EDITORIAL REVIEW

The potential use of curcumin in management of chronic disease: too good to be true?

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Current Opinion in Gastroenterology 2008, 24:173–175

Introduction

Turmeric is an approved food additive, and contains approximately 2–5% curcumin as its most active ingredient and the component responsible for the yellow color of the spice [1]. Curcumin is a polyphenol, resembling ubiquinols and other phenols that have well described antioxidant properties. Turmeric is derived from the herb *Curcuma longa*, a member of the ginger family. It was first isolated nearly 200 years ago, and its structure [1,7-bis(4-hydroxy-3-methoxyphenyl)-1-6-heptadiene-3, 4-dione] has been known since 1910. It has been well known for its ability to preserve food, and add taste and color to food, but the possibility that it may have health-promoting properties is only recently receiving attention. Initially these were less appreciated because turmeric contains a variety of phytochemicals, including many analogs of curcumin. Even today, most preparations of curcumin contain around 18% demethoxycurcumin and around 5% bisdemethoxycurcumin [2•]. It is not clear whether the analogues have equal biological activity.

Biology

Curcumin has been known to have anti-inflammatory, antimutagenic, and anticarcinogenic properties, at least in animals. In the last three decades literally hundreds of molecular targets have been identified, including activity that is largely that of downregulation or suppression of activity [2•,3]. These include activity against different transcription factors [especially nuclear factor κB (NFκB)], cytokines, growth factors, kinases, and other enzymes. Curcumin downregulates NFκB, thus limiting proinflammatory gene products. It also downregulates the expression of cyclooxygenase 2, and inhibits expression and activity of lipoxygenase 5, both of which are proinflammatory enzymes. Curcumin downregulates expression of some cell surface adhesion molecules, and various inflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and IL-8. It also inhibits the action of TNFα.

Curcumin is very lipophilic and has low oral bioavailability, but appears to be metabolized by the intestinal mucosa after absorption. Only low nanomolar levels are found in human plasma, with picomolar levels (nmol/g) in the tissues [4]. Yet, most activities of the spice against cells in culture are found at micromolar concentrations. Very low concentrations of the spice are found in the plasma of animals, but tissue concentrations up to 0.1 μmol/g have been reported in individual tissues (e.g. intestine) in which biological effects have been noted [4]. These discrepancies must be kept in mind when reading the literature about curcumin.

Curcumin has many actions that make it a potent antioxidant and anti-inflammatory reagent. It suppresses lipid peroxidation and increases expression of intracellular glutathione, as well as binding iron. It has some proinflammatory actions as well, inducing expression of reactive oxygen species by binding to thioredoxin reductase. Curcumin inhibits platelet aggregation and lowers serum cholesterol in rats when only 0.1% of the diet comprises the spice. It impairs proliferation of monocytes and T cells, as well as vascular smooth muscle cells. Curcumin inhibits the mitogen-activated protein kinase (MAPK) 38, and protects against intestinal inflammation by acting on the transient receptor potential vanilloid-1 receptor (TRPV1) [5]. Perhaps the most dramatic demonstration with potential anti-inflammatory effects is the fact that curcumin blocks the activation of NFκB by TNFα in endothelial cells [6].

The anticarcinogenic activity of curcumin is related to many factors [7]. It prevents the formation or activation of carcinogens by its inhibition of cytochrome P450s and lipoxygenases, and by its increase in glutathione transferase and epoxide hydrolase. It has antipromoter activity by restoring the immune response, inducing apoptosis, arrest of the cell cycle, and inhibition of angiogenesis. It downregulates epidermal growth factor receptors, along with the activity of EGFR 2 (HER2/neu), an important growth factor in some human carcinomas. Moreover, curcumin downregulates STAT3 activation leading to decreased IL-6 activity, and also downregulates activity of IL-2, a T-cell growth factor. Additional actions of the spice include suppression of phosphokinase C leading to lower c-jun oncogene expression [1]. It suppresses estrogen-dependent receptors that regulate growth of

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hormone-sensitive cells. It does upregulate the tissue inhibitor of metalloproteinase (TIMP1) as well as downregulating the matrix metalloproteinase MMP2, both of which activities impair tumor cell invasion. Its antitumor activity is furthered by suppressing angiogenesis through its action on vascular endothelial growth factor (VEGF), cyclooxygenase-2, fibroblast growth factor (FGF), and TNFα.

Recent studies have been performed using human tumor cell cultures, showing suppression of growth, but no single pattern of intracellular mediation has emerged. Curcumin not only suppresses growth via interaction with transcription factors, but also suppresses chemo-resistance of glioblastoma cells [8]. It also induces apoptosis and G_2/M arrest in ovarian cancer cells that are resistant to cisplatin, this time by inhibiting phosphorylation of Akt and enhancing phosphorylation of p38 MAPK [9]. In a different cell line (human glioma), cell cycle arrest was mediated via p53 and the inhibitor of growth isomer ING4 [10].

In summary, the potential molecular targets affected by curcumin are large in number, mostly involved with anti-inflammatory and anticarcinogenic activity. The discrepancy between cell culture concentrations and those achieved *in vivo* could mean either that the effects on cells are manifestations of pharmacological activity, or they could be the result of experimental necessity, providing a total cellular exposure at high concentration over short periods compared with in-vivo exposure at lower levels for longer times. Somewhat concerning, however, is the profusion of effects that are not limited to a finite number of pathways or mechanisms.

