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Research review paper

Curcumin, a component of golden spice: From bedside to bench and back

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ABSTRACT

Although the history of the golden spice turmeric (*Curcuma longa*) goes back thousands of years, it is only within the past century that we learned about the chemistry of its active component, curcumin. More than 6000 articles published within the past two decades have discussed the molecular basis for the antioxidant, anti-inflammatory, antibacterial, antiviral, antifungal, and anticancer activities assigned to this nutraceutical. Over sixty five clinical trials conducted on this molecules, have shed light on the role of curcumin in various chronic conditions, including autoimmune, cardiovascular, neurological, and psychological diseases, as well as diabetes and cancer. The current review provides an overview of the history, chemistry, analogs, and mechanism of action of curcumin.

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Introduction

Curcumin is the active ingredient of the dietary spice found in the rhizomes of *Curcuma longa*, a plant in the ginger family. Turmeric, a common oriental spice that gives curry powder its yellowish color, is frequently used in Asian cooking, particularly Indian, Pakistani, and Thai cooking. Turmeric has been consumed for medicinal purposes for thousands of years. Extensive research on curcumin over the past few decades has revealed the health benefits of this ingredient to the modern era; in fact, numerous published articles, audio recordings, and videos on this subject are available to the public. Some links to videos about curcumin's health benefits are summarized in Table 1.

Isolation of curcumin

Because curcumin is insoluble in water, an organic solvent has been used for its isolation. Anderson. et al. (2000) developed a technique for isolating curcumin from ground turmeric. They magnetically stirred the ground turmeric in dichloromethane and heated at reflux for 1 h. The mixture was suction-filtered, and the filtrate was concentrated in a hot-water bath maintained at 50 °C. The reddish–yellow oily residue was triturated with hexane, and the resulting solid was collected by suction filtration. Further TLC analysis (3% methanol–97% dichloromethane) showed the presence of all three components (Anderson et al., 2000). Recently, Bagchi (2012) described extraction of curcumin from turmeric powder with the use of a solvent consisting of a mixture of ethanol and acetone. Chemical analyses have shown that turmeric contains protein (6.3%), fat (5.1%), minerals (3.5%), carbohydrates (69.4%), and moisture (13.1%). The essential oil (5.8%) obtained by steam distillation of the rhizomes contains a-phellandrene (1%), sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%), and sesquiterpines (53%); curcumin (3%–6%) is responsible for the yellow color. Now numerous biotech companies are isolating curcumin commercially, making it available to everyone. Some of these include Biotech Pharmacal Inc., Santa Cruz Biotechnology, Curcumin-Shijiazhuang lvchuan Biotechnology Co. Ltd, Xiaoyuan Biotechnology Co., Ltd., and Anubhav Biotech Ltd.

Discovery of curcumin

Curcumin was discovered about two centuries ago by Vogel and Pelletier, who described it as a "yellow coloring-matter" from the rhizomes of *C. longa* (turmeric) (Vogel. and Pelletier., 1815). Pure curcumin was prepared in 1842 by Vogel Jr. (Vogel., 1842). The possible structure of curcumin was reported by several chemists in the subsequent

Table 1
Online video describing the use and health benefits of curcumin.

Topic	Links
How curcumin helps prevent and treat cancer	http://www.youtube.com/watch?v=QNLt1fZR1BI
Turmeric curcumin—natural cancer-fighting spice reduces tumors	http://www.youtube.com/watch?v=oP7S5VDHtFY
Truly essential curcumin cures cancer in 1 year	http://www.youtube.com/watch?v=YgG0o9EGkmo
Turmeric curcumin—cancer cure and more!	http://www.youtube.com/watch?v=cKzOyLxpSS4
Curcumin kills cancer cells	http://www.youtube.com/watch?v=pAzwGKC_Cls
Curcumin benefits—all you should know about curcumin benefits	http://www.youtube.com/watch?v=PmunAxElzoc
Curcumin for cancer prevention	http://www.youtube.com/watch?v=9iGWifv6ldo
Anti-cancer and other health properties of curcumin	http://www.youtube.com/watch?v=ArzTQsG1yVw
Samidirect cancer testimonial team chairman club	http://www.youtube.com/watch?v=3vQrgT4xric
Cancer fighting super food curcumin turmeric tumeric haldi	http://www.youtube.com/watch?v=INUbV_pgPqM
Curcumin extraction	http://www.youtube.com/watch?v=_R3fL-ucUSA
SFWC lifestyle and cancer awareness workshop 4	http://www.youtube.com/watch?v=pDmpulNjGaE
Curcumin for the prevention of polyps for FAP	http://www.youtube.com/watch?v=e7EGeVTBbqw
Why is curcumin a suitable anti-cancer agent?	http://www.youtube.com/watch?v=NJI4WsJst5g
Professor Bharat B Aggarwal discusses curcumin	http://www.youtube.com/watch?v=Zht2Q5D0RdY
Cancer cure | turmeric | natural cancer cure	http://www.youtube.com/watch?v=jqj6EqjSWW8
Curcumin for colon cancer	http://www.youtube.com/watch?v=eIQFAv6hNRo
Curcumin reduces risk of HPV-related cervical cancer	http://www.youtube.com/watch?v=2yJoE7F2lM8
Curry spice, curcumin and fermented soy research and cancer	http://www.youtube.com/watch?v=OXqN5UckhFk
Curcumin a big medicine—turmeric curcumin health talk	http://www.youtube.com/watch?v=01PcxCgtgr4
McCord curcumin cancer chemotherapy	http://www.youtube.com/watch?v=XX9nF8_SQmM
Turmeric: naturally reverse cancer, arthritis and inflammation	http://www.youtube.com/watch?v=YS-nyqBJeGc&list=PL4E92A08A28D8A361
Brain injury recovery, curcumin, minority health	http://www.youtube.com/watch?v=kTH4jBYOudA
Benefits of curcumin capsules	http://www.youtube.com/watch?v=y5mhTUkv8rU
Theracurmin—a major breakthrough in curcumin absorption	http://www.youtube.com/watch?v=EQYnkOkc6C8
Curcumin—life extension videos	http://www.youtube.com/watch?v=yULma3m9zy8
Interaction of curcumin nanoformulations with human plasma proteins	http://www.youtube.com/watch?v=4Yq7IAystYQ
Curcumin in prevention of cancer	http://www.youtube.com/watch?v=xmxlyZY9eRo
Turmeric remedy for cancer : "Arishina Cancerge Ramabhana"	http://www.youtube.com/watch?v=ofi4URRTewM
Curcumin (turmeric) is a potent anti inflammatory	http://www.youtube.com/watch?v=8PN7X3RsVRs
Turmeric with black pepper–curcumin–turmeric curcumin capsules	http://www.youtube.com/watch?v=KpCLeujpL0A
The benefits of curcumin	http://www.youtube.com/watch?v=ZHu280-mf7E
La curcumine anti cancer (incroyable)	http://www.youtube.com/watch?v=iAdMnvXEl58
Curcumin side effects	http://www.youtube.com/watch?v=TAgjkaGipHo
Curcumin and your health—your health	http://www.youtube.com/watch?v=SWbHFIb6r6Q
Turmeric curcumin, joint supplement for athletes, anti inflammatory	http://www.youtube.com/watch?v=yOasvOUZoGs
How to use turmeric	http://www.youtube.com/watch?v=cafoiHQiwPw
Using turmeric to prevent and cure cancer	http://www.youtube.com/watch?v=FXIIreujNyo
Curcumin may help prevent type 2 diabetes	http://www.youtube.com/watch?v=KnAW-aQZk6U
Curcumin–tumeric benefits–uses and curcumin capsules	http://www.youtube.com/watch?v=SoeAvQTL5Ek
Smart tips–anti-cancer kitchen spice	http://www.youtube.com/watch?v=tvahuahhrZw
Curcumin & lycopene aid prostate health & issues	http://www.youtube.com/watch?v=DT0fkvwCnmY

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decades (Daube, 1870; Ibid., 1870; Ivanow-Gajewsky, 1872). The chemical structure of curcumin as diferuloylmethane, or 1,6-heptadiene-3,5-dione-1,7-bis (4-hydroxy-3-methoxyphenyl)-(1E, 6E) was reported by Milobedzka. et al. (1910). Lampe. and Milobedzka. (1913) reported the synthesis of curcumin, however, Srinivasan (1953) for the first time used chromatography to separate and quantify the components of curcumin.

