Research & Reviews

ISSN: 2320-1215

Research and Reviews: Journal of Pharmacy and Pharmaceutical Sciences

The Potential Role of Curcumin in Cancer Prevention and Treatment.

A Pramela Rani[1]*, and V Saikishore[2]

[1]University College of Pharmaceutical Sciences, Acharya Nagarguna University, Nagarjuna Nagar, Guntur – 522510, Andhra Pradesh, India.

[2]Bapatla College of Pharmacy, Bapatla, Guntur – 522101, Andhra Pradesh, India.

Review Article

Received: 23/06/2013
Revised: 01/07/2013
Accepted: 09/07/2013

***Corresponding author**

University College of Pharmaceutical Sciences, Acharya Nagarguna University, Nagarjuna Nagar, Guntur – 522510, Andhra Pradesh, India.
Mobile: +91 9440938249

Keywords: Curcumin, Cancer, Apoptosis, Epidemiology

ABSTRACT

Most drugs currently available for the treatment of cancer have limited potential because they are very toxic, highly inefficient in treating cancer, or highly expensive and thus beyond the reach of the majority. Treatments without these disadvantages are needed. Curcumin is one such agent; derived from turmeric (*Curcumin longa*), it has been used for thousands of years in the orient as a healing agent for variety of illnesses. Research over the last few decades has shown that curcumin is a potent antiinflammatory agent with strong therapeutic potential against a variety of cancers. Curcumin has been shown to suppress transformation, proliferation, and metastasis of tumors. These effects are mediated through its regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other enzymes. Curcumin has been shown to have protective and therapeutic effects against cancers of the blood, skin, oral cavity, lung, pancreas, and intestinal tract, and to suppress angiogenesis and metastasis in rodents. Curcumin's ability to affect gene transcription and to induce apoptosis in preclinical models is likely to be of particular relevance to cancer chemoprevention and chemotherapy in patients. The current review focuses on the molecular mechanisms by which curcumin mediates its effects against various cancers.

INTRODUCTION

Phytochemicals are naturally occurring substances found in plants. There has been considerable public and scientific interest in the use of phytochemicals derived from dietary components to combat human diseases, especially cancer. India has a rich history of using plants for medicinal purposes. Turmeric (*Curcuma longa* L.) is a medicinal plant extensively used in Ayurveda, Unani and Siddha medicine as home remedy for various diseases.The dried ground rhizome of the perennial herb Curcuma longa Linn., called turmeric in English, haldi in Hindi and ukon in Japanese, has been used in Asian medicine since the second millenium BC [1]. Its utility is referred to in the ancient Hindu scripture, the Ayurveda. In addition to its aromatic, stimulant and colouring properties in the diet, turmeric is mixed with other natural compounds such as slaked lime and has been used topically as a treatment for wounds, inflammation and tumours. In contrast to the maximum dietary consumption of 1.5 g per person per day in certain South East Asian communities, smaller quantities of turmeric tend to be used for medicinal purposes [2]. The appeal of turmeric as a colouring, food preservative and flavouring is global – according to the Food and Agriculture Organization of the United Nations, over 2400 metric tons of turmeric are imported annually into the USA for consumer use.

Chemical Composition of Turmeric

Curcuma spp. contain turmerin (a water-soluble peptide), essential oils (such as turmerones, atlantones and zingiberene) and curcuminoids including curcumin [1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3, 5-dione]. Curcuminoids can be defined as phenolic compounds derived from the roots of Curcuma spp. (Zingiberaceae). Curcumin (diferuloylmethane) is a low molecular weight polyphenol, first chemically characterised in 1910, that is generally regarded as the most active constituent of and comprises 2-8% of most turmeric preparations [3,4]. Turmeric contains protein (6.3%), fat (5.1%), minerals (3.5%), carbohydrates (69.4%) and moisture (13.1%).

ISSN: 2320-1215

The essential oil (5.8%) obtained by steam distillation of rhizomes has α-phellandrene (1%), sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%) and sesquiterpines (53%)5. Curcumin (diferuloylmethane) (3-4%) is responsible for the yellow colour, and comprises curcumin I(94%), curcumin II (6%) and curcumin III (0.3%)6. It has a melting point at 176-177°C; forms a reddish-brown salt with alkali and is soluble in ethanol, alkali, ketone, acetic acid and chloroform [5,6].

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. The postulated mechanisms for these anticancer effects are multiple [7,8,9,10].

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 [12], and to inhibit telomerase activity, an important factor in tumorigenesis. One possible mechanism for the induction of tumor cell death is through the generation of reactive oxygen intermediates13. 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.