Activity in preclinical models

The demonstration of multiple molecular targets for the action of curcumin has led to the suggestion of therapeutic potential for a wide range of diseases, mostly chronic inflammatory conditions and malignancies [2•,11••]. Curcumin has prevented many animal models of tumors, especially those induced by carcinogens (phorbol esters, nitrosamines, anthracenes, azoxymethane, dimethylhydrazine), as well as those produced in the Min/+ mouse model, or by radiation. Curcumin may play a role in diabetes type II, as both NFκB and TNFα have been linked to insulin resistance, and curcumin can overcome such resistance in several animal models. Curcumin has been suggested as possibly useful in cardiovascular disease because it inhibits platelet aggregation, inhibits the inflammatory response, lowers low-density lipoprotein (LDL) and raises high-density lipoprotein (HDL), and inhibits oxidation of LDL, all in animals. The anti-inflammatory activities of curcumin have led to the largest list of potential diseases that may benefit from its use. This list includes chronic obstructive pulmonary disease (the compound inhibits transforming growth factor β and fibrogenesis), hepatic steatosis, pancreatitis, gastritis (curcumin inhibits many strains of *Helicobacter pylori*), inflammatory bowel disease (chemically induced colitis in rodents is prevented), and Alzheimer's disease (curcumin is a more potent scavenger of nitric oxide-based free radicals than vitamin E). Although the list of possible clinical targets for curcumin is very large, there are yet no convincing data of its efficacy in humans.

Clinical efficacy

Curcumin is one of multiple components of turmeric, and turmeric is frequently used along with many other spices. Epidemiology may provide a valuable clue to clinical usefulness if the associations between curcumin use and human disease were strong. There are few studies published that shed light on this point, but the issue of cancer risk and diet in India has been reviewed [12]. Cancer rates in India are in general lower than in Western countries (with the exception of oral and esophageal cancer), but these rates are rising with the shift in population from the rural areas to the cities. This shift suggests that there may be factors in addition to diet that are contributing. Rates of cancer, coronary artery disease, and diabetes, however, are increased in the Indian diaspora, suggesting the importance of a dietary component. No prospective studies examining the role of curcumin or spices containing curcumin have been performed, but these are needed to provide clues regarding associations in large populations.

Curcumin is not toxic to humans, and has been used in spices for centuries. Studies in animals have confirmed a lack of any significant toxicity at doses of up to 3.5 g/kg body weight for up to 3 months in rats, dogs, and monkeys [4]. Various studies in humans have provided 2.1–8.0 g/day to patients with inflammatory diseases, with only occasional adverse events, such as nausea or abnormal alkaline phosphatase levels [13]. In the absence of a control group these data are difficult to interpret. The drug is very insoluble, bioavailability is low, and there is rapid intestinal metabolism. Thus, it has been suggested that rather large doses would be needed to see an effect. Doses of over 10 g leave an almost unbearable aftertaste, so clinical studies have not used such large doses [14•]. A dose escalation of a powdered plant extract containing all three major curcuminoids was carried out in 24 individuals, with doses from 0.5 to 12 g given as a single dose [15]. Minimal toxicity was seen that did not seem dose related. Detectable curcumin in plasma was only seen at low levels at the doses of 10.0 and 12.0 g. In other studies there is evidence that at doses greater than 3.6 g/day curcumin is detectable in plasma, and is metabolized and excreted in the urine, although there is great interindividual variation [16••]. Thus, with current formulations, it does not seem likely

that enough drug can be delivered orally to produce any reasonable degree of plasma exposure. The reported clinical studies must be understood with this limitation.

Phase II studies in humans have involved only small numbers of patients and no observations have been repeated by other groups. Many studies did not have control groups, and no large-scale randomized trial has been reported to date [16••]. One study [17] compared curcumin 1200 mg/day to phenylbutazone 300 mg/day in 18 patients with rheumatoid arthritis. Although both groups improved, patients rated only phenylbutazone as better for controlling symptoms. Use of oral curcumin has been reported to improve various inflammatory conditions, including chronic anterior uveitis, inflammatory bowel disease, and chronic tropical pancreatitis, but the doses used did not exceed 1 g/day and the effects were modest [16••]. No control groups were included. One study [18] used an alcoholic gel of 1% curcumin to treat psoriasis, with some improvement. Two phase I studies in patients with advanced colorectal cancer reported stable disease in 20–30% of patients on 36–500 mg of curcumin [4]. There are no reported drug interactions with curcumin [19].

Ongoing studies

Nine studies using curcumin have been registered with a status of open, closed, terminated, and competed as of August 2007 [20•]. These include six studies on colon cancer, three on pancreatic cancer, two on Alzheimer's disease [21], and single studies in mucositis, multiple myeloma, psoariasis, and cystic fibrosis. Doses of up to 4 g/day are used in most of the studies. Uptake of curcumin is improved around 2000 fold in humans when low doses of piperine derived from black pepper is added [14•]. Derivatives of curcumin are being developed to overcome the poor bioavailability. The issue of patentability, however, is complex, especially because the Indian government has established traditional medicines as 'prior art' [14•].

Conclusion

Due to the limited bioavailability of curcumin and the inability to deliver high enough doses for long periods to achieve adequate and reliable exposure to tissues, it seems likely that studies using oral curcumin may not be positive. This result, however, may not end the quest for using this compound or a derivative of it. New derivatives that are more potent will be awaited with interest. Even if and when they are available, however, the challenge will be to know which of the targets already identified are mechanistically valid for a given activity, in order to screen new compounds adequately. This is a problem not unique to curcumin, but to herbal and natural preparations in general. Enough useful drugs have been derived from natural products to keep a focus on curcumin for some time to come. There does not seem to be enough evidence, however, for using current curcumin-containing products for medicinal use.

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