The biological characteristics of curcumin were scientifically identified in the mid-twentieth century. In a paper published in *Nature* in 1949, Schraufstatter and colleagues reported that curcumin is a biologically active compound that has antibacterial properties (Schraufstatter and Bernt, 1949). These authors found that curcumin was active against strains of *Staphylococcus aureus*, *Salmonella paratyphi*, *Trichophyton gypseum*, and *Mycobacterium tuberculosis*. However, research on curcumin became quiet for the next two decades.

Curcumin again became the subject of scientific investigation in the 1970s. During this decade, three independent groups discovered diverse characteristics of curcumin, including its cholesterol-lowering (Patil and Srinivasan, 1971), antidiabetic (Srinivasan, 1972), anti-inflammatory (Srimal and Dhawan, 1973), and antioxidant (Sharma, 1976) activities. Ghatak and Basu (Ghatak and Basu, 1972) showed that curcumin is more potent than hydrocortisone for inhibiting formalin-induced arthritis in rats (Fig. 1A) and carrageenin-induced rat paw edema (Fig. 1B). Later Srimal and Dhawan (Srimal and Dhawan, 1973) reported that curcumin is as potent as cortisone or phenylbutazone for the inhibition of carrageenin-induced rat paw edema (Fig. 1C). These studies indicate curcumin's potential as an anti-inflammatory agent.

The anticancer activity of curcumin was demonstrated in the 1980s by Kuttan and colleagues in both in vitro and in vivo models (Kuttan et al., 1985). In 1995, our group was the first to demonstrate that curcumin exhibits anti-inflammatory activity by suppressing the proinflammatory transcription factor nuclear factor (NF)-κB; we also delineated the molecular mechanism of the inhibition (Singh and Aggarwal, 1995).

Interest in curcumin research has increased substantially over the years. As of January 2014, more than 6000 articles on curcumin were listed in the National Institutes of Health PubMed database (www.ncbi.nlm.nih.gov/sites/entrez). The pleiotropic activity of this polyphenol is now reported by numerous groups. This polyphenol has been shown to possess activities in animal models of many human diseases. In human clinical trials, curcumin has been found to be safe and efficacious, and the U.S. Food and Drug Administration has approved curcumin as a "generally regarded as safe" compound.

Chemical and physical properties of curcumin

The powdered extracts of turmeric-dried roots may contain volatile and nonvolatile oils, proteins, fat, minerals, carbohydrates, moisture, and curcuminoids. The curcuminoids, are a mixture of three principal compounds: curcumin (curcumin I; 77%), demethoxycurcumin (DMC; curcumin II; 17%), and bisdemethoxycurcumin (BDMC; curcumin III; 3%) (Goel et al., 2008; Strimpakos and Sharma, 2008). The chemical name of curcumin is 1,7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione; the chemical formula is C21H20O6; and the pKa value is 8.54. Curcumin is practically insoluble in water at an acidic and neutral pH but is soluble in methanol, ethanol, dimethylsulfoxide, and acetone. The maximum absorption (λ_{max}) of curcumin in methanol occurs at 430 nm (Aggarwal et al., 2003; Goel et al., 2008). Studies of excited-state photophysics of curcumin revealed that it gets excited in the subnanosecond time scale and transfers hydrogen atoms (Adhikary et al., 2009). The ultrafast hydrogen atom transfer and associated conformational changes may play an important role in medicinal properties of curcumin.

The molecular configuration of curcumin can exist in the tautomeric forms bis-keto and enolate. The enol form of curcumin has three ionizable protons, corresponding to the enolic group and two phenolic groups. In acidic and neutral conditions and in a solid phase, the keto form predominates, and curcumin acts as a potent donor of hydrogen atoms. However, under alkaline conditions, the enolic form predominates (Strimpakos and Sharma, 2008). Several researchers have proven the sensitivity of curcumin to light, and as a result they suggested that biologic samples containing curcumin should be protected from light (Strimpakos and Sharma, 2008). Another stability issue occurs when curcumin is placed in phosphate buffer systems of pH 7.2; in this setting, most of curcumin (>90%) degrades within 30 min of placement (Goel et al., 2008; Wang et al., 1997).

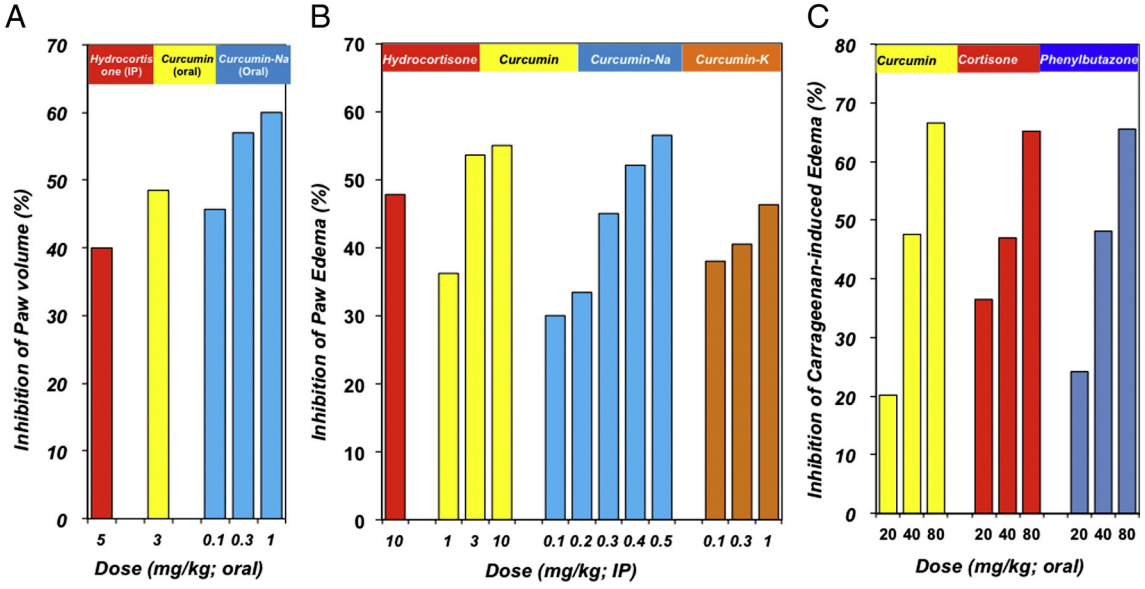

Fig. 1. Antiarthritic and anti-inflammatory efficacy of curcumin. (A) Comparative efficacy of curcumin with hydrocortisone in inhibition of formalin-induced arthritis in rats and (B) carrageenin-induced rat paw edema (*adopted from Ghatak and Basu (1972)*). (C) Comparative efficacy of curcumin with cortisone and phenylbutazone for inhibition of carrageenin-induced rat paw edema (*adopted from Srimal and Dhawan (1973)*).