The anti-inflammatory properties of curcumin are thought to be due in part to suppression of prostaglandin synthesis [11]. 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 Helicobacterpylori [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 humanbreast cancer, curcumin supplementation significantly inhibited cyclophosphamide-induced tumor regression and decreased activation of JNK and apoptosis.

Animal Studies

Curcumin has shown promising results in animal studies of cancer prevention and treatment. In a study using a mouse model of hepatocellular carcinoma (HCC), a diet consisting of 0.2% curcumin was administered starting four days before injection with N-diethylnitrosamine and continuing until death. At 42 weeks post-injection, the curcumin-fed mice showed a 62% reduction in incidence of HCC, and an 81% decrease in the number of tumors found compared to controls [14]. Mahmoud and colleagues, using a mouse model of familial adenomatous polyposis, reported a 64% decrease in tumor number in mice fed a 0.1% curcumin-containing diet compared to controls [15]. In another study using a mouse model of colon carcinogenesis, tetrahydrocurcumin, an active metabolite of curcumin, significantly reduced preneoplastic aberrant crypt foci development after treatment with 1,2-dimethylhydrazene dihydrochloride to initiate tumors, compared with controls [16].

Oral curcumin administration has been found to inhibit the development of chemically-induced cancer in animal models of oral [17,18], stomach [19,20], liver [21] and colon [22,23,24] cancer. ApcMin/+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

ISSN: 2320-1215

colorectal adenomas (polyps) and a high risk for colorectal cancer. Oral curcumin administration has been found to inhibit the development of intestinal adenomas in ApcMin/+ mice [25,26].

HUMAN CLINICAL STUDIES

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) [27].

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 [28].

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. 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. There was a significant increase in CD4 and CD8 lymphocyte counts [29].

Epidemiology

Overall cancer rates are much lower in India than in western countries. In a report comparing cancer incidence rates among Indians residing in India, the US, the UK, and Singapore, and whites in the US, overall cancer rates were shown to be the lowest among Indians in India and Singapore, and highest among whites in the US. Cancer rates for Indians residing in the US and UK were intermediate. Cancers shown to have the lowest rate in India include esophagus, colorectal, liver, pancreas, lung, breast, uterine, ovary, prostate, bladder, kidney, renal, brain, non-Hodgkin lymphoma, and leukemia. Overall cancer rates in males were three times higher for whites in the US than for Indians in India and Singapore, and 50 – 75% higher for Indians in the US and UK. Prostate cancer rates were most notably different, with the rates in US whites being 20 times higher than in India. Overall cancer rates for women were also lowest in India, and more than 180% higher in US whites. Certain cancers were found to be more prevalent in Indians. The incidence of stomach cancer in males and females was highest among Indians in Singapore. The incidence of cancers of the mouth, pharynx, gall bladder, cervix, and male larynx were highest in India [30].

CONCLUSION

Over the years, the use of naturally occurring compounds with high phenolic contents have gained wide acceptance as alternatives to chemotherapy. Cancer, one of the leading causes of death in the world can now be delayed, suppressed or reversed by these polyphenolic compounds such as curcumin. Similarly, several other phytochemicals have been employed as chemopreventive agents. Currently, the molecular mechanisms of curcumin have been extensively elucidated, thereby giving insights to its anticancer, antioxidant and anti-inflammatory properties. As curcumin is shown to be non-toxic, further work is needed to substantiate the chemopreventive potentials of curcumin as the best alternative to chemotherapeutic agents which are deleterious to cancer patients.

REFERENCES

1. Sharma RA, Gescher AJ, Steward WP. Curcumin: The story so far. European J Cancer. 2005;41:1955-1968.
2. Eigner D, Sholz D. Ferula asa-foetida and curcuma longa in traditional medical treatment and diet in Nepal. J Ethnopharmacol. 1999; 67:1-6.
3. Ammon HP, Wahl MA. Pharmacology of curcuma longa. Planta Med. 1991; 57:1-7.
4. Aggarwal BB, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res. 2003; 23: 363-398.
5. Joe B, Vijaykumar M, Lokesh BR. Biological properties of curcumin - cellular and molecular mechanisms of action. Crit Rev Food Sci Nutr. 2004; 44: 97-111.
6. Wang YJ, Pan MH, Cheng AL. Stability of curcumin in buffer solutions and characterization of its degradation products. J Pharm Biomed Anal. 1997; 15: 1867-1876.
7. Aggarwal BB, et al Anticancer potential of curcumin: Preclinical and clinical studies. Anticancer Res. 2003; 23:363-398.
8. Ramachandran C. Curcumin inhibits telomerase activity through human telomerase reverse transcriptase in MCF-7 breast cancer cell line. Cancer Lett. 2002; 184:1-6.

