Drugs of the Future 2010, 35(2): 113-119

CCC: 0377-8282/2010
DOI: 10.1358/dof.2010.35.2.1426640

REVIEW ARTICLE

CURCUMIN: MULTIPLE MOLECULAR TARGETS MEDIATE MULTIPLE PHARMACOLOGICAL ACTIONS — A REVIEW

A. Shehzad and Y.S. Lee

School of Life Sciences and Biotechnology, College of Natural Sciences, Kyungpook National University, Daegu, Korea

CONTENTS

SUMMARY

Curcumin (diferuloylmethane), the active constituent of turmeric, has been used as a treatment for a wide variety of inflammatory conditions. Extensive research over the past two decades has shown that curcumin mediates its effects through the inhibition of transcription factors (NF-κB, AP-1), enzymes (COX-1, COX-2, LOX), cytokines (TNF, IL-1, IL-6) and downregulation of antiapoptotic genes (BCL2, BCL2L1). Curcumin has been widely used for the treatment of several chronic diseases, including various cancers, Alzheimer's disease, cardiovascular diseases, diabetes, arthritis, alcohol-induced liver injury, multiple sclerosis and inflammatory eye conditions. In addition, curcumin enhances wound healing and blocks HIV replication. Studies have also shown that curcumin has no effect on normal cells and kills only tumor cells. Various pharmacological aspects of curcumin are discussed with regard to different types of chronic diseases.

INTRODUCTION

Curcumin, a naturally occurring polyphenolic compound of turmeric, was widely used in indigenous medicine for the treatment of various diseases. It is a diferuloylmethane that is isolated from extracts of the dried ground rhizome of perennial herb curcuma species (*Curcuma longa*) and belongs to the ginger (Zingiberaceae) family (1). Curcumin was first isolated in 1815 by Vogel and its chemical structure was confirmed later on by Lampe and Milobedezka in 1910. With a molecular formula of $C_{21}H_{20}O_6$ and a molecular weight of 368.37 g/mol, curcumin is a bis-α,β-unsaturated β-diketone that exists in equilibrium with its enol tautomer. The bis-keto form predominates in acidic and neutral aqueous solutions and in the cell membrane (Fig. 1). Commercially available curcumin contains approximately 77% diferuloylmethane, 18% demothoxycurcumin and 5% bis-demethoxycurcumin (2). Curcumin is insoluble in water but soluble in ethanol or dimethylsulfoxide. The steam distillation of turmeric rhizome yields essential oil (5.8%), composed of α-phellandrene (1%), sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%) and sesquiterpenes (53%) (3).

Traditionally, curcumin has been used as a remedy for the treatment of various ailments, including biliary disorders, anorexia, cough, sprains, wounds, hepatic disorders, arthritis, sinusitis and dermatological infections (1). Recent research has demonstrated that it is highly antioxidative and anti-inflammatory and possesses multifaceted pharmacological functions that explain its role in the treatment of various chronic diseases. Many studies indicated that curcumin modulates multiple molecular targets, such as enzymes, growth factors and their receptors, cytokines and various proteins regulating cell proliferation (4). Furthermore, it has potential therapeutic value for many chronic disorders, such as cancer, Alzheimer's disease, neoplastic, cardiovascular and pulmonary diseases, rheumatoid arthritis and myocardial infarction (5). According to a joint report of the Food and Agriculture Organization and the World Health Organization on food additives, the recommended maximum daily intake of curcumin is 0-1 mg/kg body weight (6), but several clinical studies dealing with its efficacy suggest that it is safe and well tolerated even when intake is as high as 12 g/day (7). Our discussion will focus on some of the major pharmacological and clinical effects of curcumin with regard to different types of diseases. We hope that the outcome of this review will be a potential step forward in understanding this agent's role in curing many chronic diseases.

MULTIPLE MOLECULAR TARGETS

Extensive evidence indicates that curcumin has direct and indirect interactions with numerous molecular targets, including transcription factors, growth factors, cytokines, kinases, enzymes, receptors and various proteins regulating cell proliferation and apoptosis (Fig. 2). Curcumin interacts directly with cyclooxygenase-2 (COX-2), DNA

Correspondence: Y.S. Lee, School of Life Sciences and Biotechnology, College of Natural Sciences, Kyungpook National University, Daegu 702-701, Korea. E-mail: yselee@knu.ac.kr.

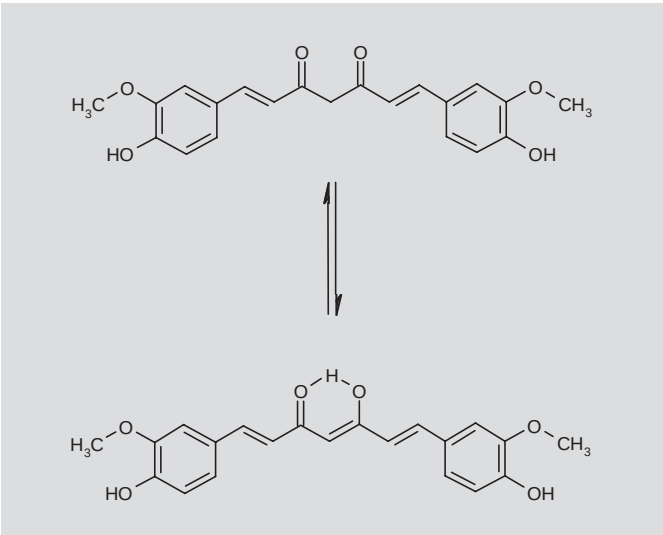

Figure 1. Tautomerism of curcumin under acidic and neutral conditions, the bis-keto form (top) predominates, whereas the enolate form is found at alkaline pH.

