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Minireview

Multiple biological activities of curcumin: A short review

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Abstract

Turmeric (*Curcuma longa* rhizomes), commonly used as a spice is well documented for its medicinal properties in Indian and Chinese systems of medicine. It has been widely used for the treatment of several diseases. Epidemiological observations, though inconclusive, are suggestive that turmeric consumption may reduce the risk of some form of cancers and render other protective biological effects in humans. These biological effects of turmeric have been attributed to its constituent curcumin that has been widely studied for its anti-inflammatory, anti-angiogenic, anti-oxidant, wound healing and anti-cancer effects. As a result of extensive epidemiological, clinical, and animal studies several molecular mechanisms are emerging that elucidate multiple biological effects of curcumin. This review summarizes the most interesting in vitro and in vivo studies on the biological effects of curcumin.
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Keywords: Curcumin; Wound healing; Anti-oxidant; Angiogenesis; Cancer

Contents

Introduction

Turmeric, *Curcuma longa* L. (Zingiberaceae family) rhizomes, has been widely used for centuries in indigenous medicine for the treatment of a variety of inflammatory conditions and other diseases (Ammon and Wahl, 1991). Its medicinal properties have been attributed mainly to the curcuminoids and the main component present in the rhizome includes curcumin (diferuloylmethane)—(1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-hepadiene-3,5-dione) (Fig. 1). Over the years, a number of studies have tried addressing the pharmacokinetics of curcumin that is poorly absorbed from intestine after oral administration of different doses of ^{3}H-curcumin in rats (Ravindranath and Chandrasekhara, 1980, 1981, 1982). It was shown that oral consumption of curcumin in rats resulted in approximately 75% being excreted in the feces and only traces appeared in the urine (Wahlstrom and Blennow, 1978), whereas intra-peritoneal (i.p) administration accounted for similar levels of fecal excretion of curcumin, with only 11% found in bile

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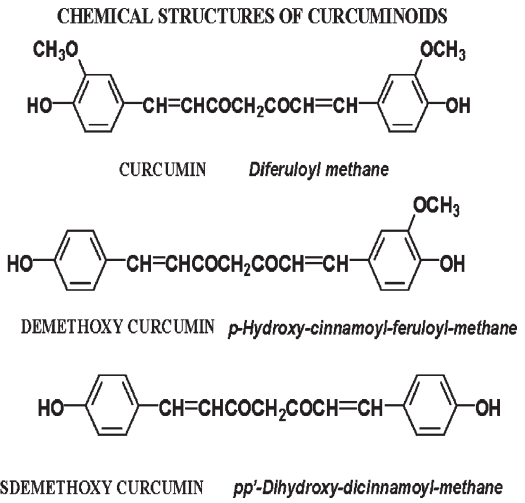

Fig. 1. Chemical structure of curcuminoids curcumin, demethoxy curcumin and bisdemetohxy curcumin that have shown antioxidant and/or anti-inflammatory properties.

(Holder et al., 1978) suggesting poor absorption of curcumin from the intestine. Numerous studies have suggested presence of different metabolites of curcumin. It has been shown to be bio-transformed to dihydrocurcumin and tetrahydrocurcumin. Subsequently, these products are converted to monoglucuronide conjugates (Pan et al., 1999). In another study, it was reported that the main biliary metabolites of curcumin are glucuronide conjugates of tetrahydrocurcumin (THC) and hexahydrocurcumin (Holder et al., 1978).

Curcumin has been shown to possess wide range of pharmacological activities including anti-inflammatory (Srimal and Dhawan, 1973; Satoskar et al., 1986), anti-cancer (Kuttan et al., 1985), anti-oxidant (Sharma, 1976; Toda et al., 1985), wound healing (Sidhu et al., 1998) and anti-microbial effects (Negi et al., 1999). Many of these biological effects of turmeric and its component curcumin, curcuminoids and curcumin oil are illustrated (Fig. 2). Recently, curcumin treatment has been shown to correct defects associated with cystic fibrosis in homozygous DeltaF508 cystic fibrosis transmembrane conductance regulator (CFTR) knock out mice (Egan et al., 2004).

