

Anticancer Potential of Turmeric

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THE RHIZOME (UNDERGROUND STEM) OR ROOT OF turmeric has been used in Asian cookery, medicine, cosmetics, and fabric dyeing for more than 2,000 years. Marco Polo wrote about turmeric in his memoirs, fostering its popularity in Europe during medieval times as a colorant and medicine.

Traditional Medicinal Use

Turmeric powder has long been used for medicinal purposes in Asia to treat gastrointestinal upsets, arthritis pain, and "low energy." In traditional Indian Ayurvedic medicine, turmeric has been used as a tonic for the digestive system and the liver; to dispel worms, strengthen the body, and dissolve gallstones; and for menstrual irregularity and arthritis. In old Hindu texts it is described as an aromatic, stimulant, and carminative (an agent that helps expel gas from the intestines and treats colic). Mixed with slaked (hydrated) lime, turmeric was a well-known household remedy for sprains and swellings caused by injury. (1)

Botany and Chemistry

Turmeric (*Curcuma longa* Linn.; syn.: *Curcuma domestica*, *Curcuma aromatica*) is a perennial from the Zingiberaceae family that is widely cultivated in the tropical regions of Asia, most extensively in India, and Latin America. Other names for turmeric include Indian saffron, turmeric root, and yellow root. Turmeric has a warm, bitter taste and should not be confused with Javanese turmeric root. The applicable part of turmeric is the root, which is rich in potassium and iron.

Chemical analysis of turmeric yields essential oils and fatty oils. An isolate from turmeric oil has been reported to have antifungal, antimutagenic, and antibacterial activity. (2) Turmeric also contains curcuminoids alataone, bisdemethoxycurcumin, dimethoxycurcumin, diaryl heptanoids, and tumerone. (3) Synthetic tumerone (turmerone) may act as an anticarcinogen.

Curcumin, a polyphenol compound, is responsible for the yellow color of turmeric and is thought to be the most active pharmacological agent. Natural curcumin, isolated from *Curcuma longa*, contains curcumin I (diferuloyl methane as the major constituent), as well as curcumin II (6%) and III (0.3%). (3) Turmeric may be standardized to contain approximately 95% curcuminoids per dose. The dried root of turmeric reportedly contains 4-8% curcumin, of which curcumin I is the most abundant, but may not be the most biologically active. (4) Curcumin is insoluble in water and ether, but is soluble in ethanol, dimethylsulfoxide, and other organic solvents. (5)

Mechanism of Action

Numerous animal and in vitro studies have demonstrated the ability of turmeric and its active component, curcumin, to suppress the growth of a variety of tumor cells. (5-9) The postulated mechanisms for these anticancer effects are multiple: (5)

* **Antiproliferative effects:** induction of apoptosis (at high concentrations), suppression of proteins that regulate apoptosis, modulation of transcription factors.

* **Suppression of cyclooxygenase-2 (COX-2)** and lipooxygenase expression, which blocks production of prostaglandins and leukotrienes, respectively.

* **Suppression of cyclin D1** which is a proto-oncogene overexpressed in many cancers (e.g., breast, esophagus, lung, liver, head and neck, colon, and prostate).

* **Suppression of adhesion molecules** that play an important role in tumor metastasis.

* **Suppression of various inflammatory cytokines**, including tumor necrosis factor.

* **Suppression of angiogenesis**, a crucial step in the growth and metastasis of many cancers.

* **Competition with carcinogens** that use the aryl hydrocarbon and cytochrome P450 pathway.

Laboratory Studies

Curcumin has been shown to **promote apoptosis in certain cancer cell lines**, (6,10) and to **inhibit telomerase activity, an important factor in tumorigenesis**. (6,7) One possible mechanism for the induction of tumor cell death is through the generation of reactive oxygen intermediates. (11)

Although curcumin is the acknowledged active principal in turmeric, the oleoresin of turmeric (after extraction of curcumin) also was found to have **antimutagenic properties**, thought to be mediated through its antioxidant action. (2)

The **anti-inflammatory properties of curcumin** are thought to be due in part to **suppression of prostaglandin synthesis**. (8) Prostaglandin synthesis from arachidonic acid is catalyzed by two isoenzymes: COX-1 and COX-2, both found in colon tumors of rodents and humans. Goel et al found that curcumin significantly **inhibited expression of COX-2 in human colon cancer cells** and in COX-2 non-expressing cell lines, without altering the expression of COX-1. This is an important benefit of curcumins since chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) and non-specific inhibition of COX-1 lead to undesirable gastrointestinal and renal side effects.