polymerase, lipoxygenase (LOX), glycogen synthase kinase-3β (GSK-3β) and an autophosphorylation-activated protein kinase (8). It interacts indirectly with several transcription factors, including nuclear factor NF-kappa-B (NF-κB), activator protein 1 (AP-1), β-catenin, signal transducer and activator of transcription (STAT) proteins and peroxisome proliferator-activated receptor γ (PPARγ) (8, 9). It was reported that curcumin suppresses the activity of various growth factors, including epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β) and various other proteins associated with growth signaling and cell proliferation. There is evidence that curcumin-induced apoptosis is associated with the decreased expression of proapoptotic proteins, vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor 1 (VEGFR-1) (10). Curcumin totally blocks the activity of various protein kinases, including EGF receptor (EGFR) kinase, endoplasmic reticulum kinase, protein kinase A (PKA), protein kinase B (PKB), protein kinase C (PKC) and Janus kinase (JAK), while it activates mitogen-activated protein kinases (MAPK) (11). Curcumin inhibits cell cycle progression in many types of tumor cells. It has been shown to arrest the cell cycle at the G_0/G_1 or G_2/M phase transition, through upreg-

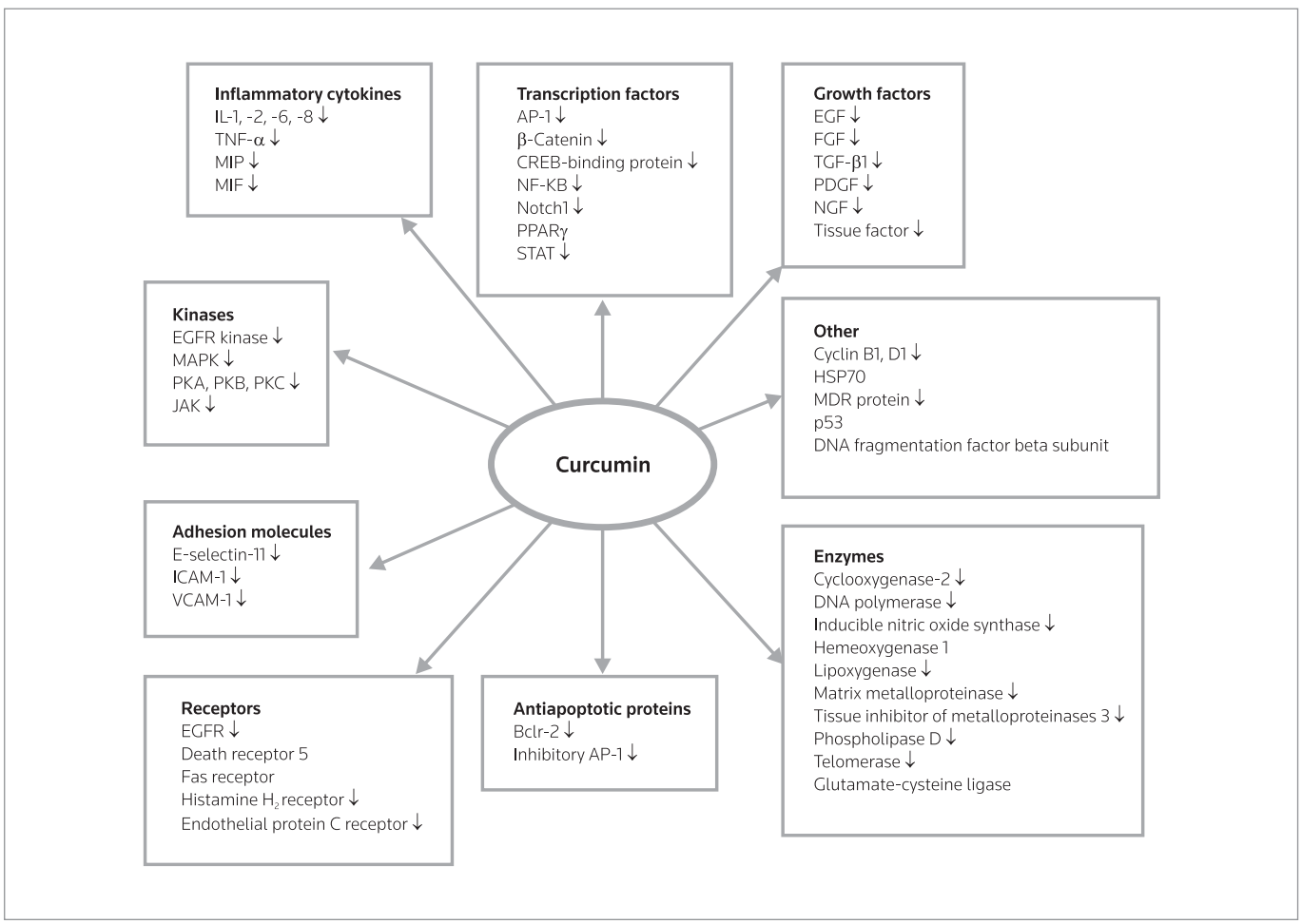

Figure 2. Multiple molecular targets of curcumin in the treatment of various diseases. The upward arrows (↑) indicate enhancement, whereas downward arrows (↓) indicate inhibition or decrease in the level of the target molecule.

ulation of the cyclin-dependent kinase inhibitors (e.g., p21, p27) and tumor suppressor p53, and downregulates G_2/mitotic-specific cyclin-B1 and cell division control protein 2 homolog (encoded by *CDC2*) in immortalized human umbilical vein endothelial (ECV304) cells (12). Curcumin induction of apoptosis is also associated with the sequential activation of caspase-8, Bcl-2 homology domain 3 (BH3)-interacting domain death agonist (BID) cleavage, Bcl-2-like protein 1 (Bcl2-L-1), cytochrome *c* release, activation of caspase-9 and caspase-3, and poly [ADP-ribose] polymerase (PARP) cleavage (13). Curcumin's ability to mediate multiple molecular targets and nontoxic nature make it a good therapeutic drug for various chronic diseases.