In vivo and in vitro studies have demonstrated curcumin's ability to inhibit carcinogenesis at three stages: tumor promotion, angiogenesis and tumor growth. Curcumin suppresses mitogen-induced proliferation of blood mononuclear cells, inhibits neutrophil activation and mixed lymphocyte reaction and also inhibits both serum-induced and platelet derived growth factor (PDGF)-dependent mitogenesis of smooth muscle cells (Huang et al., 1992). It has also been reported to be a partial inhibitor of protein kinase (Liu et al., 1993; Reddy and Aggarwal, 1994). The other salient feature of turmeric/curcumin is that despite being consumed daily for centuries in Asian countries, it has not been shown to cause any toxicity (Ammon and Wahl, 1991). Although a number of excellent reviews on curcumin are available, this short review specifically focuses on the anti-oxidant, wound healing, anti-angiogenic and anti-cancer effects of turmeric/curcumin.

Anti-oxidant activity

Oxidative stress plays a major role in the pathogenesis of various diseases including myocardial ischemia, cerebral ischemia–reperfusion injury, hemorrhage and shock, neuronal cell injury, hypoxia and cancer. Curcumin, exhibits strong antioxidant activity, comparable to vitamins C and E (Toda et al., 1985). Curcumin with its proven anti-inflammatory and antioxidant properties has been shown to have several therapeutic advantages. It was shown to be a potent scavenger of a variety of reactive oxygen species including superoxide anion radicals, hydroxyl radicals (Reddy and Lokesh, 1994) and nitrogen dioxide radicals (Unnikrishnan and Rao, 1995; Sreejayan and Rao, 1997). It was also shown to inhibit lipid peroxidation in different animal models (Reddy and Lokesh, 1992; Sreejayan and Rao, 1994). Curcumin protected oxidative cell injury of kidney cells (LLC-PK_1) by inhibiting lipid degradation, lipid peroxidation and cytolysis (Cohly et al., 1998) and also decreased ischemia-induced biochemical changes in heart in a feline model (Dikshit et al., 1995). Vascular endothelial cells treated with curcumin prevented oxidant mediated injury by increased heme oxygenase production (Motterlini et al., 2000).

Curcumin was found to protect rat myocardium against isoprenaline (ISO) induced myocardial ischemic damage (Nirmala and Puvanakrishnan, 1996a, b) and the protective effect was attributed to its antioxidant properties by inhibiting free radial generation (Manikandan et al., 2004). It caused a decrease in the degree of degradation of the existing collagen matrix and collagen synthesis, two weeks after the second dose of ISO. These effects were attributed to free radical scavenging properties and inhibition of lysosomal enzyme release by curcumin (Nirmala et al., 1999). Treatment with curcumin showed beneficial effects on renal injury by its ability to inhibit the expression of the apoptosis-related genes Fas and Fas-L (Jones et al., 2000).

Studies in our laboratory have shown that pretreatment with curcumin resulted in significant restoration of the liver cytokines IL-1alpha, IL-1beta, IL-2, IL-6, and IL-10 to normal levels that were increased by hemorrhage/resuscitation regimen in rats. In fact, IL-1beta levels were lower than sham levels. NF-kappaB and AP-1 were differentially activated at 2 and 24 h post-hemorrhage and were inhibited by curcumin pretreatment. Serum aspartate transaminase estimates indicated decreased liver injury in curcumin-pretreated animals subjected

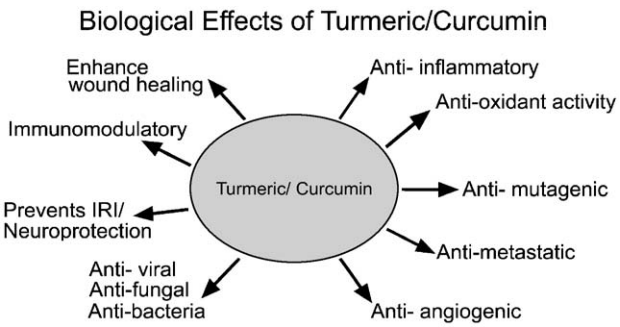

Fig. 2. Schematic showing multiple biological activities of turmeric/curcumin.

