Original Article

Curcumin: It's Pharmacological and Therapeutic Properties
Running Head: Drug Delivery

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Abstract

Curcumin is a small molecular weight, polyphenolic compound, isolated from the roots of *curcuma longa* L. (family zingiberaceae), has been used traditionally for centuries in Asia for medicinal, culinary and other purposes. A large number of in vitro and in vivo studies in both animals and man have indicated that Curcumin has strong antioxidant, anti-inflammatory, anti-carcinogenic, anti-microbial, and anti-parasitic and other activities. The mechanisms of some of these actions have recently been intensively investigated. The compound inhibits the activity of growth factor receptors. The anti-inflammatory properties of curcumin are mediated through their effects on cytokines, lipid mediators, eicosanoids and proteolytic enzymes. Curcumin scavenges the superoxide radical, hydrogen peroxide and nitric oxide, and inhibits lipid peroxidation. These actions may be the basis for many of its pharmacological and therapeutic properties.

Keywords: Curcumin, *Curcuma longa*, anti-oxidant, anti-inflammatory, anti-cancer.

Introduction

Curcumin is a phenolic pigment of yellow color, obtained from crushed rhizome of C. longa Linn. Fig.1 (Family-Zingiberaceae) (Schmidt *et al*., 2007). It is the main constituent of oleoresin of turmeric. In crude extracts of rhizome of C. Longa, almost 70-76% of curcumin is present along with approximately 16 and 8 percent of demethoxycurcumin and bisdemethoxycurcumin respectively. Turmeric powder is used as a medicine to treat variety of diseases and extensively used for imparting flavor and color to eatables. Research on curcumin confirms a wide spectrum of therapeutic effects including antibacterial, antiviral, antispasmodic, antitumor, anti-inflammatory and hepatoprotective. Its efficacy in auto immune deficiency syndrome (AIDS) has been revealed in the last decade by different group of scientists (Araujo CAC and Leon LL., 2001; Maheshwari *et al*., 2006: Chattopadhyay *et al*., 2004).

The aim of this article is to invite the researchers to investigate the new curcumionid derivatives with chemical modifications, based in structure and biological activity relationship, in order to find new drugs that are less toxic to humans and also used for treatment of many diseases.

Chemical Properties of Curcumin

In Turmeric, Curcumin (1, 7-bis (hydroxyl-3-methoxyphenyl)-1,6- heptadiene-3, 5-dione) (Fig. 2), is a vital active ingredient responsible for its biological activity. It was first isolated in 1815, but it took another hundred years to elucidate its structure, which was solved in 1913. Curcumin is soluble in ethanol and acetone whereas insoluble in water. The naturally occurring ratios of curcuminoids in curcumin are about 80% curcumin, 15% demethoxycurcumin, and minute quantities of bisdemethoxycurcumin (Ireson *et al*., 2001).

Curcumin is comparatively unstable in phosphate buffer at pH 7.4 but the stability increases by either lowering the pH, or by augmenting it by glutathione, rat liver microsomes, *N* acetyl cysteine or ascorbic acid. Chemical synthesis of curcumin analogues results in various compounds with stronger anti-oxidant and tumor chemoprotective activities (Youssef *et al*., 2004).

Fig. 1. Source of curcumin (*C. longa*)

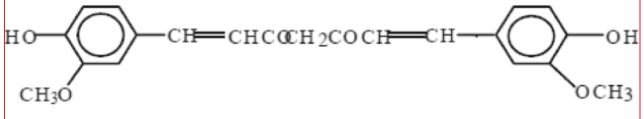

Fig. 2. Chemical structure of Curcumin

Curcumin Bioavailability and Pharmacokinetics

Various studies highlight the biotransformation of curcumin, which occurs in liver, kidney and GIT. It is first biotransformed to tetrahydrocurcumin and dihydrocurcumin and then these compounds are converted

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to monoglucuronide (Lin *et al*., 2000). Thus the major metabolites of curcumin are tetrahydrocurcumin, dihydrocurcumin-glucuronide, tetrahydrocurcumin-glucuronide and curcumin-glucuronide.

The systemic bioavailability of Curcumin is not very high, so the pharmacological actions and activity of Curcumin may be displayed, in parts, by its metabolites. Hexahydrocurcuminol and hexahydrocurcumin are the major metabolites of Curcumin involved in the suspension of human hepatocytes, while Curcumin glucuronide and Curcumin sulfate are the predominant metabolites of Curcumin in human plasma *in vivo* (Ireson *et al*., 2002).

