arrested to allow for DNA repair or, if the damage cannot be repaired, for activation of pathways leading to cell death (apoptosis) (30). Defective cell-cycle regulation may result in the propagation of mutations that contribute to the development of cancer. Curcumin has been found to induce cell-cycle arrest and apoptosis in a variety of cancer cell lines grown in culture (1, 31-35). The mechanisms by which curcumin induces apoptosis are varied but may include inhibitory effects on several cell-signaling pathways. However, not all studies have found that curcumin induces apoptosis in cancer cells. Curcumin inhibited apoptosis induced by the tumor suppressor protein p53 in cultured human colon cancer cells (36, 37), and one study found that curcumin inhibited apoptosis induced by several chemotherapeutic agents in cultured breast cancer cells at concentrations of 1-10 micromoles/liter (38).

Inhibition of Tumor Invasion and Angiogenesis

Cancerous cells invade normal tissue with the aid of enzymes called matrix metalloproteinases. Curcumin has been found to inhibit the activity of several matrix metalloproteinases in cell culture studies (39-43). To fuel their rapid growth, invasive tumors must also develop new blood vessels by a process known as angiogenesis. Curcumin has been found to inhibit angiogenesis in cultured vascular endothelial cells (44, 45) and in an animal model (46).

Note: It is important to keep in mind that many of the biological activities discussed above were observed in cells cultured in the presence of curcumin at higher concentrations than are likely to be achieved in cells of humans consuming curcumin orally (see Metabolism and Bioavailability above).

Disease Prevention

Cancer

The ability of curcumin to induce apoptosis in cultured cancer cells by several different mechanisms has generated scientific interest in the potential for curcumin to prevent some types of cancer (1). Oral curcumin administration has been found to inhibit the development of chemically-induced cancer in animal models of oral (47, 48), stomach (49, 50), liver (51), and colon (52-54) cancer. Apc^{Min/+} mice have a mutation in the Apc (adenomatous polyposis coli) gene similar to that in humans with familial adenomatous polyposis, a genetic condition characterized by the development of numerous colorectal adenomas (polyps) and a high risk for colorectal cancer. Oral curcumin administration has been found to inhibit the development of intestinal adenomas in

Apc^{Min/+} mice (55, 56). In contrast, oral curcumin administration has not consistently been found to inhibit the development of mammary (breast) cancer in animal models (52, 57, 58).

Although the results of animal studies are promising, particularly with respect to colorectal cancer, there is presently little evidence that high intakes of curcumin or turmeric are associated with decreased cancer risk in humans. A phase I clinical trial in Taiwan examined the effects of oral curcumin supplementation up to 8 g/day for three months in patients with precancerous lesions of the mouth (oral leukoplakia), cervix (high grade cervical intraepithelial neoplasia), skin (squamous carcinoma in situ), or stomach (intestinal metaplasia) (8). Histologic improvement on biopsy was observed in two out of seven patients with oral leukoplakia, one out of four patients with cervical intraepithelial neoplasia, two out of six patients with squamous carcinoma in situ, and one out of six patients with intestinal metaplasia. However, cancer developed in one out of seven patients with oral leukoplakia and one out of four patients with cervical intraepithelial neoplasia by the end of the treatment period. This study was designed mainly to examine the bioavailability and safety of oral curcumin, and interpretation of its results is limited by the lack of a control group for comparison. As a result of the promising findings in animal studies, several controlled clinical trials in humans designed to evaluate the effect of oral curcumin supplementation on precancerous colorectal lesions, such as adenomas, are under way (59).