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Natural analogs of curcumin

Commercially available curcumin consists primarily of a curcumin mix, collectively called curcuminoids. This curcumin mix is used in in vitro and in vivo research and in clinical trials.

Although much information is available for commercial-grade curcumin, very few studies of pure curcumin, DMC, or BDMC have been conducted. However, available reports suggest that DMC and BDMC have potent biological activities. One study reported that commercial-grade curcumin, pure curcumin, or DMC had an equally potent inhibitory effect on 12-O-tetradecanoylphorbol-13-acetate (TPA) and 7,12-dimethylbenz[a]anthracene-induced skin tumor development in mice. BDMC and another analog of curcumin, tetrahydrocurcumin (THC), were less active (Huang et al., 1995). Additionally they found that commercial-grade curcumin, pure curcumin, DMC, and BDMC had about the same potent inhibitory effect on TPA-induced inflammation of mouse ears, as well as on TPA-induced transformation of cultured JB6 (P+) cells (Huang et al., 1995). The suppression of inflammatory transcription factor NF-κB activation was found to be higher with the use of curcumin than with other analogs (Cur > DMC > BDMC), suggesting the critical role of methoxy groups on the phenyl ring. THC, which lacks the conjugated bonds in the central seven-carbon chain, was completely inactive for suppression of the transcription factor (Sandur et al., 2007). NF-κB-initiated inflammatory molecules iNOS and COX-2 were also inhibited by DMC and BDMC. In addition, both DMC and BDMC significantly inhibited carrageenan-induced paw edema in mice (Guo et al., 2008).

Curcumin is considerably more active than DMC and BDMC as an antioxidant and as an oxidative DNA cleaving agent. Curcumin was most effective in the DNA cleavage reaction and as a reducer of Cu(II), followed by DMC and BDMC. The rate of formation of hydroxyl radicals by the three curcuminoids showed a similar pattern (Ahsan et al., 1999). The curcumin analog is capable of playing a major role against heavy metal-induced neurotoxicity and has neuroprotective properties. Animals treated with curcumin and DMC, but not BDMC, showed high glutathione and less oxidized proteins in the hippocampus. Also, curcumin- and DMC-treated animals retained spatial reference memory (Dairam et al., 2007). It has also been shown that curcumin and DMC reduced advanced glycation end products (AGEs)-induced reactive oxygen species (ROS) generation in mesangial cells. Furthermore, curcumin and DMC dramatically elevated AGEs-decreased superoxide dismutase activity and increased malondialdehyde content in cell culture supernatant. These two compounds also restored AGEs-induced apoptosis to normal levels ($IC_{50} = 3.874 \times 10(-11)$ M for curcumin and $IC_{50} = 6.085 \times 10(-11)$ M for DMC) (Liu et al., 2012).

The differential potency of curcumin analogs for inhibition of cancer cell invasion has also been studied. One study found cancer cell invasion potency to be BDMC ≥ DMC > curcumin, whereas cell migration was not affected. Furthermore, BDMC and DMC showed higher potency than curcumin did in suppressing uPA, active-MMP-2, and MMP-9. Importantly, BDMC and DMC at 10 μM showed reductions in MT1-MMP and TIMP-2 protein expression, but curcumin slightly reduced only MT1-MMP but not TIMP-2 (Yodkeeree et al., 2009).

DMC inhibits the migration of vascular smooth muscle cells by reducing the expression of matrix metalloproteinase 2/9 via down-regulation of the focal adhesion kinase/phosphatidylinositol 3-kinase (PI3K)/AKT (protein kinase B) and phosphoglycerate kinase 1/extracellular signal regulated kinase 1/2 signaling pathways (Sheu et al., 2013). A study in cultured human umbilical vein endothelial cells (HUVECs) using cDNA microarray analysis found that among the 1024 human cancer-focused genes arrayed, 187 genes were up-regulated and 72 genes were down-regulated at least 2-fold by DMC. Interestingly, 9 angiogenesis-related genes were down-regulated more than 5-fold in response to DMC, suggesting that genetic reprogramming was crucially involved in antiangiogenesis by the compound (Kim et al., 2002).

Curcumin analogs also affect gene methylation. It was found that BDMC possesses the strongest demethylation function in vitro compared with the other two curcuminoids. The WIF-1 promoter region was demethylated by DMC and BDMC but failed to respond to curcumin (Liu et al., 2011).

Curcumin metabolites

Various metabolites of curcumin have been reported, including dihydrocurcumin (DHC), THC, hexahydrocurcumin (HHC), octahydrocurcumin (OHC), curcumin glucuronide, DHC-glucuronide, THC-glucuronide, and curcumin sulfate. DHC and THC have been shown to be the first biotransformed product of curcumin, and these compounds subsequently converted to monoglucuronide conjugates. THC is one of the major metabolites of curcumin and has been found to be very stable. Moreover, THC has been found to be more stable than curcumin (Pan et al., 1999). DHC metabolites were also isolated from cultured cell clumps that had been induced from buds on turmeric rhizomes (Kita et al., 2009).

Numerous studies have revealed that THC has antioxidative, anti-inflammatory, and anticancer activities. It inhibits radiation-induced lipid peroxidation in rat liver microsomes (Khopde et al., 2000). THC induced antioxidant enzymes, such as glutathione peroxidase, glutathione S-transferase, and NADPH:quinone reductase, and scavenged Fe-NTA-induced free radicals in vitro (Okada et al., 2001). THC exhibits protection against erythromycin estolate-induced hepatocellular damage by inhibiting increased levels of the serum enzymes aspartate transaminase, alanine transaminase, alkaline phosphatase, bilirubin, cholesterol, triglycerides, phospholipids, free fatty acids, plasma thiobarbituric acid reactive substances (TBARS), and hydroperoxides (Pari and Murugan, 2004).

THC has been shown to induce autophagic cell death in human HL-60 promyelocytic leukemia cells by increasing autophage marker acidic vascular organelle (AVO) formation (Wu et al., 2011). The chemopreventive property of THC has been reported in animal models. In rats, dietary administration of THC reduced aberrant crypt foci and polyp formation in azoxymethane (AOM)-induced colon carcinogenesis. At the molecular level, THC exhibited anti-inflammatory activity by decreasing the levels of inducible NOS and COX-2 through down-regulation of ERK1/2 activation. In addition, THC significantly decreased AOM-induced Wnt-1 and β-catenin protein expression, as well as the phosphorylation of GSK-3β in colonic tissue (Lai et al., 2011).

The other product of curcumin biotransformation by hepatocytes is HHC, which has less ability than curcumin to inhibit COX-2 expression (Ireson et al., 2001). However, a molecular modeling and docking study revealed that HHC's binding energy to the proinflammatory enzyme phospholipase A2 is better than that of curcumin (Dileep et al., 2011). The cytotoxicity of HHC and its effect on the cell cycle in SW480 human colorectal cancer cells have also been studied. HHC resulted in a massive accumulation of SW480 cells in the G1/G0 phase of the cell cycle (Chen et al., 2011). Besides these findings, HHC, together with 5-FU, was shown to exert a synergistic effect in inhibiting the growth of HT-29 colorectal cancer cells by suppressing COX-2 expression (Srimuangwong et al., 2012) and to exhibit antioxidant activity in murine macrophages (Li et al., 2012b).