PHARMACOLOGICAL ACTIONS OF CURCUMIN

Although curcumin was isolated in the 19th century, its pharmacological activities and medicinal application have been known since the Vedic ages. Curcumin is effective against various chronic diseases, which are discussed below.

Curcumin in cancer

Since ancient times, curcumin has been known for its anti-inflammatory, antioxidant and anticarcinogenic properties. The pleiotropic role of this dietary compound includes the modulation of several molecular targets at multiple levels, which enhances its antiproliferative properties in a wide variety of cancer cells. Several reports have described the therapeutic activity of curcumin in gastrointestinal cancers, such as esophageal, gastric, intestinal, pancreatic and colorectal cancer. It was found to inhibit the cytokine-induced activation of inducible nitric oxide synthase (iNOS), MAPK, vascular cell adhesion protein (VCAM), β-catenin, COX-2, VEGF, EGFR, matrix metalloproteinases (MMPs), Ca^{2+} mobilization, Bcl2-L-1 and phosphorylated STAT3. In addition, curcumin activates caspase-3 and caspase-8 and induces PARP cleavage in the previously mentioned gastrointestinal cancers (14). Curcumin blocks tumor initiation and promotion and suppresses the growth of various cancer cells, including B-cell and T-cell leukemia, colon and breast carcinoma and multiple myeloma (15). In human head and neck squamous carcinoma cells curcumin was found to block NF-κB signaling and IKK activation, suppressing various cellular proliferative and survival genes (e.g., those encoding Bcl-2, G_1/S-specific cyclin-D1 (BCL-1), IL-6, COX-2 and MMP-9), caspase activation and PARP cleavage (16). Apart from causing tumor cell death, curcumin was also found to stop the invasion and metastasis of cancer cells. It was reported to inhibit COX-2 upregulation, MMP-9 overexpression and phorbol ester-induced metastasis by blocking ERK-1/ERK-2 phosphorylation and NF-κB transcriptional activity in MCF-10A human breast epithelial cells (17).

A number of clinical trials addressed the agent's pharmacokinetics, safety and efficacy in different types of cancers and found that it reduces or even eliminates cancer growth, modulating multiple molecular targets and exhibiting therapeutic potential against a wide range of different cancers (Table I). A randomized, double-blind, placebo-controlled, multicenter study investigated the efficacy of curcumin as maintenance therapy in 89 patients with quiescent ulcerative colitis. The participants were randomized to receive curcumin (1 g) plus sulfasalazine or mesalamine after breakfast and the evening meal (n = 45) or placebo plus sulfasalazine or mesalamine (n = 45). After 6 months of treatment, curcumin proved to be a promising compound for the prevention of relapse of ulcerative colitis and a safe therapeutic for the disease (18). Currently, several randomized and nonrandomized phase I and II clinical trials are being performed to investigate the agent's effect in different kinds of human cancers.

Curcumin in Alzheimer's disease

A progressive neurodegenerative disorder and the most common type of presenile and senile dementia, Alzheimer's disease is charac-

Table I. *Molecular targets of curcumin in various cancers (14).*

Cancer type	Molecular targets
Gastrointestinal cancer	
Esophageal cancer	NF-κB, MAPK, VCAM, iNOS
Gastric cancer	Caspase-3, ABCB5 P-gp, MDR
Intestinal cancer	COX-2, β-catenin
Hepatic cancer	Caspase-3, PARP, MMP-9, COX-2, VEGF
Pancreatic cancer	NF-κB, COX-2, STAT3, IL-8, EGFR, MAPK
Colorectal cancer	Caspase-3/8, PARP, Bcl2-L-1, MAPK, COX-2, NF-κB, HSP, MMP-2/9, ROS, IL-8, EGFR, VEGF, AP-1
Genitourinary cancer	
Bladder cancer	NF-κB, p21, cyclin-A, AP-1
Kidney cancer	c-AKT, Bcl-2, Bcl2-L-1, IAP, TRAIL, ROS
Prostate cancer	AP-1, NF-κB, cyclin-D1, c-AKT, p21 MMP-2/9, CREB, EGF
Gynecological cancer	
Cervical cancer	MDR, ABCB5 P-gp, NF-κB, AP-1
Ovarian cancer	NF-κB, MDR
Thoracic, head and neck cancer	
Pulmonary cancer	IκBα, AP-1, COX-2, NAT, STAT
Oral cancer	NF-κB, COX-2, CYPIA1/IB1
Thymic cancer	NF-κB, IL-1, TNF-α, IRAK
Hematological cancer	
Leukemia	NF-κB, AP-1, caspase-3/8, PARP, STAT3, cyclin-D3, pRb, p21, p27, COX-2
Lymphoma	NF-κB, JAK1, STAT3, c-AKT
Multiple myeloma	IL-6, TrkB, NF-κB, STAT3
Other	
Breast cancer	NF-κB, AP-1, COX-1/2, LOX, VEGF, FGF, TIMP-1, p21, p27, MMP-2, cyclin-E, IL-6/11, TGF-β, MMP-9/13
Bone cancer	VEGF, ERK
Brain tumor	Bcl-2, HSP, TRAIL, MMP, PARP, ING4
Melanoma	FASLG receptor, caspase-8, NF-κB, COX-1/2, FAK, MMP-2, nm23/E-cadherin

MDR, multidrug resistance protein

terized by an increased inflammatory (cytokine) response to amyloid plaques and activated microglia (19). It is well known that curcumin has potent anti-inflammatory effects, which might contribute to its role in the treatment of Alzheimer's disease.

