Curcumin: from food spice to cancer prevention.


Abstract

Curcumin [1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6 heptadiene-3, 5-dione] is an orange-yellow component of turmeric (Curcuma longa), a spice often found in curry powder. It is known to have a variety of biologic and pharmacologic activities, including anti-inflammatory, anti-oxidant, and anticarcinogenic potential. It is a potent inhibitor of cytochrome P450 with capacity to simultaneously induce detoxifying enzymes such as glutathione S-transferase and as such may find application as a chemopreventive agent. Curcumin is a potent inhibitor of cyclooxygenase-2, lipooxygenase, ornithine decarboxylase (ODC), nuclear factor-kappaB, c-Jun N-terminal kinase and protein kinase C and has also been demonstrated to play a vital role against pathological conditions such as cancer, atherosclerosis, and neurodegenerative diseases.

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Introduction

Dietary improvement is reported to modify the pathophysiological processes of various metabolic disorders and can be an effective preventive strategy for various disease processes most of which are known to involve oxidative damage (Krishnaswamy and Raghuramulu, 1998). Several natural substances have been shown to have greater antioxidant effects than conventional vitamins, including various polyphenols, flavonoids and curcumenoinds. Both nutrient and non-nutrient components in the diet have been recognized for their anti-oxidant and other potential benefits. Curcumin [1, 7-bis (4-hydroxy-
3-methoxyphenyl)-1, 6 heptadiene-3, 5-dione] is an orange-yellow component of turmeric (Curcuma longa), a spice often found in curry powder (Jagetia and Aggarwal, 2007) (see Figure 1). A variety of pharmacological effects of curcumin have been reported, including anti-inflammatory (Mukhopadhyay et al., 1982), anti-oxidant (Sharma, 1976; Kunchandy, 1990) anticarcinogenic (Huang et al., 1994; Rao et al., 1995; Babu and Srinivasan, 1997), hypolipidemic and anti-diabetic/hypoglycemic activities (Sajithlal et al., 1998; Arun and Nalini, 2007). Curcumin is thought to play a vital role against these pathological conditions (Menon and Sudheer, 2007). It has been reported that the anti-cancer property of curcumin is mediated in part by its anti-angiogenic activity (Li et al., 2005; Yoysungnoen et al., 2005; 2006; Lin et al., 2007). Free radical-mediated peroxidation of membrane lipids and oxidative damage of DNA and proteins are known to be associated with a variety of chronic pathological complications such as cancer, atherosclerosis and neurodegenerative diseases. Curcumin and related phytochemicals have potentials to inhibit free radical generation and act as free radical scavengers (Kunchandy and Rao, 1990; Joe and Lokesh, 1994; Reddy and Lokesh, 1994) and antioxidants (Ruby et al., 1995), inhibiting lipid peroxidation (Rajakumar and Rao, 1994; Sreejayan and Rao, 1994) and oxidative DNA damage (Subramanian et al., 1994). Curcumin has been noted to be a potent inhibitor of cytochrome P450 (Oetari et al., 1996) with potential to induce detoxifying enzymes such as glutathione S-transferase (Susan and Rao, 1992) and as such, has been proposed as a potential chemoprotective agent (Wargovich, 1997). Components of turmeric have been shown to be non-toxic and inhibit mediators of inflammation as NFkappa B, cyclooxygenase-2 (COX-2), lipooxygenase (LOX), and inducible nitric oxide synthase (iNOS) (Bengmark et al., 2007).

Roles of Inflammation in Carcinogenesis
A wide array of phenolic substances, particularly those present in edible and medicinal plants, have been reported to possess substantial anticarcinogenic and antimutagenic activities. The majority of naturally occurring phenolic compounds retain antioxidative and anti-inflammatory properties which appear to contribute to their chemopreventive or chemoprotective activity. Cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) are important enzymes that mediate inflammatory processes. In the same vein, improper upregulation of COX-2 and/or iNOS has potential to initiate pathophysiology of certain types of human cancers as well as inflammatory disorders. Since inflammation is closely linked to tumour
promotion, substances with potent anti-inflammatory activities are anticipated to exert significant chemopreventive effects on multi-stage carcinogenesis, particularly the promotion stage (Surh et al., 2001). Several chemopreventive phytochemicals have been shown to inhibit COX-2 and iNOS expression by blocking improper NF-kappa B activation.