to hemorrhage. These results suggested that protection by curcumin pretreatment against hemorrhage/resuscitation injury might have resulted from the inactivation of transcription factors involved and regulation of cytokines to beneficial levels (Gaddipati et al., 2003). Similarly, in chronically hypoxic rabbit hearts Hsp70i trans-located from the particulate to the cytosolic fraction and curcumin reversed this subcellular redistribution (Rafiee et al., 2003) through protein kinase pathways (Rafiee et al., 2002).

It is suggested that dietary supplementation with curcumin may be beneficial in neurodegenerative diseases such as Alzheimer's disease (Calabrese et al., 2003; Yang et al., 2005). In a focal cerebral ischemia model of rats, curcumin offered significant neuroprotection through inhibition of lipid peroxidation, increase in endogenous antioxidant defense enzymes and reduction in peroxynitrite formation (Thiyagarajan and Sharma, 2004). In conclusion, curcumin exhibits a variety of beneficial effects and appears to have a significant potential in the treatment of multiple diseases that are a result of oxidative stress. These protective effects of curcumin are attributed mainly to its antioxidant properties and should be further exploited to develop novel drugs.

Curcumin enhances wound healing

Tissue repair and wound healing are complex processes that involve inflammation, granulation and tissue remodeling. Injury initiates a complex series of events that involves interactions of multiple cell types, various cytokines, growth factors, their mediators and the extra-cellular matrix proteins (ECM). Local application of turmeric is a household remedy in India for several conditions such as skin diseases, insect bites and chicken pox (Nadkarni, 1976). Based on the ancient use of turmeric in wound healing, our earlier studies evaluated the effect of curcumin on enhancement of wound healing. We used full thickness punch wound model to study its effect on wound healing. Curcumin treated wound biopsies showed a large number of infiltrating cells such as macrophage, neutrophils and fibroblasts as compared to untreated wound. The presence of myofibroblast in curcumin treated wound demonstrated faster wound contraction (Sidhu et al., 1998). Migration of various cells represents potential sources of growth factors required for the regulation of biological processes during wound healing. Transforming growth factor (TGF-β1) is important in wound healing as it stimulates the expression of fibronectin (FN) and collagen by fibroblasts and increases the rate of formation of granulation tissue in vivo (Varga et al., 1987; Quaglino et al., 1990). Curcumin treatment resulted in enhanced fibronectin (FN) and collagen expression (Sidhu et al., 1998). Furthermore, the treatment led to an increased formation of granulation tissue including greater cellular content, neo-vascularization and a faster re-epithelialization of wound in both diabetic as well as hydrocortisone impaired wounds (Sidhu et al., 1999) by regulating the expression of TGF-β1, its receptors and nitric oxide synthase during wound healing (Mani et al., 2002). Other studies involving systemic administration of curcumin have shown its beneficial effects by the enhancement of muscle regeneration after trauma in vivo by modulating NF-κB activity (Thaloor et al., 1999). Recent studies have suggested that curcumin inhibited the damage caused by hydrogen peroxide in human keratinocytes and fibroblasts (Phan et al., 2001) suggesting the antioxidant role in enhanced wound repair. Similarly, Curcumin incorporated collagen matrix treatment showed increased wound reduction, enhanced cell proliferation and efficient free radical scavenging as compared with control and collagen treated rats (Gopinath et al., 2004). Curcumin pretreatment enhanced the synthesis of collagen, hexosamine, DNA, nitrite, and histologic assessment of wound biopsy specimens showed improved collagen deposition and an increase in fibroblast and vascular densities suggesting that curcumin may be able to improve radiation-induced delay in wound repair (Jagetia and Rajanikant, 2005). It has also been studied for anti-ulcer activity in acute ulcer model in rat by preventing glutathione depletion, lipid peroxidation and protein oxidation. Denudation of epithelial cells during damage of gastric lumen is reversed by curcumin through re-epithelialization. Furthermore, both oral and intraperitoneal administration of curcumin blocked gastric ulceration in a dose dependent manner. It accelerated the healing process and protected gastric ulcer through attenuation of MMP-9 activity and amelioration of MMP-2 activity (Swarnakar et al., 2005). These studies clearly suggested that curcumin treatment resulted in faster closure of wounds, better regulation of granulation tissue formation and induction of growth factors. It suggests that it acts at different levels to enhance wound repair. Further studies are warranted to evaluate turmeric/curcumin as a potential therapeutic agent in clinical setting of wound healing.