Curcumin has been reported to reduce inflammation by inhibiting early growth response protein 1 (EGR-1) and its DNA-binding activity in human acute monocytic leukemia THP-1 cells (20). In addition, curcumin reduces the release of reactive oxygen species (ROS), inhibits COX-2, AP-1, NF-κB, activation of proinflammatory TNF-α and IL-1 (21). In a study conducted in rats, curcumin oil (500 mg/kg i.p.) was administered 15 min before 2-h middle cerebral artery occlusion followed by 24-h reflow. Treatment with curcumin oil was associated with diminished infarct volume and improved neurological deficit. Moreover, it counteracted oxidative stress, significantly inhibited the mitochondrial membrane potential, ROS, peroxynitrite levels and caspase-3 activity (22). Curcumin also prevented cerebral ischemia/reperfusion injury by protecting blood–brain barrier integrity. In another study conducted in rats, a single 30-min i.v. injection of curcumin (1 and 2 mg/kg) extensively diminished the infarct volume after focal cerebral ischemia/reperfusion and improved neurological deficit, in addition to reducing mortality and the water content of the brain (23). In view of its pharmacological safety and efficacy, curcumin has well-established therapeutic effects for the treatment and prevention of Alzheimer's disease.

Curcumin in cardiovascular disease

Many studies indicate that curcumin has preventive effects against various cardiovascular diseases, including atherosclerosis and myocardial infarction. The compound's effect on the proliferation of peripheral blood mononuclear cells and vascular smooth muscle cells was investigated by the evaluation of fetal calf serum-stimulated [^{3}H]-thymidine uptake. Curcumin (1-100 mM) concentration-dependently inhibited the serum-stimulated [^{3}H]-thymidine incorporation into both A7r5 cells and vascular smooth muscle cells from rabbits. Cell cycle analysis revealed G_0/G_1 arrest and a reduced number of cells in the S phase. Curcumin also induced apoptosis in vascular smooth muscle cells and extensively reduced the membranous protein tyrosine kinase activity, c-Myc mRNA and Bcl-2 mRNA. Several studies suggest that curcumin inhibits LDL oxidation in atherosclerosis, a disease characterized by oxidative damage, which affects lipoproteins and the walls of the blood vessels. Curcumin (10 μM) effectively inhibited LDL oxidation (40-85%), as indicated by inhibition of the formation of thiobarbituric acid-reactive substances after copper ion-induced lipid peroxidation (24). In addition, curcumin was found to correct cystic fibrosis through opening of the cystic fibrosis transmembrane conductance regulator channels (25). Curcumin has a protective role in myocardial infarction, which is caused by closure of the coronary artery that supplies blood to the heart muscle. In addition, it was found to prevent cardiac hypertrophy and myocardial infarction through the inhibition of histone acetyltransferase p300 (26). Curcumin also blocked aorta banding-induced inflammation and fibrosis by disrupting histone acetyltransferase p300-dependent signaling pathways. This indicates that curcumin may soon provide a novel therapeutic strategy for cardiovascular diseases.

Curcumin in diabetes

Several studies have shown that curcumin has the ability to lower blood glucose levels by increasing the activity of an enzyme that plays a key role in blunting the blood sugar rise that follows meals and produces insulin. A pharmacokinetic study of curcumin was conducted in diabetic albino rats. In this model, it reduced blood sugar, as well as hemoglobin, glycosylated hemoglobin, oxidative stress (as demonstrated by lower levels of thiobarbituric acid-reactive substances) and the enzymatic activity of sorbitol dehydrogenase, which catalyzes the conversion of sorbitol to fructose (27). Furthermore, curcumin controls the symptoms associated with type 2 diabetes, a disorder associated with a failure to use insulin properly. Several studies have linked inflammation and obesity to the development of type 2 diabetes. Curcumin was reported to control diabetes in high-fat diet-induced obesity and leptin-deficient *ob/ob* male C57BL/6J mice. It reduced macrophage infiltration, hepatic NF-κB activity and markers of hepatic inflammation, and increased adiponectin production in adipose tissue. These results suggest that curcumin potentially controls the inflammatory and metabolic derangements associated with obesity and that it improves glycemic control in mouse models of type 2 diabetes (28). Furthermore, curcumin lowered the cholesterol and phospholipid levels in streptozotocin-induced diabetic animals. The diabetic animals were divided into two groups and fed a diet containing 0.5% curcumin or high cholesterol for 8 weeks. Dietary curcumin increased the catalytic activity of hepatic cholesterol 7-α hydroxylase, suggesting a hypocholesterolemic action and a higher rate of cholesterol catabolism (29). Curcumin's ability to lower blood glucose and cholesterol and antioxidant and free radical-scavenging properties make it a potential therapeutic for the treatment of diabetes.