Curcumin also was shown by Mahady et al to **inhibit the growth of Helicobacter pylori**, (12) a group 1 carcinogen, as a possible explaining mechanism for its role in prevention of gastric and colon cancers in rodents.

The most significant, recent article hypothesized that curcumin's inhibition of the generation of reactive oxygen species (ROS) might interfere with the efficacy of chemotherapeutic drugs that induce apoptosis through the generation of ROS and the JNK pathway. (13) Studies in tissue culture showed that curcumin did inhibit the induction of apoptosis by several agents (camptothecin, mechlorethamme, and doxorubicin). This effect was dose- and time-dependent, but occurred after even brief three-hour exposures. In their in vivo model of human breast cancer, curcumin supplementation significantly inhibited cyclophosphamide-induced tumor regression and decreased activation of JNK and apoptosis.

Human Clinical Studies

In a Phase I clinical trial, Sharma et al gave curcuma extracts (containing 36-180 mg of curcumin) to 15 patients with refractory colorectal cancer. (14) The curcuma extracts were well-tolerated orally and no dose-limiting toxicity was observed. Radiologically stable disease was demonstrated in five patients during 2-4 months of treatment. The study showed that curcuma extract can be safely administered in doses of up to 2.2 g/d (180 mg of curcumin), has low oral bioavailability in humans, and may undergo intestinal metabolism.

The review article by Aggarwal et al examining **the anticancer effect of turmeric/curcumin** reported a study in China by Cheng et al of 25 patients with one of five high-risk conditions: recently resected bladder cancer, arsenic Bowen's disease of the skin, uterine cervical intraepithelial neoplasm (C1N), oral leucoplakia, and intestinal metaplasia of the stomach. (15) Curcumin was administered orally for three months with doses ranging from 500 to 12,000 mg/d. Curcumin was found to be non-toxic in doses of up to 8,000 mg/d orally for three months. The results also showed that one of four patients with C1N and one of seven patients with oral leucoplakia developed frank malignancies in spite of treatment with curcumin. However, histological improvement was seen in one of two patients with bladder cancer, two of seven patients with leucoplakia, one of six patients with intestinal metaplasia, one of four patients with C1N, and two of six patients with Bowen's disease. (6)

Turmeric given to 16 **chronic smokers** in doses of 1.5 g/d for 30 days **reduced the urinary excretion of mutagens** in a controlled trial. (16) There was no change in mutagen excretion in the urine of controls. Although suggestive, measuring surrogate outcomes, such as urinary mutagens, does not necessarily correlate with reduction in cancer incidence. In a follow-up to pharmacological research on the effects of curcumin on HIV cell replication, 18 HIV-positive patients were given an average dose curcumin of 2 g/d for 127 days. (16) There was a significant increase in CD4 and CD8 lymphocyte counts. The subsequent phase I/II study using doses of 2.7-4.8 g/d of curcumin failed to show any benefit on viral loads or CD4 count in HIV-positive individuals, It was suggested that the poor bioavailability of curcumin could be a factor in these negative results.

Epidemiology

Cancer of the colon, breast, prostate, and lung, common cancers in the United States, are not as prevalent in India, where curcumin frequently is consumed. Adenomas are rare in elderly Indians undergoing colonoscopy, as are small bowel cancers. The low prevalence for large and small bowel cancers does not remain low in Indians who have immigrated and urban Indians, supporting a role for environmental risk factors, including diet. (6)

Dosage

Turmeric should be taken as a powdered rhizome or a 1:1 liquid extract prepared using at least 45% ethanol. (16) For adults age 18 and older, usual doses range from 1.5 to 3 g/d of turmeric root in divided doses. Due to low solubility, tea preparations are not recommended. Turmeric tincture is dosed at 5-15 mL/d in 4-5 divided doses. To enhance absorption, turmeric often is formulated with bromelain or in a lipid base of lecithin, fish oils, or essential fatty acids. Average intake in the Indian population is 2-2.5 g daily (60-200 mg curcumin).