The reason behind the poor bioavailability of Curcumin is due to its rapid metabolism in the liver and intestinal wall. Piperine can increase the bioavailability of curcumin as it is a well-known inhibitor of hepatic and intestinal glucuronidation and in addition to this; it also increases the serum concentration, degree of absorption and thus the bioavailability of curcumin in homo sapiens (Shoba *et al*., 1998).

Mechanisms of Action

Antioxidant Effects

Water soluble and fat soluble extracts of turmeric and curcumin shows strong anti-oxidant activity as compared to vitamin C and E (Toda *et al*., 1985). Curcumin pretreatment decreases ischemia induced changes in the feline heart. An in vitro measuring the effects of curcumin on endothelial heme oxygenase-1 (inducible stress protein), was conducted utilizing bovine aortic endothelial cells. Enhanced cellular resistance to oxidative damage resulted with curcumin incubation (18 hrs) (Dikshit *et al*., 1995).

Hepatoprotective Effects

Turmeric has hepatoprotective properties similar to silymarin. Animal studies demonstrated turmeric's hepatoprotective effects from a variety of hepatotoxic insults, including carbon tetrachloride (CCl4), (Deshpande *et al*., 1998) galactosamine, acetaminophen (paracetamol), and Aspergillus aflatoxin. Hepatoprotective effect is mainly due to anti-oxidant property of turmeric. In rats acute and subactue liver injury was induced with CCl4, curcumin administration significantly decreased liver injury in rats as compared to controls. Turmeric and curcumin also reversed biliary hyperplasia, fatty changes and necrosis induced by aflatoxin production (Aspergillus parasiticus). Sodium curcuminate also exerts choleretic effects by increasing biliary excretion of bile salts, cholesterol and bilirubin, as well as increasing bile solubility. (Ramprasad C and Sirsi M., 1957).

Anti-inflammatory Effects

Curcumin of *curcuma long* shows potent anti-inflammatory effects (Chandra and Gupta S., 1972). Orally administered curcumin in instance of acute inflammation was found to be as effective as cortisone or phenylbutazone, and one half as effective in case of chronic inflammation. Oral administration of curcumin significantly reduced inflammatory swelling compared to control in rats with Freunds adjuvant-induced arthritis. In monkeys, curcumin inhibited neutrophil aggregation associated with inflammation (Srivastava R, 1989). *C. longa's* anti-inflammatory properties may be attributed to its ability to inhibit both biosynthesis of inflammatory prostaglandins from arachidonic acid and neutrophil function during inflammatory states. Curcumin may also be applied topically to the skin to counteract the inflammation and irritation associated with inflammatory skin conditions and allergies (Mukhopadhyay *et al*., 1982).

Anticarcinogenic Effects

Various studies including animals, invitro and humans show curcumin ability to inhibit carcinogenesis at three stages: tumor promotion, angiogenesis and tumor growth (Thaloor *et al*., 1998: Limtrakul *et al*., 1997). Curcumin inhibited tumor growth and cell proliferation, shown in studies of colon and prostate cancer. Curcumin is also capable of suppressing the activity of several common mutagens and carcinogens in a variety of cell types in both invitro and invivo studies (Mehta R.G. and Moon R.C., 1991). The anticarcinogenic effects of turmeric and curcumin are due to direct antioxidant and free-radical scavenging effects, as well as their ability to indirectly increase glutathione levels, thereby aiding in hepatic detoxification of mutagens and carcinogens, and inhibiting nitrosamine formation (Pizorrno and Murray M.T., 1999).

Antimicrobial Effects

Turmeric extracts and essential oils of curcuma longa inhibit the growth of variety of bacteria, fungi, and parasites. A study of chicks infected with parasite *Eimera maxima* demonstrated that diets supplemented with 1% turmeric resulted in a reduction in small intestinal lesions scores and improved weight gain (Allen *et al*., 1998). Another animal study, in which guinea pigs were infected with either dermatophytes, pathogenic molds, or yeast, found that topically applied turmeric oil inhibited dermatophytes and pathogenic fungi, but neither curcumin nor turmeric oil affected the yeast isolates. Improvements in lesions were observed in the dermatophyte- and fungi-infected guinea pigs, and at seven days post-turmeric application the lesions disappeared. Curcumin has also been found to have moderate activity against *Plasmodium falciparum* and *Leishmania major* organisms (Rasmussen *et al*., 2000).