Disease Treatment

Cancer

The ability of curcumin to induce apoptosis in a variety of cancer cell lines and its low toxicity have led to scientific interest in its potential for cancer therapy as well as cancer prevention (60). To date, most of the controlled clinical trials of curcumin supplementation in cancer patients have been Phase I trials. Phase I trials are clinical trials in small groups of people, which are aimed at determining bioavailability, safety, and early evidence of the efficacy of a new therapy (61). A phase I clinical trial in patients with advanced colorectal cancer found that doses up to 3.6 g/day for four months were well-tolerated, although the systemic bioavailability of oral curcumin was low (62). When colorectal cancer patients with liver metastases took 3.6 g/day of curcumin orally for seven days, trace levels of curcumin metabolites were measured in liver tissue, but curcumin itself was not detected (11). In contrast, curcumin was measurable in normal and malignant colorectal tissue after patients with advanced colorectal cancer took 3.6 g/day of curcumin orally for seven days (10). These findings suggest that oral curcumin is more likely to be effective as a therapeutic agent in cancers of the gastrointestinal tract than other tissues. Phase II trials are clinical trials designed to investigate the effectiveness of a new therapy in larger numbers of people, and to further evaluate short-term side effects and safety of the new therapy. Phase II clinical trials of curcumin in patients with colorectal cancer are currently under way (59). A phase II clinical trial in patients with advanced pancreatic cancer found that curcumin exhibited some anticancer activity in two out of 21 patients; however, bioavailability of curcumin was extremely poor (63). Due to low systemic bioavailability and the fact that curcumin is hydrophobic, the authors proposed that intravenous administration of liposome-encapsulated curcumin be used in future clinical trials (63).

Inflammatory Diseases

Although the anti-inflammatory activity of curcumin has been demonstrated in cell culture and animal studies, few controlled clinical trials have examined the efficacy of curcumin in the treatment of inflammatory conditions. A preliminary intervention trial that compared curcumin with a nonsteroidal anti-inflammatory drug (NSAID) in 18 rheumatoid arthritis patients found that improvements in morning stiffness, walking time, and joint swelling after two weeks of curcumin supplementation (1,200 mg/day) were comparable to those experienced after two weeks of phenylbutazone (NSAID) therapy (300 mg/day) (64). A placebo-controlled trial in 40 men who had surgery to repair an inguinal hernia or hydrocele found that oral curcumin supplementation (1,200 mg/day) for five days was more effective than placebo in reducing post-surgical edema, tenderness and

pain, and was comparable to phenylbutazone therapy (300 mg/day) (65). Two uncontrolled studies found that oral curcumin (1,125 mg/day) for 12 weeks or longer improved anterior uveitis and idiopathic inflammatory orbital pseudotumor, two inflammatory conditions of the eye (66, 67). However, without a control group, it is difficult to draw conclusions regarding the anti-inflammatory effects of curcumin in these conditions. Larger randomized controlled trials are needed to determine whether oral curcumin supplementation is effective in the treatment of inflammatory diseases, such as rheumatoid arthritis.

Cystic Fibrosis

Cystic fibrosis is a hereditary disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (62). CFTR is a transmembrane protein that acts as a chloride channel and plays a critical role in ion and fluid transport. In the lungs, CFTR mutations ultimately result in increased mucus concentration and decreased mucus clearance, which leads to progressive lung disease. The most common CFTR mutation contributing to the development of cystic fibrosis is the delta F508 mutation, which results in CFTR protein misfolding and degradation before the protein can be targeted to the cell membrane. However, the mutated protein retains some ability to function as a chloride channel if it can be inserted in the cell membrane. In 2004, a study in mice with the delta F508 mutation found that oral curcumin administration corrected abnormal ion transport and improved the survival of these mice (68). However, unlike humans, mice with the delta F508 mutation experience only the digestive complications of cystic fibrosis without the lung complications, and treatment benefits in the mouse model are not always realized in humans (62). More recently, another group of scientists was unable to duplicate the beneficial effects of curcumin in the same mouse model given the same dose of curcumin (69). It is unclear whether curcumin supplementation will be of benefit to humans with cystic fibrosis. In a phase I clinical trial funded by the Cystic Fibrosis Foundation, curcumin did not correct the function of the defective CRTR protein; a follow-up study using higher curcumin dosages is currently under way (70). Until the safety and efficacy of curcumin in individuals with cystic fibrosis has been evaluated in clinical trials, the Cystic Fibrosis Foundation does not recommend the use of curcumin as a therapy for cystic fibrosis (71).

Alzheimer's Disease

In Alzheimer's disease, a peptide called amyloid beta forms aggregates (oligomers), which accumulate in the brain and form deposits known as amyloid plaques (72). Inflammation and oxidative damage are also associated with the progression of Alzheimer's disease (73). Curcumin has been found to inhibit amyloid beta oligomer formation in vitro (74). When injected peripherally, curcumin was found to cross the blood brain barrier in an animal model of Alzheimer's disease (74). In animal models of Alzheimer's disease, dietary curcumin has decreased biomarkers of inflammation and oxidative damage, amyloid plaque burden in the brain, and amyloid beta-induced memory deficits (74-77). It is not known whether curcumin taken orally can cross the blood brain barrier or inhibit the progression of Alzheimer's disease in humans. As a result of the promising findings in animal models, clinical trials of oral curcumin supplementation in patients with early Alzheimer's disease are under way (59, 78). The results of a 6-month trial in 27 patients with Alzheimer's disease found that oral supplementation with up to 4 g/day of curcumin was safe (4). Larger controlled trials are needed to determine whether or not oral curcumin supplementation is efficacious in Alzheimer's disease.