Similarly, an increase in prostaglandin (PG) synthesis may influence tumour growth in human beings and experimental animals, and numerous studies have illustrated the effect of PG synthesis on carcinogen metabolism, tumour cell proliferation and metastatic potential (Cuendet and Pezzuto, 2001). PGs produced by cyclooxygenase (COXs) are represented by a large series of compounds that mainly enhance cancer development and progression, acting as carcinogens or tumour promoters, with profound effects on carcinogenesis (Cuendet and Pezzuto, 2001; Pidgeon et al., 2007). Substantial evidence supports a functional role for Cyclooxygenase and lipooxygenase-catalyzed arachidonic and linoleic acid metabolism in cancer development (Pidgeon et al., 2007). Arachidonic acid-derived eicosanoids or linoleic acid-derived hydroperoxy fatty acid signaling are likely to be involved in driving carcinogenesis via cell growth, cell survival, angiogenesis, cell invasion, metastatic potential and immunomodulation (Fürstenberger et al., 2007).

In response to various growth factors, hormones or cytokines, published data have shown that arachidonic acid can be mobilized from phospholipids pools and converted to bioactive eicosanoids through cyclooxygenase (COX), lipooxygenase (LOX) or P-450 epoxygenase pathway (Nie and Honn, 2004; Catalano and Procopio, 2005; Wang et al., 2007). The COX pathway generates five major prostanoids (prostaglandin D (2), prostaglandin E (2), prostaglandin F (2) alpha, prostaglandin I(2) and thromboxane A(2)) that play important roles in diverse biological processes. Studies suggest that different prostanoids and their own synthase can play distinct roles in tumour progression and cancer metastasis (Wang et al., 2007). COX-2 and PGE (2) synthase have been most well documented in the regulation of various aspects of tumour progression and metastasis. PGE (2), for example, can stimulate angiogenesis or other signaling pathways by binding to its receptors termed EPs (Wang et al., 2007). The involvement of eicosanoids in tumour angiogenesis and progression is implicated by the observations that nonsteroidal anti-inflammatory drugs (NSAIDs) reduce tumour growth and angiogenesis (Catalano and Procopio, 2005). Subsequently and ultimately, it is has been found that the levels of COX-2 and/or 12-LOX are frequently increased in various cancers (Nie and Honn, 2004; Catalano and Procopio, 2005).

**Anti-inflammatory Activities of Curcumin**

Curcumin has proven to be beneficial in the prevention and treatment of a number of inflammatory diseases. Several lines of evidence support a functional role for cyclooxygenase- and lipooxygenase-catalyzed arachidonic and linoleic acid metabolism in cancer development (Fürstenberger et al., 2007). Arachidonic acid-derived lipid
mediators that are intimately involved in inflammation are biosynthesized by pathways dependent on cyclooxygenase (COX) and lipoxygenase (LOX) enzymes (Rao, 2007). The anti-inflammatory effect of curcumin is most likely mediated through its ability to inhibit cyclooxygenase-2 (COX-2), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS), which are important enzymes mediating inflammatory processes (Menon and Sudheer, 2007). Anti-inflammatory and anticarcinogenic potential of curcumin has also been reported (Hong et al., 2004).

Figure 2. Molecular Mechanisms: Curcumin Prevents Nuclear Translocation of NF-κB, thereby Causing Cancer

Cells to Commit Suicide


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Curcumin and Chemoprevention

Curcumin, the active component of turmeric, is a dietary constituent that has received a great deal of attention recently as a chemoprotective agent (Shishu et al., 2002; Duvoix et al., 2003). Previous published reports have shown that curcumin has antioxidant and antiinflammatory activities, as well as anticarcinogenic activity in colon cancer, breast cancer (Aggarwal et al., 2005; Choudhuri et al., 2005) and leukaemia (Gautam, 2000).