Another metabolite, OHC, has also shown anti-inflammatory and antioxidant properties. Pan (Pan et al., 2000) has shown that OHC has much less NF-κB suppressive activity than curcumin does; this study also revealed antioxidant activity by suppressing the AAPH-induced linoleic oxidation and DPPH scavenging activity. The scavenging activity of OHC is higher than that of curcumin (Somparn et al., 2007). As stated earlier, curcumin first biotransformed to DHC and THC and these compounds subsequently converted to monoglucuronide conjugates in animals. In HT29 cancer cells, it was reported that curcumin metabolizes to curcumin glucuronides. In human cancer cells, only the parent curcumin molecule showed mitotic catastrophe, whereas reductive

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metabolism and chemical degradation rendered curcumin inactive (Dempe et al., 2008). Recently, we showed that none of the curcumin mono- or di-glucuronides showed the level of biological activity (e.g., anti-inflammatory or antiproliferative activity) that curcumin showed (Pal et al., 2014)).

Besides these metabolites, another product of curcumin biotransformation identified in animals and patients is curcumin sulfate. Curcumin was sulfated by human phenol sulfotransferase isoenzymes SULT1A1 and SULT1A3 (Ireson et al., 2002). An experimental study showed that curcumin sulfate has less biological activity than curcumin has. Specifically, curcumin sulfate's ability to inhibit PGE2 activity, compared with that of curcumin, was very poor (Ireson et al., 2001), indicating better efficacy of curcumin than of its biotransformed products.

Man-made analogs

Various experimental studies and clinical trials have suggested that the systemic bioavailability of orally administered curcumin is relatively low and that in most cases, it is the metabolites of curcumin, rather than curcumin itself, that are detected in plasma or serum after oral administration. Therefore, to overcome this problem, various curcumin derivatives have been designed. Recently, high-level, ab initio, and computationally intensive calculations showed that the optimized structure of curcumin is planar and linear (Balasubramanian and Eckert, 2004). Curcumin is a homodimer of feruloylmethane containing a methoxy group and a hydroxyl group, a heptadiene with two Michael acceptors, and an α,β-diketone. The curcumin derivatives are synthesized by its derivatization. For instance, the phenolic hydroxy group can be acylated, alkylated, glycosylated, and amino acylated (Barthelemy et al., 1998; Kumar et al., 2000; Mishra et al., 2008). The hydroxy groups may be synthesized by the demethylation of the methoxy groups (Sharma, 1976). An arylidene group (Ar–CH–) may be used for acylation, alkylation, or substitution of the reactive methylene group of the linker (Mishra et al., 2008), thus bringing in substituents on the C7 chain.

Biological activities of curcumin

Anticancer effects

Curcumin has shown to display chemotherapeutic and chemopreventive effects in diverse cancers. A mono-carbonyl analog of curcumin B63 was synthesized through several chemical modifications of the basic structure of curcumin to increase its biological activity and bioavailability. In vitro assays showed that this curcumin derivative had greater antiproliferative effects on colon cancer cells than curcumin had. Also in vivo, 50 mg/kg of B63 inhibited tumor growth similarly to 100 mg/kg of curcumin in a mouse xenograft model using SW620 cells (Zheng et al., 2013). Another derivative, hydrazinobenzoylcurcumin (HBC), induced A549 cell autophagy and inhibited the viability of A549 cells to 76.68% after 24 h of treatment (Zhou et al., 2014). The curcumin derivative bis-DeHydroxyCurcumin (bDHC) also has been shown to induce autophagy on human colon cancer cells, but not on human normal cells. Autophagy is elicited by bDHC before cell death (Basile et al., 2013). HBC (4-[3,5-bis-[2-(4-hydroxy-3-methoxy-phenyl)-ethyl]-4,5-dihydropyrazol-1-yl]-benzoic acid), a curcumin derivative, exhibits potent inhibitory activities against the proliferation of several tumor cell lines. It inhibits the cell cycle progression of colon cancer cells via antagonizing Ca2 +/CaM functions (Shim et al., 2004). Thus, synthetic curcumin derivatives induce apoptosis of different cancer cells via various mechanisms.

Anti-inflammatory effects

A lipophilic derivative of curcumin, diacetyl curcumin (DAC), and a hydrophilic derivative, diglutaryl curcumin (DGC) were shown in vivo to have analgesic and anti-inflammatory activities. A carrageenan-induced paw edema model indicated anti-inflammatory activity of all curcumin derivatives. The percentage inhibition of paw edema was higher in DAC than in curcumin (Jacob et al., 2013). Besides these, other curcumin derivatives were also evaluated for their chemopreventive potential. Based on COX-2 inhibition, 2,6-bis(3-fluoro-4-hydroxybenzylidene) cyclohexanone (IC_{50} = 5.5 μM) has more efficacy followed by curcumin (IC_{50} = 15.9 μM) and 1,7-bis(3-fluoro-4-hydroxyphenyl)-1,6-heptadiene-3,5-dione (IC_{50} = 23.7 μM). Tricyclic derivatives 2,6-bis(4-hydroxy-3-methoxybenzylidene) cyclohexanone, 2,6-bis(4-hydroxy-3,5-dimethoxybenzylidene) cyclohexanone and 2,5-bis(4-hydroxy-3,5-dimethoxybenzylidene) cyclopentanone inhibited LPS-induced COX-2 and iNOS gene expression in murine macrophages with potency equal to that of curcumin (Gafner et al., 2004).

Pan et al. (2013) reported that curcumin analog B06 exhibits enhanced anti-inflammatory activity compared with that of curcumin through inhibition of c-Jun N-terminal kinase/NF-κB activation. In vivo, B06-treated animals displayed significant decreases in inflammatory mediators in the serum and kidneys and in heart and renal macrophage infiltration. Another analog, 2,6-bis-4-(hydroxyl-3-methoxybenzylidine)-cyclohexanone, or BHMC, inhibited the synthesis of several inflammatory mediators. It suppressed iNOS gene and enzyme expression and strongly inhibited secretion and gene expression of TNF-alpha MCP-1, IL-10, and IL-6 (Tham et al., 2010). Thus, these curcumin analogs potently inhibit inflammatory factors.

Antioxidant effects

Although curcumin exhibits antioxidant activity, various analogs have been designed to improve its antioxidant properties. Dolai et al. (2011) showed that compared with curcumin, a synthetic sugar-derivative of curcumin has more powerful antioxidant properties. Curcumin inhibits amyloid-β and tau peptide aggregation at micromolar concentrations, whereas the sugar–curcumin conjugate inhibits this aggregation at concentrations as low as the nanomolar level (Dolai et al., 2011). 5-Chlorocurcumin, prepared from natural curcumin, has free radical scavenging activity (Al-Amiery et al., 2013). CNB-001, a pyrazole derivative of curcumin, protects neuronal cells against toxicity by decreasing ROS formation, and reduces apoptosis by its action on mitochondria (Jayaraj et al., 2013). A semicarbazone derivative of curcumin (CRSC) has also shown efficient antioxidant and antiproliferative activity, although its antiradical activity was less than that of curcumin. The probable site of attack for CRSC is both the phenolic OH and the imine carbonyl position (Dutta et al., 2005).