Modulation of angiogenesis by curcumin

Angiogenesis is the growth of new vascular capillary channels from preexisting vessels and is of fundamental importance in a number of physiological processes such as embryonic development, reproduction, wound healing and bone repair. On the other hand, uncontrolled angiogenesis is pathological and is often associated with tumor growth, rheumatoid arthritis, diabetic retinopathy and hemangiomas. Three decades of intensive research has strongly indicated involvement of angiogenesis in expansion of primary tumors and their metastasis to distant organs (Folkman and Shing, 1992; Folkman, 1995). We have earlier reported that curcumin treatment resulted in inhibition of angiogenic differentiation of human umbilical vein endothelial cells (HUVEC) on matrigel and endothelial cell infiltration and vessel formation in matrigel plug, indicating the anti-angiogenic activity (Thaloor et al., 1998). Subsequently, it was shown to inhibit basic fibroblast growth factor (bFGF)-induced corneal neo-vascularization in the mouse cornea (Arbiser et al., 1998). This angiostatic efficacy in the cornea was also observed when curcuminoids were provided to mice in the diet (Mohan et al., 2000). Recent studies have demonstrated that several other curcumin analogs show inhibitory effect on angiogenesis as seen by chicken chorioallantoic membrane assay (Shim et al., 2002), invasion assay, and tube formation assay. These effects of curcumin analogs were shown

to be due to decrease expression of angiogenesis-associated genes, vascular endothelial growth factor (VEGF) and MMP-9 (Hahm et al., 2004). Several reports indicate that metalloproteinases (MMPs) and their specific inhibitors play a major regulatory role in matrix re-organization and the initiation of angiogenesis (Schnaper et al., 1993). Others and we have shown (Hahm et al., 2004; Kim et al., 2002; Thaloor et al., 1998) that curcumin and its analogs inhibited MMPs that were responsible for decreased angiogensis. More in vivo studies are required to elucidate the mechanisms of reported biological effects of curcumin.

Anti-cancer effects of curcumin

Recent studies have found that curcumin has a dose-dependent chemopreventive effect in several animal tumor bioassay systems including colon, duodenal, stomach, esophageal and oral carcinogenesis. It has been shown to reduce tumors induced by benz(a) pyrene and 7, 12 dimethyl benz(a) anthracene (Singh et al., 1998; Deshpande et al., 1997; Azuine and Bhide, 1992), tumor promotion induced by phorbol esters (Huang et al., 1988) on mouse skin, on carcinogen-induced tumorigenesis in the fore stomach and *N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine-induced duodenal tumors (Huang et al., 1994). Low incidence of bowel cancer in Indians has been attributed to the use of turmeric in Indian cookery (Mohandas and Desai, 1999). Also the antioxidant activities for these derivatives were shown to differ under different conditions (Sreejayan and Rao, 1994; Sugiyama et al., 1996). Comparison of the effect of curcuminoids on MCF-7 cell proliferation indicated significant variations in their effect on the cell growth (Simon et al., 1998). Two analogues of curcumin, aromatic enone and aromatic dienone have excellent anti-angiogenic properties (Robinson et al., 2003). Likewise curcuminoids, curcumin, I, II and III isolated from *C. longa* were also compared for their cytotoxic, tumour reducing and antioxidant activities. The data showed curcumin III to be more effective cytotoxic agent and was able to significantly inhibit Ehrlich ascites tumor in mice (Ruby et al., 1995).