Curcumin in arthritis

Arthritis is a chronic disease characterized by inflammation of the joints. Curcumin has been reported to suppress proinflammatory cytokines (e.g., TNF and IL-1), proinflammatory enzymes (e.g., COX-2, LOX) and MMPs and blocks the NF-κB signaling pathway. In a 2-week, short-term, double-blind, crossover study, the antirheumatic activity of curcumin (1200 mg/day) was compared with that of phenylbutazone (300 mg/day) in 18 patients with rheumatoid arthritis. There were remarkable improvements in morning stiffness, walking time and joint swelling. In a similar trial in which the number of patients was increased to 31 and the dose level was increased to 1800-2100 mg/day for longer periods of time (5-6 weeks), significant improvements were observed in all patients (30). The cartilage degeneration in arthritis is believed to be initiated by IL-1. Curcumin inhibits IL-1, MAPK, AP-1 and NF-κB and downregulates the expression of genes encoding MMPs in articular chondrocytes. In human chondrocytes, it repressed MMP-3 expression by 48-99% and MMP-13 expression by 45-97%, whereas these values were 8-100% and 32-100%, respectively, in bovine chondrocytes (31). Curcumin's ability to inhibit inflammatory signal transduction could be useful for suppression of the symptoms associated with arthritis.

Curcumin in alcohol-induced liver disease

Curcumin protects against alcohol-induced liver disease by inhibiting the gene expression associated with NF-κB activation. This effect

has been observed in a study conducted in rats, in which one group of animals received fish oil plus ethanol and the other group received fish oil, ethanol and curcumin 75 mg/kg/day. Rats fed fish oil plus ethanol developed fatty liver, necrosis, inflammation and NF-κB activation, while in the curcumin-treated group, the alcohol-induced pathological and biochemical changes were prevented. In the same study, curcumin suppressed the stimulatory effects of endotoxin in isolated Kupffer cells, an effect that is implicated in the pathogenesis of alcohol-induced liver disease (32). Current research has implicated the activation of inflammatory pathways in the pancreas that damage pancreatic tissue. Curcumin attenuated the expression of several proinflammatory cytokines (e.g., TNF, IL-6 and IL-8) through inhibition of the transcription factors NF-κB and AP-1, and has therapeutic potential for the treatment of acute and chronic pancreatitis. In addition, curcumin has been reported to ameliorate both ethanol- and non-ethanol-induced experimental pancreatitis through the inhibition of NF-κB and AP-1 and the degradation of inhibitory IκB proteins, and it suppressed the induction of cytokine mRNA expression (e.g., TNF and IL-6) (33). The effects of curcumin were also examined in hepatic fibrogenesis. During liver injury in rats, the level of PPARγ is considerably diminished, along with activation of hepatic stellate cells. Curcumin inhibits the proliferation of activated hepatic stellate cells by inducing PPARγ gene expression and revitalizing PPARγ activation (34). Curcumin's antioxidant potential, its ability to reduce activated hepatic stellate cell growth and lack of associated adverse effects make it a promising potential therapeutic for the prevention and treatment of hepatic fibrosis.

Curcumin in multiple sclerosis

A debilitating neurological disorder, multiple sclerosis is considered an autoimmune disease of the central nervous system (CNS) in which the patient's own immune system attacks the myelin sheath that normally surrounds and protects the nerve cells. The progression of multiple sclerosis results from the myelin antigen-sensitized T cells in the CNS. The demyelination and destruction of oligodendrocytes in the CNS is the hallmark of this disease. Curcumin has been shown to exhibit an inhibitory effect on the production of inflammatory cytokines by human monocytes and was also inhibitory in an animal model of multiple sclerosis, experimental autoimmune encephalomyelitis, in association with a decrease in IL-12 production and STAT4 activation. Type I interferon (IFN) has the ability to suppress both IL-12 and the IFN-α/β signal through the activation of STAT4 by phosphorylation in human T cells (35). In vitro treatment of activated T cells with curcumin inhibited IL-12-induced tyrosine phosphorylation of JAK2, STAT3 and STAT4. The inhibition of the JAK/STAT pathway by curcumin resulted in a decrease of IL-12-induced T-cell proliferation and T helper 1 (Th1) cell differentiation. These findings suggest that curcumin blocks IL-12 signaling in T cells and has potential in the treatment of multiple sclerosis and other inflammatory diseases mediated by Th1 cells.

Curcumin in wound healing

Wound healing consists of an orderly progression of events that include inflammation, granulation and tissue remodeling. During wound healing, the migration of various cells represents potential contact with growth factors required for the regulation of biological processes. TGF-β-1 is an important factor in wound healing as it stimulates the expression of fibronectin and collagen in fibroblasts and increases the rate of granulation. Curcumin modulates TGF-β-1 activity, encourages the formation of new skin (re-epithelialization) and also enhances a signal to the immune system that recruits macrophages to "recycle" dead tissue. A preclinical study of topical curcumin was conducted in a dexamethasone-impaired cutaneous rat model of wound healing. Curcumin significantly accelerated wound healing with or without dexamethasone treatment by enhanced expression of TGF-β-1 and TGF-β receptor type-2 (TGFR-2). The levels of iNOS were increased following curcumin treatment in unimpaired wounds, but not in dexamethasone-impaired wounds, indicating that topical curcumin enhanced the dexamethasone-impaired wound repair along with differential regulatory effects on TGF-β-1, TGF receptors and iNOS in this model of cutaneous wound healing (36). Curcumin-treated wounds were found to heal much faster, as indicated by improved rates of epithelialization and wound contraction. Curcumin decreased the levels of lipid peroxides while significantly increasing the levels of superoxide dismutase, catalase and glutathione peroxidase, thereby exhibiting antioxidant properties to accelerate wound healing (37). The antioxidant effects of curcumin on hydrogen peroxide (H_2O_2) and xanthine dehydrogenase/oxidase-induced damage to cultured human keratinocytes and fibroblasts were investigated. Curcumin showed considerable protective effects against H_2O_2 in human keratinocytes (10 μg/mL) and it also exhibited promising effects against H_2O_2 in human dermal fibroblasts (2.5 μg/mL). These findings indicate that curcumin indeed possesses the potential to inhibit H_2O_2 damage in human keratinocytes and fibroblasts, which may enhance wound healing (38).