Hypoglycemic effect

Several studies have highlighted curcumin's benefit as a hypoglycemic agent. In spite of these benefits, a number of curcumin analogs have been synthesized to improve its efficacy. For instance, a novel curcumin derivative (NCD) was developed through covalent modification of the curcumin molecule on sites remote from its natural functional groups. This NCD was tested in diabetic rats to determine whether it exhibits a hypoglycemic effect. Results showed that it lowered plasma glucose by 27.5% and increased plasma insulin by 66.67% (Abdel Aziz et al., 2012). Later, it was observed that this NCD was partially mediated by induction of the HO-1 gene (Aziz et al., 2013) Another curcuminoid derivative, bis(o-hydroxycinnamoyl)methane, inhibited these levels of plasma glucose in diabetic rats. Thus, curcumin derivatives exhibit anti-diabetic activities.

Molecular targets

Recent advances and insights into the molecular pathogenesis of thousands of molecular targets have been investigated for the prevention and treatment of inflammatory diseases, which could provide unprecedented opportunities for the discovery and development of novel, molecularly targeted diagnostic, therapeutic, and preventative

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strategies and agents. One important advance is the suppression of certain cell signaling pathways that results in suppression of tumorigenesis. With increased understanding of molecular targets of signaling pathways in the pathogenesis of inflammatory diseases, these pathways may be modulated. The goal of analysis of specific molecular targets in cancer therapy is to create a "magic bullet" that selectively kills cancer cells, but not normal cells. In a succession of therapeutic approaches involving molecular targets, an advanced therapeutic approach called *targeted molecular therapy* was developed. In this therapy, monoclonal antibodies, gene therapy, and other agents have been used which can completely shut off the target genes. Because every gene has importance in the proper functioning of body organs, these genes should be in a normal state. Thus agents are needed that can only dial down the overexpressing genes. Curcumin is safe and cost-effective and is known to modulate several molecular targets efficiently. Numerous reports have suggested that curcumin can modulate the molecules involved in almost every stage of disease development by regulating transcription factors, growth factors, receptors, cytokines, kinases, enzymes, cell survival, metastatic and apoptotic molecules (Fig. 2).

Disease targets of curcumin

Curcumin has been used as traditional medicine in India and China to treat sprain and swelling caused by injury, wound healing, and abdominal problems (Surh, 1999). Extensive research over the past 30 years has indicated that curcumin has therapeutic potential against a wide range of diseases such as cancer, lung diseases, neurological diseases, liver diseases, metabolic diseases, autoimmune diseases, cardiovascular diseases, and various other inflammatory diseases. Some of the most common disease targets of curcumin are shown in Fig. 3 (Aggarwal and Harikumar, 2009; Kannappan et al., 2011).

Anticancer properties

Numerous studies have reported that curcumin has potential against several cancers including leukemia, lymphoma, melanoma, and sarcoma, as well as gastrointestinal, genitourinary, breast, ovarian, head and neck, lung, and neurological cancers (Anand et al., 2008). Curcumin acts at several stages of cancer development. It blocks transformation, tumor initiation, tumor promotion, invasion, angiogenesis, and metastasis. In vitro and animal studies have revealed that curcumin suppresses carcinogenesis and inhibits the proliferation of a wide variety of tumor cells (Aggarwal et al., 2003). Curcumin modulates growth of tumor cells through regulation of multiple cell signaling pathways including cell proliferation pathway (cyclin D1, c-myc), cell survival pathway (Bcl-2, Bcl-xL, cFLIP, XIAP, c-IAP1), caspase activation pathway (caspase-8, 3, 9), tumor suppressor pathway (p53, p21) death receptor pathway (DR4, DR5), mitochondrial pathways, and protein kinase pathway (JNK, Akt, and AMPK) (Ravindran et al., 2009).

Cardioprotective properties

In vitro, preclinical, and clinical evidence indicates that curcumin has cardioprotective and lipid-lowering effects. A meta-analysis report showed that supplementation with curcumin was associated with a significant reduction in circulating C-reactive protein levels, a strong predictor and independent risk factor of cardiovascular disease (Sahebkar, 2014) and activation of SIRT1 (Yang et al., 2013). Curcumin has also been shown to be effective against atherosclerosis and myocardial infarction (Aggarwal and Shishodia, 2004). It inhibits proliferation of peripheral blood mononuclear cells and vascular smooth muscle cells, which are hallmarks of atherosclerosis. In addition, curcumin prevents the oxidation of low-density lipoproteins (LDLs), inhibits platelet aggregation, and reduces the incidence of myocardial infarction.

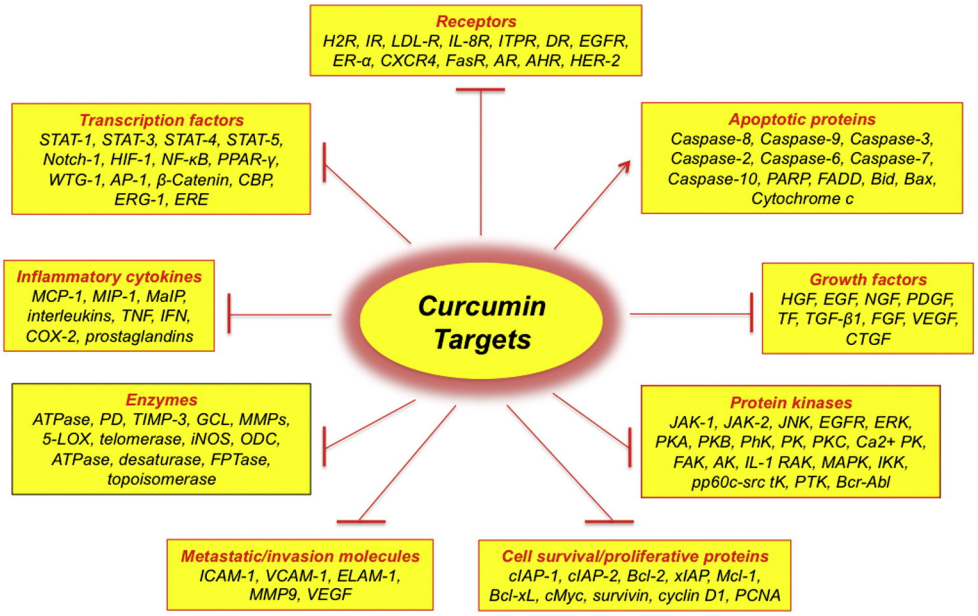

Fig. 2. Molecular target of curcumin. STAT, Signal transducer and activator of transcription; HIF-1, Hypoxia-inducible factors-1; NF-κB, Nuclear factor kappaB; PPAR-γ-Peroxisome proliferator-activated receptors-γ; AP-1, Activator protein-1; CBP, CREB1-binding protein; ERG, ETS (erythroblast transformation-specific)-related gene; ERE, Estrogen response elements; MCP-1, Monocyte chemotactic protein-1; MIP-1, Macrophage inflammatory protein 1; TNF, Tumor necrosis factor; IFN, Interferon; COX-2, Cyclooxygenase-2; TIMP, Tissue inhibitors of metalloproteinases; MMP, Matrix metalloproteinase; 5-LOX, 5-Lipooxygenase; iNOS, Inducible nitric oxide synthase; ODC, Ornithine decarboxylase; FPTase, Farnesyl-protein transferase; ICAM-1, Intercellular adhesion molecule-1; VCAM-1, Vascular cell adhesion molecule-1; ELAM-1, Endothelial-leukocyte adhesion molecule-1; VEGF, Vascular endothelial growth factor; cIAP, Cellular inhibitor of apoptosis protein; Bcl-2, B-cell lymphoma-2; Bcl-xL B-cell lymphoma-extra large; PCNA, Proliferating cell nuclear antigen; JAK, Janus kinase; JNK, c-Jun amino-terminal kinase; EGFR, Epidermal growth factor receptor; ERK1/2, Extracellular signal-regulated kinase 1/2; PKA/B/C, Protein kinase A/B/C; PhK, Phosphorylase kinase; FAK, Focal adhesion kinase; AK, Adenylate kinase; IRAK, Interleukin-1 receptor-associated kinase; IKK, IκB kinase; MAPK, Mitogen-activated protein kinase; srcTK, pp60c-src tyrosine kinase; PTK, Protein tyrosine kinase; FGF, Fibroblast growth factors; EGF, Epidermal growth factor; NGF, Nerve growth factor; PDGF, Platelet-derived growth factor; TF, Tissue factor; TGF, Transforming growth factor; FGF, Fibroblast growth factors; CTGF, Connective-tissue growth factor; PARP, Poly (ADP-ribose) polymerase; FADD, Fas-associated protein with death domain; H2R, Histamine H2 receptor; IR, Insulin receptor; LDL-R, Low-density lipoprotein receptor; ITPR, Inositol 1,4,5-triphosphate receptors; ER, Estrogen receptor; CXCR4, C-X-C chemokine receptor type 4; FasR, Fas receptor; AR, Androgen receptor; AHR, Aryl hydrocarbon receptor.