Curcumin administration during both the initiation and post-initiation periods significantly inhibited colon tumorigenesis. In addition, administration of the synthetic curcumin in the diet during the promotion/progression stage significantly suppressed the incidence and multiplicity of noninvasive adenocarcinomas and also strongly inhibited the multiplicity of invasive adenocarcinomas of the colon (Kawamori et al., 1999).

The molecular basis of anti-carcinogenic and chemopreventive effects of curcumin is attributed to its effect on several targets including transcription factors, growth regulators, adhesion molecules, apoptotic genes, angiogenesis regulators and cellular signaling molecules (reviewed in Aggarwal et al., 2003). Curcumin has been shown to down regulate the production of pro-inflammatory cytokines tumor necrosis factor-α (TNF-α?), IL-1β and inhibit the activation of transcription factors nuclear factor-κB (NF-κB) and activator protein-1 (AP-1), which regulate the genes for pro-inflammatory mediators and protective antioxidant genes (Chan, 1995; Surh et al., 2000). Curcumin inhibited NF-κB activation by blocking phosphorylation of I-κB (Singh and Aggarwal, 1995) through inactivation of I-κB kinase complex (Jobin et al., 1999). Suppression of AP-1 was due to a direct interaction of curcumin with AP-1 binding to its DNA binding motif (Bierhaus et al., 1997) and also due to inhibition of c-*Jun* and c-*fos*, components of AP-1 (Park et al., 1998; Huang et al., 1995). It is also reported to suppress the activity of a number of enzymes such as cytochrome P450 and COX-2 (reviewed in Leu and Maa, 2002). Other studies have identified reduction in radiation induced DNA damage in rat lymphocytes (Thresiamma et al., 1998) and its anti-mutagenic potential (Shukla et al., 2002).

The key regulators involved in apoptosis are well characterized and include caspases, Bcl-2 family, TNF receptor family and other adapter proteins (Boedefeld et al., 2003). Androgen-dependent prostate tumors undergo apoptosis in response to androgen-ablation and expression of Bcl-2 and caspases correlate with the prostate cancer cell's sensitivity to the therapy. Curcumin has been demonstrated to induce apoptosis in a variety of cells including prostate cancer cells (Dorai et al., 2001). Curcumin treatment suppressed the constitutive activation of NFκB and AP-1 in DU145 cells and in turn down regulates endogenous bcl-2 and bax_{xL} (Mukhopadhyay et al., 2001). Curcumin in combination with TNF-related apoptosis-inducing ligand (TRAIL), enhanced cell death in LNCaP cells (Deeb et al., 2003). Studies using p53-null cells established the involvement of p53 in curcumin-induced apoptosis (Choudhuri et al., 2002). However, in melanoma cells apoptosis is induced through a Fas receptor/capsae-8 pathway and that is independent of p53 (Bush et al., 2001). It has also been shown to affect the activity of a number of enzymes such as cyclooxygenase (Zhang et al., 1999), protein kinase C (Liu et al., 1993) and protein tyrosine kinases (Chen and Huang, 1998). Recently, it has been suggested that curcumin affected arachidonic acid metabolism by blocking the phosphorylation of cytosolic phospholipase (cPLA(2)) and decreasing the expression of cyclooxygenase-2 (COX-2). Furthermore, it also inhibited catalytic activities of 5-lipoxygenase (LOX) (Hong et al., 2004). These activities may contribute to the anti-inflammatory and anti-carcinogenic actions of curcumin and its analogs (Hong et al., 2004). Elevated activities of antioxidant and phase II enzymes by Curcumin in mice are also suggested as the mechanisms of cancer chemopreventive effects associated with it (Iqbal et al., 2003).

In conclusion, the approach of anti-angiogenesis for the prevention and treatment of certain diseases like cancer, chronic inflammation or atherosclerosis looks very promising. Furthermore, our studies demonstrate curcumin modulates cytokines, growth factors and transcription factors, which may be responsible for its beneficial effects during tissue injuries caused by wound, trauma and hemorrhagic shock. In most of these disease states a long-term treatment will be necessary. Thus, oral administration of turmeric/curcumin with minimal acute or chronic toxicity will be of great value in combating these chronic illnesses.

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