Curcumin in HIV

Curcumin blocks the transcription of HIV-1 by inhibiting the activity of its long terminal repeat. Curcumin inhibited the production of p24 antigen in cells infected with HIV-1 through the transcriptional repression of the long terminal repeat. Concomitant administration of curcumin and boron was reported to have promising effects on HIV-1 and HIV-2 proteases. The increased affinity of the boron complexes may reflect binding of the orthogonal domains of the inhibitor in intersecting sites within the substrate-binding cavity of the enzymes, while activation of curcumin's carbonyl group by boron chelation probably accounts for time-dependent inhibition of the enzyme (39). It was also shown that lysine-136 plays an important role in viral DNA binding and the two curcumin analogues, dicaffeoylmethane and rosmarinic acid, inhibited the activities of mutant as well as wild-type integrase with IC_{50} values below 10 mM. Furthermore, a synergistic inhibition of integrase was observed upon concomitant administration of a curcumin analogue and the integrase inhibitor NSC-158393 (40). It was suggested that Tat protein secreted by HIV-1-infected cells might have an additional effect in AIDS pathogenesis because of its ability to be taken up by noninfected cells. Curcumin also inhibited Tat-mediated transactivation of the HIV-1 long terminal repeat by 70-80%, as determined by a lacZ assay in immortalized cervical cancer HeLa cells (41). Current research does appear to offer hope for a curcumin-based treatment of HIV.

Curcumin in eye diseases

Curcumin has been implicated in the treatment of certain eye diseases and conditions, including chronic anterior uveitis, an inflammatory condition of the vascular layer, particularly the iris. In a small study, curcumin (375 mg t.i.d.) was administered orally for 12 weeks to 32 patients with chronic anterior uveitis. The participants were divided into two groups; the first received only curcumin while the second was treated with a combination of curcumin and antitubercular therapy. All patients treated with curcumin alone improved, compared with a response rate of 86% among those receiving the combination therapy (42). Recently, a study was conducted on curcumin's potential to treat dry eye disease and to protect against hyperosmosis-induced IL-1β elevation via MAPK pathways in human corneal epithelial cells. Human corneal epithelial cells cultured in the hyperosmotic medium for 24 h showed an increase of IL-1β, IL-6 and TNF-α levels. Curcumin (1–30 μM) did not affect the viability of cultured corneal epithelial cells, but pretreatment with curcumin (5 μM) completely abolished the increased production of IL-1β, p38 phosphorylation and NF-κB induced by the hyperosmotic medium (43). These studies suggest that curcumin may be an effective therapeutic for a variety of inflammatory eye conditions.

CURCUMIN SELECTIVITY

Curcumin selectively kills tumor cells because its cellular uptake is higher than in normal cells. Several studies indicated that curcumin mainly distributes to the cell membrane and nucleus. In addition, it interacts with thioredoxin reductase, which is overexpressed in tumor cells, and causes the enzyme to be converted to NADPH oxidase, thus leading to increased production of H_2O_2 in tumor cells. Furthermore, glutathione levels in tumor cells tend to be lower than in normal cells, thus enhancing the sensitivity of tumor cells to curcumin (44). Finally, most tumor cells express constitutively active NF-κB which mediates their survival, whereas normal cells do not. Curcumin can suppress the survival and proliferation of tumor cells by suppressing NF-κB-regulated gene products.

FUTURE PROSPECTS

The information provided above demonstrates that curcumin has a diverse range of molecular targets, including transcription factors growth factors and their receptors, cytokines, enzymes and genes regulating cell proliferation and apoptosis. In addition, the phytochemical has the potential to modulate multiple molecular targets known to be crucial for most chronic diseases. Curcumin has shown therapeutic effects against a variety of chronic diseases, including various cancers, Alzheimer's disease, cardiovascular diseases, multiple sclerosis, HIV infection and diabetes. Various animal models and human studies proved that it is extremely safe, even at very high doses.

Numerous studies confirm curcumin's potential role in animal models, yet further study is required to confirm its function in humans. High-throughput ligand-interacting technology may reveal more molecular targets of curcumin. In the future, microarray gene chip technology may reveal which genes are regulated by curcumin. The development of curcumin-related drugs is very challenging due to the agent's poor absorption and low bioavailability; studies are still in their early stage. However, based on the the compound's multifaceted pharmacological actions, it appears that curcumin will emerge as a promising therapeutic drug for the treatment and prevention of various chronic diseases.

DISCLOSURES

The authors state no conflicts of interest.