Curcumin is a potent inhibitor of cyclooxygenase-2, lipoxygenase, ornithine decarboxylase (Okazaki et al., 2005; Gafner et al., 2004; Leu and Maa, 2002), c-Jun/AP-1, nuclear factor-kappa B (Dikshit et al., 2006; Lee et al., 2005), c-Jun N-terminal kinase, and protein kinase C; further contributing to its anticancer properties (Woo et al., 2005; Cho et al., 2005). Curcumin inhibited epidermal growth factor receptor activity in various tumours; including prostate carcinoma (Dorai et al., 2000). Curcumin has been reported to cause a marked decrease in cell proliferation and apoptosis in prostate tumours (Dorai et al., 2001). Curcumin, EGCG and resveratrol have been reported to suppress activation of NF-kappa B (Bengmark, 2006). One of the plausible mechanisms underlying inhibition of NF-kappa B activation by curcumin phytochemicals involves repression of degradation of the inhibitory unit of I kappa B alpha (i Ba), which prevent subsequent nuclear translocation of the functionally active subunit of NF-kappa B (Bengmark, 2006). Also, curcumin was reported to inhibit tumour formation in several murine tissues and antagonizes both initiation and promotion of tumours in rodent epithelial and colon cancer models (Ammon and Wahl, 1991; Lin et al., 2000). Most recently, curcumin has demonstrated antiangiogenic properties in several laboratories and in vivo model systems (Arbiser et al., 1998; Mohan et al., 2000; Dorai et al., 2001).

Topical application of curcumin inhibited TPA-induced increase in the percent of epidermal cells in synthetic (S) phase of the cell cycle (Huang et al., 1997). Topical application of curcumin inhibits tumour initiation by B[a]P and tumour promotion by TPA in mouse skin. Dietary curcumin (commercial grade) inhibits B[a]P-induced forestomach carcinogenesis, N-ethyl-N-nitro-N-nitrosoguanidine (ENNG)-induced duodenal carcinogenesis, and azoxymethane (AOM)-induced colon...
carcinogenesis (Huang et al., 1997). Curcumin has potent anticancer activity against intestinal adenoma probably by modulating lymphocyte-mediated immune functions (Churchill et al., 2000). Many environmental chemicals and pesticides have been found to be estrogenic and shown to stimulate the growth of estrogen receptor-positive (ER-positive) human breast cancer cells (Verma et al., 1998).

Curcumin and genistein have been reported as the most potent inhibitors against the growth of human breast tumour cells (Verma et al., 1998).

**Molecular Targets of Curcumin**

Multiple lines of compelling evidence indicate that extracellular-regulated protein kinase (ERK) and p38 mitogen-activated protein kinase (MAPK) are key elements of the intracellular signaling cascades responsible for NF-kappa B activation in response to a wide array of external stimuli. The anticancer potential of curcumin stems from its ability to suppress proliferation of a wide variety of tumour cells, down-regulate transcription factors NF-kappa B, AP-1 and Egr-1, and the expression of COX2, LOX, iNOS, MMP-9, TNF, chemokines, cell surface adhesion molecules and cyclin D1 (see Figure 3). It also down-regulates growth factor receptors (such as EGFR and HER2) and inhibits the activity of c-Jun N-terminal kinase, protein tyrosine kinases and protein serine/threonine kinases (Aggarwal et al., 2003). Curcumin inhibited growth of LNCaP xenografts in nude mice by inducing apoptosis and inhibiting proliferation and sensitized these tumours to undergo apoptosis by TRAIL. In xenografted tumours, curcumin up-regulated the expression of TRAIL-R1/DR4, TRAIL-R2/DR5, Bax, Bak, p21/WAF1, and p27/KIP1, and inhibited the activation of NF-κB and its gene products (Shankar et al., 2008). Curcumin treatment with TRAIL in combination with genistein sensitized TRAIL-resistant AGS gastric adenocarcinoma cells to TRAIL-mediated apoptosis. Curcumin has been reported to induce apoptosis in human melanoma cells through a Fas receptor/caspase-8 pathway independent of p53 (Bush et al., 2001). Another property ascribed to curcumin is that of inhibition of c-jun/AP-1 function (Huang et al., 1991) and JNK activation (Chen and Tan, 1998).

**Conclusions**

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.
Figure 3. Molecular Targets of Curcumin

References


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