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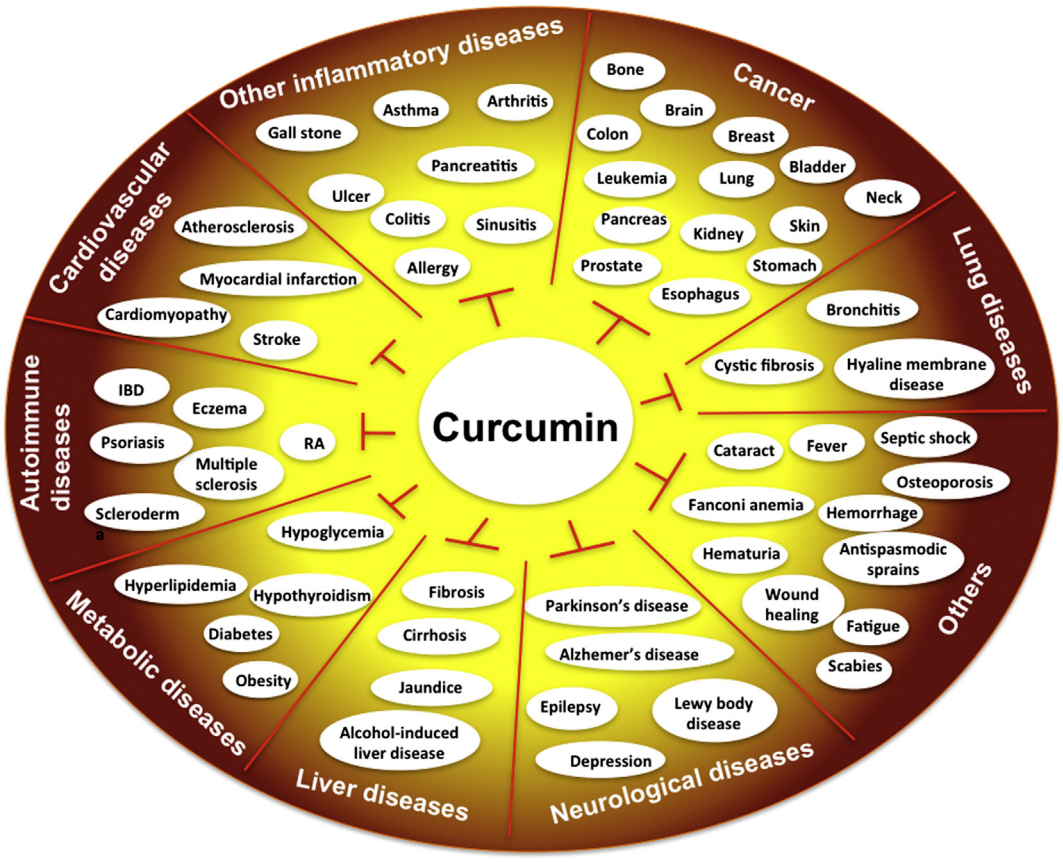

Fig. 3. Diseases targeted by curcumin.

In animals, curcumin treatment attenuated ischemia/reperfusion through the activation of the JAK2/STAT3 signaling pathway, which transmits a survival signal to the myocardium (Duan et al., 2012). The protection against regional myocardial I/R injury by curcumin was also reported through the activation of prosurvival kinases involving PI3K-Akt, ERK1/2, and GSK-3β, and attenuation of p38 and JNK (Jeong et al., 2012). The doxorubicin induced cardiomyopathy was also found to be prevented by treatment of curcumin in animals. It restored the level of biomarker enzymes like LDH and CPK and biochemical parameters such as AST, ALT and ALP back to normal. Curcumin also increased doxorubicin induced reduced level of GSH, SOD and CAT and decreased the elevated level of malondialdehyde in cardiac tissue (Swamy et al., 2012).

Protection against skin diseases

Numerous reports suggest that curcumin is effective against various skin diseases such as dermatitis, scleroderma, psoriasis, and skin carcinogenesis. Oral curcumin, given during radiotherapy, has been shown to reduce the severity of dermatitis induced by radiation in breast cancer patients (Ryan et al., 2013); oral curcumin has furthermore inhibited TPA-induced skin tumor development in mice through abrogation of ODC activity and the dermal infiltrating inflammatory cells (Ishizaki et al., 1996). Another study revealed that curcumin is beneficial in scleroderma and other associated organ pathologies. It exerts a protective effect by mainly modulating the protein kinase C (PKC) pathway (Jimenez et al., 2001). Psoriasis, a chronic skin disease characterized by keratinocyte hyperproliferation and abnormal differentiation, may also be treated by curcumin. In a mouse model, curcumin relieves the psoriasis-like inflammation by decreasing the levels of IL-17A, IL-17F, IL-22, IL-1β, IL-6 and TNF-α cytokines (Sun et al., 2013). Numerous other reports suggest that curcumin accelerates wound healing. In addition, curcumin prevents the formation of scars and plays a role in muscle regeneration after trauma (Aggarwal and Shishodia, 2004).

Antidiabetic properties

Curcumin has been shown to be effective against diabetes in patients and in experimental animal models. In rats with alloxan-induced diabetes, in streptozotocin (STZ)-induced rats models, and in STZ-nicotinamide–induced rats models (Pari and Murugan, 2007), oral administration of various dosages of curcumin was able to prevent loss of body weight; reduce levels of glucose, hemoglobin, and glycosylated hemoglobin in the blood (Arun and Nalini, 2002); and improve insulin sensitivity (Murugan and Pari, 2007). In rat models of high-fat diet-induced insulin resistance and type 2 diabetes, oral administration of curcumin showed an antihyperglycemic effect and improved insulin sensitivity, which was attributed by its anti-inflammatory properties as evident by attenuating TNF-α levels (El-Moselhy et al., 2011).

Diabetic rats maintained on a curcumin diet for 8 weeks excreted less albumin, urea, creatinine, and inorganic phosphorus. Dietary curcumin also partially reversed the abnormalities in plasma albumin, urea, creatine, and inorganic phosphorus in diabetic animals (Aggarwal et al., 2003). In patients with diabetic microangiopathy and retinopathy, administration of Meriva (curcumin and phosphatidylcholine) at a dose of 2 tablets/day (each 500-mg tablet corresponding to 100 mg of curcumin) for at least 4 weeks was found to be helpful (Steigerwalt et al., 2012). Further study in diabetic patients also revealed that curcumin lowers the atherogenic risks by reducing the insulin resistance, triglyceride, uric acid, visceral fat and total body fat. In addition, curcumin helps to improve relevant metabolic profiles in type 2 diabetic population (Chuengsamarn et al., 2014).