REFERENCES

1. Singh, S. *From exotic spice to modern drug?* Cell 2007, 130(5): 765-8.
2. Goel, A., Kunnumakkara, A.B., Aggarwal, B.B. *Curcumin as "curecumin" from kitchen to clinic*. Biochem Pharm 2008, 75(4): 787-809.
3. Chattopadhyay, I., Biswas, K., Bandyopadhyay, U., Banerjee, R.K. *Turmeric and curcumin: Biological actions and medicinal applications*. Current Science 2004, 87(1): 44-53.
4. Steward, W.P., Gescher, A.J. *Curcumin in cancer management: Recent results of analogue design and clinical studies and desirable future research*. Mol Nutr Food Res 2008, 52(9): 1005-9.
5. Anand, P., Kunnumakkara, A.B., Newman, R.A., Aggarwal, B.B. *Bioavailability of curcumin: Problems and promises*. Mol Pharm 2007, 4(6): 807-18.
6. WHO Geneva. *Evaluation of certain food additives*. WHO Technical Report Series 891, 2000.
7. Lao, C.D., Ruffin, M.T., Normolle, D. et al. *Dose escalation of a curcuminoid formulation*. BMC Complement Altern Med 2006, 6: 10.
8. Aggarwal, B.B., Sung, B. *Pharmacological basis for the role of curcumin in chronic diseases: An age-old spice with modern targets*. Trends Pharmacol Sci 2009, 30(2): 85-94.
9. Shishodia, S., Singh, T., Chaturvedi, M.M. *Modulation of transcription factors by curcumin*. Adv Exp Med Biol 2007, 595: 127-48.
10. Chadalapaka, G., Jutooru, I., Chintharlapalli, S., Papineni, S., Smith, R. III, Li, X., Safe, S. *Curcumin decreases specificity protein expression in bladder cancer cells*. Cancer Res 2008, 68(13): 5345-54.
11. Aggarwal, B.B., Bhatt, I.D., Ichikawa, H. et al. *Curcumin — Biological and medicinal properties*. In: Turmeric: The Genus Curcuma. Ravindran, P.N., K.N. Babu, Sivaraman. K. (Eds.). CRC Press: Florida, 2006, 297-368.
12. Park, M.J., Kim, E.H., Park, I.C. et al. *Curcumin inhibits cell cycle progression of immortalized human umbilical vein endothelial (ECV304) cells by up-regulating cyclin-dependent kinase inhibitor, p21WAF1/CIP1, p27KIP1 and p53*. Int J Oncol 2002, 21(2): 379-83.
13. Anto, R.J., Mukhopadhyay, A., Denning, K., Aggarwal, B.B. *Curcumin (diferuloylmethane) induces apoptosis through activation of caspase-8, BID cleavage and cytochrome c release: Its suppression by ectopic expression of Bcl-2 and Bcl-xl*. Carcinogenesis 2002, 23(1): 143-50.
14. Anand, P., Sundaram, C., Jhurani, S., Kunnumakkara A.B., Aggarwal B.B. *Curcumin and cancer: An "old-age" disease with an "age-old" solution*. Cancer Lett 2008, 267(1): 133-64.
15. Aggarwal, B.B., Kumar, A., Bharti, A.C. *Anticancer potential of curcumin: Preclinical and clinical studies*. Anticancer Res 2003, 23(1A): 363-98.
16. Aggarwal, S., Takada, Y., Singh, S., Myers, J.N., Aggarwal, B.B. *Inhibition of growth and survival of human head and neck squamous cell carcinoma cells by curcumin via modulation of nuclear factor-kappaB signaling*. Int J Cancer 2004, 111(5): 679-92.
17. Lee, K.W., Kim, J.H., Lee, H.J., Surh, Y.J. *Curcumin inhibits phorbolester-induced up-regulation of cyclooxygenase-2 and matrix metalloproteinase-9 by blocking ERK1/2 phosphorylation and NF-kappaB transcriptional activity in MCF10A human breast epithelial cells*. Antioxid Redox Signal 2005, 7(11-12): 1612-20.