Adverse Effects

As a dietary supplement, turmeric has Generally Recognized as Safe (GRAS) status in the United States.

Contact dermatitis has been reported with occupational exposure and a small number of patients using turmeric topically reported pruritis at the site. (17,18) Anecdotal reports of mild giddiness have been published. Turmeric can cause gastrointestinal irritation, especially in high doses or after prolonged use. Caution should be exercised when turmeric is used to treat gastrointestinal problems. In a study of duodenal ulcer patients, 6 g of turmeric caused epigastric burning in 27% of subjects vs. 13% of placebo patients. (19) In another study, 8% of patients taking 1 g oral turmeric for dyspepsia reported nausea vs. 3% of placebo patients. (20) The ulcerogenic effect of curcumin/turmeric may be dose-related. (1)

In animal studies, curcumin [the isolate alone] was shown to induce abnormalities in liver function tests. In human studies, 750 mg of turmeric twice daily for 30 days did not change liver function tests; (21) the same result was reported using 20 mg of curcumin for 60 days. (22) Oral curcumin has been associated with

gallbladder contraction in humans over a two-hour period after administration of a single 20 mg dose. (23) Therefore, curcumin use may be inadvisable in patients with cholelithiasis.

In vitro and animal studies have reported **inhibition of platelet aggregation by turmeric**; (24) therefore, turmeric may increase bleeding risk. [Reviewer's note: it is highly unlikely that turmeric would increase bleeding risk; no evidence exists to support this.] However, there is no report of bleeding problems in the small number of human studies even at high doses.

Precautions

Turmeric should be avoided in patients allergic to turmeric or any of its constituents (including curcumin), yellow food colorings, or other members of the Zingiberaceae (ginger) family. It should be avoided in patients with bile duct obstruction or cholelithiasis, and gastric or duodenal ulcers or other hyperacidity disorders. [Reviewer's note: whole turmeric, not the isolated curcumin, is in fact, recommended in small amounts in these conditions.]

Turmeric is considered **safe for pregnant and lactating women** when used as a spice in foods. Turmeric should not be taken in large amounts during pregnancy as it might stimulate menstrual flow and uterine contraction. Animal studies have not shown any teratogenicity. There is insufficient evidence of safety to support use of large amounts of turmeric during lactation.

Drug and Herb Interactions

Because of turmeric's reported inhibition of platelet aggregation, turmeric theoretically may potentiate the effects of other agents that increase bleeding risk such as anticoagulants, NSAIDs, and antiplatelet medications, (25) as well as herbs with anticoagulant activity. [Reviewer's note: it is highly unlikely that turmeric would increase bleeding risk; no evidence exists to support this.]

Turmeric has positive benefits on lipid profiles in animal Studies (25) and may **potentiate the effect of lipid-lowering agents**. Turmeric also may potentiate other lipid-lowering substances, including fish oil, garlic, guggul, or niacin. Theoretically, turmeric may **reduce the frequency of ulcers** caused by indomethacin and NSAIDs, by increasing intestinal wall mucous. (26) Turmeric was shown in the same animal study to reduce the frequency of reserpine-induced gastric and duodenal ulcers. Curcumin was shown in animal models to protect against acute doxorubicin-induced myocardial toxicity. (27)

Conclusion

Turmeric is **safe and non-toxic for most patients**, It has been shown to have diverse biological effects in humans and animals. Turmeric/curcumin is a potent anti-inflammatory and antioxidant. The evidence suggests that it can suppress tumorigenesis, tumor promotion, and metastasis and, therefore, has enormous potential as an anticancer agent. Further study is needed to determine whether it, like other antioxidants, should be avoided during chemotherapy.

Recommendation

There is sufficient evidence to support the safety of turmeric except when contraindicated as above. Due to its potential as an antitumor remedy, use of turmeric for the treatment and prevention of cancer should be considered, except during chemotherapy.

Adoption of a diet similar to that traditionally found in India would provide therapeutic amounts of turmeric for prevention measures. Beyond that, supplementation is more reliable for treating specific conditions. When

choosing an extract of turmeric, it should be standardized to 95% curcumin. It may be wise, however, to purchase whole root products, given the biological activity of components other than curcumin.

*Note: Passages in bold are added for emphasis and are not the author's.

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