ISSN: 2320-1215

9. Goel A. Specific inhibition of cyclooxygenase-2 (COX-2) expression by dietary curcumin in HT-29 human colon cancer cells. Cancer Lett. 2001; 172:111-118.
10. Villasenor IM. Comparative potencies of nutraceuticals in chemically induced skin tumor prevention. Nutr Cancer. 2002; 44:66-70.
11. Kuttan R. Potential anticancer activity of turmeric (Curcuma longa). Cancer Lett. 1985;29:197-202.
12. Mahady GB. Turmeric (Curcuma longa) and curcumin inhibit the growth of Helicobacter pylori, a group 1 carcinogen. Anticancer Res. 2002; 22:4179-4181.
13. Somasundaram S. Dietary curcumin inhibits chemotherapy-induced apoptosis in models of human breast cancer. Cancer Res. 2002; 62:3868-3875.
14. Chuang SE, Kuo ML, Hsu CH. Curcumin-containing diet inhibits diethylnitrosamine-induced murine hepatocarcinogenesis. Carcinogenesis. 2000; 21:331-5.
15. Mahmoud NN, Carothers AM, Grunberger D. Plant phenolics decrease intestinal tumors in an animal model of familial adenomatous polyposis. Carcinogenesis. 2000;21:921-7.
16. Kim JM, Araki S, Kim DJ. Chemopreventive effects of carotenoids and curcumins on mouse colon carcinogenesis after 1,2-dimethylhydrazine initiation. Carcinogenesis. 1998;19: 81-5.
17. Krishnaswamy K, Goud VK, Sesikeran B, Mukundan MA, Krishna TP.Retardation of experimental tumorigenesis and reduction in DNA adducts by turmeric and curcumin. Nutr Cancer .1998;30(2):163-166.
18. Li N, Chen X, Liao J, et al. Inhibition of 7,12-dimethylbenz[a]anthracene (DMBA)-induced oral carcinogenesis in hamsters by tea and curcumin. Carcinogenesis. 2002; 23(8): 1307-1313.
19. Ikezaki S, Nishikawa A, Furukawa F, et al. Chemopreventive effects of curcumin on glandular stomach carcinogenesis induced by N-methyl-N'-nitro-N-nitrosoguanidine and sodium chloride in rats. Anticancer Res. 2001; 21(5): 3407-3411.
20. Huang MT, Lou YR, Ma W, Newmark HL, Reuhl KR, Conney AH.Inhibitory effects of dietary curcumin on forestomach, duodenal, and colon carcinogenesis in mice. Cancer Res. 1994; 54(22): 5841-5847.
21. Chuang SE, Kuo ML, Hsu CH. Curcumin-containing diet inhibits diethylnitrosamine-induced murinehepato. Carcinogenesis. 2000; 21(2): 331-335.
22. Pereira MA, Grubbs CJ, Barnes LH. Effects of the phytochemicals, curcumin and quercetin, upon azoxymethane-induced colon cancer and 7, 12-dimethylbenz[a]anthracene-induced mammary cancer in rats. Carcinogenesis. 1996; 17(6): 1305-1311.
23. Rao CV, Rivenson A, Simi B, Reddy BS. Chemoprevention of colon carcinogenesis by dietary curcumin, a naturally occurring plant phenolic compound. Cancer Res. 1995; 55(2):259-266.
24. Kawamori T, Lubet R, Steele VE. Chemopreventive effect of curcumin, a naturally occurring anti-inflammatory agent, during the promotion/progression stages of colon cancer. Cancer Res. 1999; 59(3): 597-601.
25. Mahmoud NN, Carothers AM, Grunberger D. Plant phenolics decrease intestinal tumors in an animal model of familial adenomatous polyposis. Carcinogenesis. 2000; 21(5):921-927.
26. Perkins S, Verschoyle RD, Hill K. Chemopreventive efficacy and pharmacokinetics of curcumin in the min/+ mouse, a model of familial adenomatous polyposis. Cancer Epidemiol Biomarkers Prev. 2002; 11(6): 535-540.
27. Cheng AL, Hsu CH, Lin JK. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res. 2001; 21(4): 2895-2900.
28. Aggarwal BB, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res. 2003;23: 363-98.
29. Mohan R, Sivak J, Ashton P. Curcuminoids inhibit the angiogenic response stimulated by fibroblast growthfacto r-2, including expression of matrix metalloproteinase gelatinase. J Biol Chem.2005; 275: 10405-12.
30. Rostogi T, Devesa S, Mangtani P. Cancer incidence rates among South Asians in four geographic regions: India, Singapore, UK and US. Int J Epidemiol. 2008; 37: 147-60.