18. Hanai, H., Iida, T., Takeuchi, K. et al. *Curcumin maintenance therapy for ulcerative colitis: Randomized, multicenter, double-blind, placebo-controlled trial*. Clin Gastroenterol Hepatol 2006; 4(12): 1502-6.
19. Mishra, S., Pelanalvenu, K. *The effect of curcumin (turmeric) on alzheimers disease*. Ann Indian Acad Neurol 2008, 11(1): 13-9.
20. Giri, R.K., Rajagopal, V., Kalra, V.K. *Curcumin, the active constituent of turmeric, inhibits amyloid peptide-induced cytochemokine gene expression and CCR5-mediated chemotaxis of THP-1 monocytes by modulating early growth response-1 transcription factor*. J Neurochem 2004, 91(5): 1199-210.
21. Kim, G.Y., Kim, K.H., Lee, S.H. et al. *Curcumin inhibits immunostimulatory function of dendritic cells: MAPKs and translocation of NF-kappa B as potential targets*. J Immunol 2005, 174(12): 8116-24.
22. Rathore, P., Dohare, P., Varma, S., Ray, A., Sharma, U., Jagannathan, N.R., Ray, M. *Curcuma oil: Reduces early accumulation of oxidative product and is anti-apoptogenic in transient focal ischemia in rat brain*. Neurochem Res 2008, 33(9): 1672-82.
23. Jiang, J., Wang, W., Sun, Y.J., Hu, M., Li, F., Zhu, D.Y. *Neuroprotective effect of curcumin on focal cerebral ischemic rats by preventing blood–brain barrier damage*. Eur J Pharmacol 2007, 561(1-3): 54-62.
24. Naidu, K.A., Thippeswamy, N.B. *Inhibition of human low density lipoprotein oxidation by active principles from spices*. Mol Cell Biochem 2002, 229(1-2): 19-23.
25. Egan, M.E., Pearson, M., Weiner S.A. et al. *Curcumin, a major constituent of turmeric, corrects cystic fibrosis defects*. Science 2004, 304(5670): 600-2.
26. Li, H.L., Liu, C., de Couto, G. et al. *Curcumin prevents and reverses murine cardiac hypertrophy*. J Clin Invest 2008, 118(3): 879-93.
27. Arun, N., Nalini, N. *Efficacy of turmeric on blood sugar and polyol pathway in diabetic albino rats*. Plant Foods Hum Nutr 2002, 57(1): 41-52.
28. Weisberg, S.P., Leibel, R., Tortoriello, D.V. *Dietary curcumin significantly improves obesity-associated inflammation and diabetes in mouse models of diabesity*. Endocrinology 2008, 149(7): 3549-58.
29. Babu, P.S., Srinivasan, K. *Hypolipidemic action of curcumin, the active principle of turmeric (Curcuma longa) in streptozotocin induced diabetic rats*. Mol Cell Biochem 1997, 166(1-2): 169-75.
30. Premila, M.S. *Antirheumatic agents*. In: Ayurvedic Herbs: A Clinical Guide to the Healing Plants of Traditional Indian Medicine. The Haworth Press: New York, 2006, 163-92.
31. Liacini, A., Sylvester, J., Li, W.Q., Zafarullah, M. *Inhibition of interleukin-1-stimulated MAP kinases, activating protein-1 (AP-1) and nuclear factor kappa B (NF-kB) transcription factors down-regulates matrix metalloproteinase gene expression in articular chondrocytes*. Matrix Biol 2002, 21(3): 251-62.
32. Nanji, A.A., Jokelainen, K., Tipoe, G.L., Rahemtulla, A., Thomas, P., Dannenberg, A.J. *Curcumin prevents alcohol-induced liver disease in rats by inhibiting the expression of NF-kappa B-dependent genes*. Am J Physiol Gastrointest Liver Physiol 2003, 284(2): G321-7.
33. Gukovsky, I., Reyes, C.N., Vaquero, E.C., Gukovskaya, A.S., Pandol, S.J. *Curcumin ameliorates ethanol and nonethanol experimental pancreatitis*. Am J Physiol Gastrointest Liver Physiol 2003, 284(1): G85-95.
34. Xu, J., Fu, Y., Chen, A. *Activation of peroxisome proliferator-activated receptor-gamma contributes to the inhibitory effects of curcumin on rat hepatic stellate cell growth*. Am J Physiol Gastrointest Liver Physiol 2003, 285(1): G20-30.
35. Fahey, A.J., Adrian, Robins, R., Constantinescu, C.S. *Curcumin modulation of IFN-beta and IL-12 signalling and cytokine induction in human T cells*. J Cell Mol Med 2007, 11(5): 1129-37.
36. Mani, H., Sidhu, G.S., Kumari, R., Gaddipati, J.P., Seth, P., Maheshwari, R.K. *Curcumin differentially regulates TGF-beta1, its receptors and nitric oxide synthase during impaired wound healing*. Biofactors 2002, 16(1-2): 29-43.
37. Panchatcharam, M., Miriyala, S., Gayathri, V.S., Suguna, L. *Curcumin improves wound healing by modulating collagen and decreasing reactive oxygen species*. Mol Cell Biochem 2006, 290(1-2): 87-96.
38. Phan, T.T., See, P., Lee, S.T., Chan, S.Y. *Protective effects of curcumin against oxidative damage on skin cells in vitro: Its implication for wound healing*. J Trauma 2001, 51(5): 927-31.
39. Sui, Z., Salto, R., Li, J., Craik, C., Ortiz de Montellano, P.R. *Inhibition of the HIV-1 and HIV-2 proteases by curcumin and curcumin boron complexes*. Bioorg Med Chem 1993, 1(6): 415-22.
40. Mazumder, A., Neamati, N., Sunder, S., Schulz, J., Pertz, H., Eich, E., Pommier, Y. *Curcumin analogs with altered potencies against HIV-1 integrase as probes for biochemical mechanisms of drug action*. J Med Chem 1997, 40(19): 3057-63.
41. Barthelemy, S., Vergnes, L., Moynier, M., Guyot, D., Labidalle, S., Bahraoui, E. *Curcumin and curcumin derivatives inhibit Tat-mediated transactivation of type 1 human immunodeficiency virus long terminal repeat*. Res Virol 1998, 149(1): 43-52.
42. Lal, B., Kapoor, A.K., Asthana, O.P., Agrawal, P.K., Prasad, R., Kumar, P., Srimal, R.C. *Efficacy of curcumin in the management of chronic anterior uveitis*. Phytother Res 1999, 13 (4): 318-22.
43. Chen, M., Hu, D.N., Pan, Z., Lu, C.W., Xue, C.Y., Aass, I. *Curcumin protects against hyperosmoticity-induced IL-1beta elevation in human corneal epithelial cell via MAPK pathways*. Exp Eye Res 2009, In press.
44. Syng-Ai, C., Kumari, A.L., Khar, A. *Effect of curcumin on normal and tumor cells: Role of glutathione and bcl-2*. Mol Cancer Ther 2004, 3(9): 1101-8.