Cardiovascular Effects

Lowering the triglyceride and cholesterol levels, inhibiting platelet aggregation and reducing propensity of low density lipoprotein (LDL) to lipid peroxidation are some of the turmeric's protective effects on the cardiovascular system (Srivastava R *et al*., 1984). Even with low doses of turmeric produces these effects. A study of eighteen atherosclerotic rabbits given low-dose (1.6-3.2 mg/kg body weight daily) turmeric extract long-establish decreased susceptibility of LDL to lipid peroxidation, as well as lowering the triglyceride and plasma cholesterol levels. Higher doses did not decrease lipid peroxidation of LDL,

on the other hand decrease in the levels of cholesterol and triglyceride were noted, although to a lesser extent than with the lower dose (Ramirez-Tortosa *et al*., 1999).

The mechanism of action of the effect of turmeric extract's on cholesterol levels is doubted to be due to reduced cholesterol uptake in the intestines and better conversion of cholesterol to bile acids in the liver. Potentiation of prostacyclin synthesis and inhibition of thromboxane synthesis are thought to be the reason behind the inhibition of platelet aggregation by *C. longa* constituents (Srivastava *et al*., 1984).

Clinical Indications

Hepatoprotection, Cholelithiasis, and Cholestasis

Hepatoprotective effects of turmeric are seen in a number of animal studies, suggesting that it is a strong candidate to be used in cases of toxic insult caused by exogenous toxins from lifestyle and living environment. Curcumin may also be helpful in treating gallstones, as it has also shown choleretic activity in different studies. (Deshpande *et al*., 1998).

Inflammation

Curcumin is a strong anti-inflammatory agent with specific COX-2 inhibiting and lipoxygenas properties. It effectively reduces both acute and chronic inflammations *in vitro* and *in vivo* studies (Srivastava R., 1989). In a crossover, placebo-controlled study of forty-two patients with osteoarthritis, a combination product containing turmeric, zinc, *Boswellia serrate* and *Withania somnifera* were used and after three months on the combination or placebo, patients noted a significant relief in pain ($p<0.001$) and disability ($p<0.05$) (Kulkarni *et al*., 1991).

Cancer

Various studies demonstrated that turmeric shows some anticarcinogenic effects. Whereas its flavonoids component curcumin shows its effects against colon, prostate and breast cancers, in addition to this, it also works against melanomas (Chauhan DP, 2002: Reddy BS and Rao CV, 2002: Ramachandran C. *et al*., 2002: Somasundaram S. *et al*., 2002). A study conducted on twenty-five patients with high risk of premalignant lesions or neoplasia showed histologic improvement in two of seven patients with oral leukoplakia, one of two patients with resected bladder cancer, one of four patients with cervical intraepithelial neoplasm, one of six patients with intestinal metaplasia of the stomach and two of six patients with Bowen's disease. Further studies need to be performed to elucidate the potential of this natural product in treating or preventing cancers (Somasundaram S. *et al*., 2002).

Hyperlipidemia

Numerous studies show that turmeric is effective in decreasing the lipid concentration in blood but less is known to be able to confirm these findings and utilize this therapeutic activity in our daily lives, so further clinical studies and experiments need to be designed in this area to discover optimal dosage and efficacy for cardiovascular protection and lipid lowering (Ramirez-Tortosa *et al*., 1999).

Gastric Ulcer

A study on patients with endoscopically diagnosed peptic ulcer showed promising results of turmeric as an antiulcer drug. Participants were given 600mg of powdered turmeric five times a day and ulcer was completely healed in 48% of patients after a 4 week time. The efficacy of turmeric increased over time and no significant adverse reaction or blood abnormalities were seen (Prucksunand *et al*., 2001).

Chronic Anterior Uveitis

Curcumin is also found to be effective in corticosteroid therapy, results of a study conducted on 32 patients with chronic anterior uveitis, who were given 375mg of Curcumin thrice a day for 12 weeks showed promising results and Curcumin was found effective in 86% of individuals (Lal B. *et al*., 1999).

Conclusions

Curcumin is a natural substance with many pharmacological and therapeutic activities, some of which have been experimentally and clinically utilized in both man and animals. Notable among these are the antioxidant, anti-inflammatory and anti-carcinogenic properties, all three of which seem to be interrelated. It is encouraging that Curcumin is of low toxicity. Despite a plethora of phytochemical, pharmacological, biochemical and toxicological data on Curcumin, large well-designed clinical trials and epidemiological data are warranted to substantiate it usefulness in the treatment and/or prevention of cancer, rheumatoid arthritis and other conditions of human patients.

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