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Antiarthritic properties

Curcumin has been shown to possess antirheumatic and antiarthritic effects, most likely through inhibition of inflammatory molecules such as NF-kB, AP-1 and Egr-1, COX2, LOX, NOS, MMP-9, uPA, TNF and chemokines (Aggarwal et al., 2003). When the safety and effectiveness of curcumin were evaluated in patients with rheumatoid arthritis (RA), curcumin was found to be safe and to improve the disease condition (Chandran and Goel, 2012). Exposure of synovial fibroblasts, obtained from patients with RA, to curcumin resulted in growth inhibition and induction of apoptosis by down-regulation of anti-apoptotic Bcl-2 and the XIAP as well as the up-regulation of pro-apoptotic Bax (Park et al., 2007). In vivo studies also showed that curcumin inhibits collagen (Huang et al., 2013) and Freund's complete adjuvant-induced arthritis in animals. Mechanistic studies revealed that curcumin suppresses IFNγ-induced BAFF expression, STAT1 phosphorylation and nuclear translocation thereby attenuated the progression and severity of RA (Huang et al., 2013). In addition, when a subtherapeutic dose of methotrexate was used in combination with curcumin, curcumin potentiated the effect of methotrexate to improve the arthritic condition (Banji et al., 2011).

Protection against multiple sclerosis

Multiple sclerosis is characterized by the destruction of oligodendrocytes and myelin sheath in the central nervous system. Curcumin is effective against multiple sclerosis because of its anti-inflammatory and neuroprotective effects. Curcumin specifically protects axons, but not neuronal cell bodies, from nitric oxide–mediated degeneration (Tegenge et al., 2013). Mechanistically, curcumin blocks the Kv1.3 channels predominantly expressed in T(EM) cells. Also, it inhibits proliferation and cytokine secretion of T(EM) cells isolated from patients with multiple sclerosis (Lian et al., 2013). Curcumin inhibits experimental allergic encephalomyelitis by blocking interleukin (IL)-12 signaling in T cells, suggesting that it would be effective in the treatment of multiple sclerosis (Aggarwal et al., 2003).

Protection against Alzheimer disease

Curcumin shows an array of activities that can be helpful in ameliorating Alzheimer disease (AD) symptoms acting on various target sites (Dohare et al., 2008; Lin et al., 2008; Sreejayan and Rao, 1994). The therapeutic benefits of curcumin for Alzheimer diseases appear multifactorial via regulation of transcription factors, cytokines and enzymes associated with NF-κB activity (Lee et al., 2013). Curcumin has been reported to inhibit Aβ fibril formation (Kim et al., 2005) and to prevent Aβ peptide-induced cellular insult (Kim et al., 2001), suggesting its potential in neurodegenerative diseases. Curcumin has also been shown to suppress oxidative damage, inflammation, cognitive deficits, and amyloid accumulation in AD (Yang et al., 2005). Furthermore, various in vivo studies have provided supporting evidence for the therapeutic potential of curcumin in AD. Administration of curcumin to an AD mouse model resulted in a decreased serum Aβ level as well as reduced Aβ burden in the brain, and this effect was prominently shown in the neocortex and hippocampus (Wang et al., 2009). These studies indicate that curcumin probably interferes with the formation of plaques and can therefore improve the disease condition.

Protection against inflammatory bowel disease

Various studies have reported that curcumin is effective in preventing and treating inflammatory bowel disease (IBD). Ukil et al. (2003) investigated the protective effects of curcumin on IBD induced in a mouse model. Pretreatment of mice with curcumin for 10 days significantly ameliorated the diarrhea and the disruption of the colonic architecture. In a recent pilot study with patients with Crohn disease or ulcerative colitis, 500 mg of curcumin was given twice a day for 3 weeks, leading to improved disease scores. The study authors therefore suggested that curcumin may be used as adjunctive therapy for individuals seeking a combination of conventional and alternative medicines (Suskind et al., 2013). In addition, curcumin used in conjunction with conventional medications for IBD has been shown to be effective and offers a less expensive alternative (Taylor and Leonard, 2011). It has been also found that oral curcumin treatment decreases colon injury which is associated with decreased inflammatory reactions, lipid peroxidation, apoptotic cell death, and modulating p38- and JNK-MAPK pathways (Topcu-Tarladacalisir et al., 2013). The possible role of curcumin against IBD have shown to be through the inhibition of free radicals, increasing antioxidants, and influencing multiple signaling pathways, especially the kinases (MAPK, ERK), inhibiting myeloperoxidase, COX-1, COX-2, LOX, TNF-α, IFN-γ, iNOS and NF-κB (Baliga et al., 2012).

Protection against cystic fibrosis

Cystic fibrosis (CF), the most common lethal hereditary disease in the white population, is caused by mutations in the cystic fibrosis transmembrane conductance regulator gene (CFTR). Curcumin's potential activity in CF has received considerable attention. Curcumin is a sarcoplasmic/endoplasmic reticulum calcium (SERCA) pump inhibitor and thus may prevent CFTR degradation and improve the manifestation of CF (Bilmen et al., 2001). Egan et al. (2004) demonstrated that curcumin corrected CF defects in DeltaF508 CF mice. Moreover, other studies have suggested possible mechanisms for curcumin's enhancement of CFTR, including the involvement of phosphorylation and activation of protein kinase alpha (PKA) (Wang et al., 2007), remodeling and activation of the keratin 18 (K18) network implicated in CFTR trafficking (Lipecka et al., 2006), and suppression of calreticulin, an ER protein that down-regulates CFTR expression (Harada et al., 2007). In addition, it has been reported that curcumin opens CFTR channels without involving ATP and nucleotide-binding domain (Wang et al., 2007).

Protection against other diseases

Curcumin has been shown to be effective against several other diseases. It potently and selectively inhibited human immunodeficiency virus (HIV-1) long-terminal repeat-directed gene expression, which governs the transcription of type 1 HIV-1 provirus (Aggarwal et al., 2003). Curcumin also exerts inhibitory effect against HIV-1 gp120-induced rat neuronal damage by reducing the production of ROS, TNF-α and MCP-1. Curcumin has shown to exhibit these biological activities through inhibition of the delayed rectification and transient outward potassium (K^+) current in neurons (Guo et al., 2013). Cells infected with dengue virus type 2 were treated with curcumin, and curcumin was found to interfere with the infection processes of dengue virus; this interference resulted from curcumin's effects on various cellular systems such as the cytoskeleton, the ubiquitin–proteasome system, or the apoptosis process (Padilla et al., 2014). In rat pups, curcumin suppressed selenite-induced cataractogenesis through suppression of oxidative stress (Manikandan et al., 2010). Treatment with curcumin also prevented experimental alcoholic liver disease. Curcumin has a protective effect on cyclophosphamide-induced early lung injury. Furthermore, nephrotoxicity, a problem observed in patients who are administered chemotherapeutic agents, can be prevented with curcumin (Aggarwal et al., 2003).