Sources

Food Sources

Tumeric is the dried ground rhizome of *Curcuma longa* Linn (79). It is used as a spice in Indian, Southeast Asian, and Middle Eastern cuisines. Curcuminoids comprise about 2-9% of turmeric (80). Curcumin is the most abundant curcuminoid in turmeric, providing about 75% of the total curcuminoids, while demethoxycurcumin provides 10-20% and bisdemethoxycurcumin

generally provides < 5%. Curry powder contains turmeric along with other spices, but the amount of curcumin in curry powders is variable and often relatively low (81). Curcumin extracts are also used as food-coloring agents (82).

Supplements

Curcumin extracts are available as dietary supplements without a prescription in the U.S. The labels of a number of these extracts state that they are standardized to contain 95% curcuminoids, although such claims are not strictly regulated by the U.S. Food and Drug Administration (FDA). Some curcumin preparations also contain piperine, which may increase the bioavailability of curcumin by inhibiting its metabolism. However, piperine may also affect the metabolism of drugs (see [Drug Interactions](#) below). Optimal doses of curcumin for cancer chemoprevention or therapeutic uses have not been established. It is unclear whether doses less than 3.6 g/day are biologically active in humans (see [Metabolism and Bioavailability](#) above).

Safety

Adverse Effects

In the United States, turmeric is generally recognized as safe (GRAS) by the FDA as a food additive by the FDA (82). Serious adverse effects have not been reported in humans taking high doses of curcumin. A dose escalation trial in 24 adults found that single oral dosages up to 12 g were safe, and adverse effects were not dose-related (5). In a [phase I trial](#) in Taiwan, curcumin supplementation up to 8 g/day for three months was reported to be well-tolerated in patients with precancerous conditions or noninvasive cancer (8). In another clinical trial in the UK, curcumin supplementation ranging from 0.45-3.6 g/day for four months was generally well-tolerated by people with advanced colorectal cancer, although two participants experienced diarrhea and another reported nausea (9). Increases in serum alkaline phosphatase and lactate dehydrogenase were also observed in several participants, but it was not clear whether these increases were related to curcumin supplementation or cancer progression (1). Curcumin supplementation of 20-40 mg has been reported to increase [gallbladder](#) contractions in healthy people (83, 84). Although increasing gallbladder contractions could decrease the risk of gallstone formation by promoting gallbladder emptying, it could potentially increase the risk of symptoms in people who already have gallstones.

Pregnancy and Lactation

Although there is no evidence that dietary consumption of turmeric as a spice adversely affects pregnancy or lactation, the safety of curcumin supplements in pregnancy and lactation has not been established.

Drug Interactions

Curcumin has been found to inhibit [platelet aggregation in vitro](#) (85, 86), suggesting a potential for curcumin supplementation to increase the risk of bleeding in people taking [anticoagulant](#) or antiplatelet medications, such as aspirin, clopidogrel (Plavix), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, ticlopidine (Ticlid), and warfarin (Coumadin). In cultured breast cancer cells, curcumin inhibited [apoptosis](#) induced by the [chemotherapeutic](#) agents, camptothecin, mechlorethamine, and doxorubicin at concentrations of 1-10 micromoles/liter (38). In an animal model of breast cancer, dietary curcumin inhibited cyclophosphamide-induced tumor regression. Although it is not known whether oral curcumin administration will result in breast tissue concentrations that are high enough to inhibit cancer chemotherapeutic agents in humans (11), it may be advisable for women undergoing chemotherapy for breast cancer to avoid curcumin supplements (38). Some curcumin supplements also contain piperine, for the purpose of increasing the [bioavailability](#) of curcumin. However, piperine may also increase the bioavailability and slow the elimination of a number of drugs, including phenytoin (Dilantin), propranolol (Inderal), and theophylline (87, 88).

References

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