Curcumin in the clinic

The safety and efficacy of curcumin in a number of human diseases have been evaluated in clinical trials. More than 65 human clinical trials of curcumin, which included more than 1000 patients, have been completed, and as many as 35 clinical trials are under way (Gupta et al.,

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2013). Curcumin is now used as a supplement in several countries including the United States, India, Japan, Korea, Thailand, China, Turkey, South Africa, Nepal, and Pakistan. The most common human diseases against which curcumin has exhibited activities by human clinical trials include cancer, arthritis, cardiovascular disease, gastric ulcer, Crohn disease, ulcerative colitis, uveitis, ulcerative proctitis, peptic ulcer, oral lichen planus, gastric inflammation, vitiligo, psoriasis, acute coronary syndrome, atherosclerosis, diabetes, Dejerine–Sottas disease, diabetic nephropathy, diabetic microangiopathy, idiopathic orbital inflammatory pseudotumor, lupus nephritis, renal conditions, irritable bowel disease, tropical pancreatitis, β-thalassemia, acquired immunodeficiency syndrome, cholecystitis, and chronic bacterial prostatitis.

In these clinical trials, curcumin was used either alone or in combination with other agents such as gemcitabine, soy isoflavones, bioperine, quercetin, mesalamine, acetylcysteine, prednisone, lactoferrin, piperine, docetaxel, sulfasalazine, and pantoprazole. Among these human participants, various formulations of curcumin, including nanoparticles, liposomal encapsulation, emulsions, capsules, tablets, and powder, have been examined. At the molecular level, curcumin has been shown to modulate the activities of numerous signaling molecules such as proinflammatory cytokines, NF-κB, COX-2, apoptotic proteins, STAT3, C-reactive protein, prostaglandin E_2, phosphorylase kinase, transforming growth factor-β, adhesion molecules, creatinine, prostate-specific antigen, 5-LOX, ET-1, triglyceride, HO-1, AST, and ALT in human participants.

Although the therapeutic use of *Curcuma*, the source of curcumin, was recorded as early as 1748 (Loeber., 1748), it was not until 1937 that curcumin was first tested in humans by Oppenheimer (Oppenheimer., 1937). In this study, curcumin produced remarkably good results against cholecystitis. The first indication of curcumin's anticancer activities in human participants was shown in 1987 by Kuttan and co-workers (Kuttan et al., 1987), who demonstrated the efficacy of topical curcumin in patients with external cancerous lesions. To date, curcumin has demonstrated potential against breast cancer, prostate cancer, colorectal cancer, multiple myeloma, pancreatic cancer, oral cancer, lung cancer, and head and neck squamous cell carcinoma.

Curcumin's potential against arthritis was first reported in 1980 in patients with RA (Deodhar et al., 1980). In this study, curcumin's efficacy was compared with that of the prescription drug phenylbutazone. Curcumin exerted an antirheumatic activity identical to that of phenylbutazone and was found to be well tolerated without any adverse effects (Deodhar et al., 1980). Curcumin's efficacy in patients with peptic ulcers was demonstrated by a phase II clinical trial from Thailand (Prucksunand et al., 2001). Forty-five patients (24 men and 21 women, aged 16–60 years) were included in the study. Two capsules (300 mg each) of turmeric were given orally five times daily over 4 weeks. After 4 weeks of treatment, ulcers were absent in 12 patients; after 8 weeks of treatment, ulcers were absent in 18 patients; and after 12 weeks of treatment, ulcers were absent in 19 patients (Prucksunand et al., 2001). The beneficial effects of curcumin in improving lipid profiles in patients with acute coronary syndrome was demonstrated in another study (Alwi et al., 2008). Curcumin has also been shown to act as a chemopreventive agent against atherosclerosis (Soni and Kuttan, 1992).

Curcumin's efficacy against various human ailments is being evaluated by numerous ongoing clinical trials. The most common human diseases for which curcumin is being evaluated are cancer, inflammatory conditions, arthritis, neurological conditions, and diabetes (www.clinicaltrials.gov). In these clinical trials, curcumin is being used primarily in the form of nanoparticles, capsules, tablets, powder, and solutions. These trials are in various stages of development, and curcumin doses range from 0.18 to 8 g/day. For some diseases, curcumin is being administered in combination with other agents (nutraceuticals) and therapies (such as chemotherapy and radiotherapy). We hope that the results from these clinical trials will provide a deeper understanding of curcumin's therapeutic potential and will help to place this fascinating molecule at the forefront of novel therapeutics.

Strategies for improvement of bioavailability of curcumin

Accumulated evidences suggest that curcumin is effective and safe. Despite these, bioavailability of curcumin still remains a major concern. However, numerous studies revealed that oral treatment of curcumin is bioavailable in serum and plasma of experimental animals (Chang et al., 2013; Yang et al., 2007). Moreover, in a human clinical trial, 3.6 g of curcumin via oral route was found to produce a plasma curcumin level of 11.1 nmol/L after an hour of dosing (Sharma et al., 2004). Besides these, in attempts to improve the bioavailability of curcumin, several strategies have been explored such as modulation of route and medium of curcumin administration, blocking of metabolic pathways by concomitant administration with other agents, and conjugation and structural modifications of curcumin.

One of the major strategies implemented to increase the bioavailability of curcumin is conjugation and structural modifications of curcumin which include nanocurcumin, polylactic-co-glycolic acid (PLGA) encapsulated curcumin, liposome-encapsulated curcumin (LEC), silica-coated and uncoated flexible liposomes loaded curcumin (CUR-SLs), N-trimethyl chitosan chloride (TMC)-coated curcumin liposomes and cyclodextrin encapsulated curcumin (CDC). Ex vivo study showed that the curcumin formulation of nanoglobule-based nanoemulsion has much higher release of curcumin from nanoemulsion than curcumin suspension (Kumar et al., 2012). The nanoparticle of curcumin prepared by Cheng et al. (2013) produced significantly higher curcumin concentration in plasma and six times higher residence time in mice brain than regular curcumin. Other effective formulation PLGA encapsulated curcumin also exhibited almost twice as high serum concentration of PLGA-curcumin than curcumin in animals (Anand et al., 2010).

Liposomal curcumin formulation is further designed for the improvement of bioavailability of curcumin because liposomes are considered as effective drug carriers. In a study, oral administration of LEC in rat showed high bioavailability of curcumin (Takahashi et al., 2009). In other studies, CUR-SLs and curcumin incorporated TMC-coated liposomes exhibited enhanced bioavailability, compared with curcumin encapsulated by uncoated liposomes and curcumin suspension (Chen et al., 2012; Li et al., 2012a). CDC, cyclic oligosaccharides, has been also used in order to improve curcumin's delivery and bioavailability via its encapsulation with CD. It increases cellular uptake and longer half-life in the cancer cells compared with free curcumin (Yadav et al., 2010). Thus, these studies indicate that the strategies used to improve the bioavailability are effective in animals as well as in humans.

Conclusions

Overall, it is clear from the studies described here that curcumin, like most natural products, is highly promiscuous. These studies make it clear that a simple chemical structure such as that of curcumin can interact with multiple molecular targets involved in a wide variety of diseases. The affinity toward these targets could vary a great deal, from the pM to mM range. For drug development, however, the safety, efficacy, and affordability of the drug are important criteria. Curcumin meets most of these criteria. In vitro, in vivo, and human clinical studies have all established curcumin's promise and revealed its therapeutic value. More clinical studies are needed to further realize its potential.

Designing analogs that are more potent than the parent compound is also very much desired. As summarized above various synthetic curcumin and its formulation have been designed to evaluate the enhanced biological activity of curcumin. These include adjuvants, nanoparticles, liposomes, micelles, phospholipid complexes, etc. However, the efficacy of these curcumin analogs and derivatives has been mostly studied in vitro. Thus, more studies including those in vivo are needed to unravel curcumin analogs for further human clinical trials.

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