REVIEW

Curcumin-free turmeric exhibits anti-inflammatory and anticancer activities: Identification of novel components of turmeric

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Turmeric, a dried powder derived from the rhizome of *Curcuma longa*, has been used for centuries in certain parts of the world and has been linked to numerous biological activities including antioxidant, anti-inflammatory, anticancer, antigrowth, anti-arthritic, anti-atherosclerotic, antidepressant, anti-aging, antidiabetic, antimicrobial, wound healing, and memory-enhancing activities. One component of turmeric is curcumin, which has been extensively studied, as indicated by more than 5600 citations, most of which have appeared within the past decade. Recent research has identified numerous chemical entities from turmeric other than curcumin. It is unclear whether all of the activities ascribed to turmeric are due to curcumin or whether other compounds in turmeric can manifest these activities uniquely, additively, or synergistically with curcumin. However, studies have indicated that turmeric oil, present in turmeric, can enhance the bioavailability of curcumin. Studies over the past decade have indicated that curcumin-free turmeric (CFT) components possess numerous biological activities including anti-inflammatory, anticancer, and antidiabetic activities. Elemene derived from turmeric is approved in China for the treatment of cancer. The current review focuses on the anticancer and anti-inflammatory activities exhibited by CFT and by some individual components of turmeric, including turmerin, turmerone, elemene, furanodiene, curdione, bisacurone, cyclocurcumin, calebin A, and germacrone.

Keywords:
Apoptosis / Cancer / Inflammation / Turmeric / Turmeric components

1 Introduction

Turmeric is the dried rhizome of *Curcuma longa* and is synonym with *Curcuma aromatica* (wild turmeric), *Curcuma wenyujin* (in China), and *Curcuma domestica* (in Thailand). *C. longa* is a rhizomatous herbaceous perennial plant of the family Zingiberaceae. The genus name *Curcuma* originates from the Arabic word *kurkum*, meaning "saffron," in reference to the color of turmeric, and more than 70 different species of *Curcuma* have been identified. The word *turmeric* is derived from Medieval Latin, *terra merita*, meaning "deserving earth." Turmeric has also been recognized traditionally as an agent of beauty and health [1]. The use of turmeric in Ayurveda and in traditional Chinese medicine is well documented for a wide variety of ailments including gastric problems, inflammatory conditions, hepatic disorders, gynecological problems, infectious diseases, sprains, boils, cough, cold, asthma, and dental problems. Extensive preclinical and clinical research over the past two decades has provided a scientific basis for the use of this spice against such human ailments and has revealed its safety at gram doses in humans. The utilities of turmeric in traditional and modern medicine have

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Abbreviations: **BHA**, butylated hydroxyanisole; **BP**, benzo[a]-pyrene; **CFT**, curcumin-free turmeric; **COX-2**, cyclooxygenase-2; **DR4**, death receptor 4; **MMP-9**, matrix metalloproteinase-9; **NF-κB**, nuclear factor-κB; **PGE2**, prostaglandin E2; **PPAR**, peroxisome proliferator-activated receptor; **PUMA**, p53 upregulated modulator of apoptosis; **ROS**, reactive oxygen species; **TNF**, tumor necrosis factor; **TPA**, 12-O-tetradecanoylphorbol-13-acetate

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been extensively reviewed in previous manuscripts from this laboratory [2, 3].

Several breakthroughs in turmeric research have occurred. Turmeric's anti-inflammatory activity was probably first demonstrated in 1971 by Arora et al. [4]. The group examined the anti-inflammatory effects of turmeric in cotton pellet granuloma, formalin-induced arthritis, and granuloma pouch models of inflammation in rats. The effect of turmeric was comparable to that of hydrocortisone, a steroidal drug prescribed for the treatment of many inflammatory and allergic conditions. The anticancer activity of turmeric in vitro was probably first demonstrated in 1985 by Kuttan et al. [5], who used tissue culture methods; and in vivo studies in mice. Turmeric extracts at a concentration of 0.4 mg/mL inhibited tumor growth and reduced the development of tumors in animals. The anticancer activities of turmeric in human participants were first demonstrated by the same group in 1987 [6]. They used an ethanol extract of turmeric that produced remarkable symptomatic relief in patients with external cancerous lesions. Reduction in smell was noted in 90% of participants and reduction in itching in almost all cases. Dry lesions were observed in 70% of cases, and a small number of patients (10%) experienced reduced lesion size and less pain. Although the effects continued for several months in many patients, an adverse reaction was noticed in only 1 of the 62 patients evaluated.

Curcumin (diferuloylmethane), which constitutes 2–5% of dried turmeric root, is the most extensively studied component of this spice, as indicated by more than 5600 citations, and thus will not be discussed in this review. Commercial "curcumin" is often a mixture of three major curcumnnioids: curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Although curcumin is believed to account for most activities of turmeric, research over the past decade has indicated that curcumin-free turmeric (CFT) is as effective as or even more effective than curcumin-containing turmeric. Numerous components of turmeric such as turmerin, turmerone, elemene, furanodiene, curdione, bisacurone, cyclocurcumin, calebin A, and germacrone are reported to possess potent biological activities. In the following sections, and in Tables 1 and 2, we discuss the anti-inflammatory and anticancer activities of CFT and some common chemical entities that have been identified in CFT.

2 Chemical composition of turmeric

Turmeric is chemically diverse: to date, approximately 235 compounds, primarily phenolic compounds and terpenoids, have been identified in this spice (The major components of turmeric, other than curcumin, are shown in Fig. 1.) [7]. These noncurcumin compounds are chemically diverse (Fig. 2). Of these compounds, 22 are diarylheptanoids and diarylpentanoids; also included are 8 phenylpropenes and other phenolic compounds, 68 monoterpenes, 109 sesquiterpenes, 5 diterpenes, 3 triterpenoids, 4 sterols, 2 alkaloids, and 14 other compounds. Extracts of turmeric are prepared by using ethanol, methanol, water, or ethyl acetate. Turmeric extracts are both water-soluble and water-insoluble. The water-insoluble fraction consists of turmeric oil and polyphenols, which are primarily diarylheptanoids, also called curcuminoids. The latter consists of curcumin (80%), demethoxycurcumin (18%), and bisdemethoxycurcumin (2%). Whereas 70% ethanol is preferred for extraction of curcuminoids from turmeric [8], hydrodistillation followed by hexane extraction is the procedure of choice to separate essential oils from turmeric. Curcumin, demethoxycurcumin, and bisdemethoxycurcumin together may account for over 30% of the ethanol extract of turmeric [7]. Another unique component of turmeric is cyclocurcumin, found only in *C. longa* [9].

From the root tuber of *C. longa*, Wang et al. [10] isolated a new quinoline alkaloid and seven known bisabolane sesquiterpenes: (1) 2-(2′-methyl-1′-propenyl)-4, 6-dimethyl-7-hydroxyquinoline, (2) 2, 5-dihydroxybisabola-3, 10-diene, (3) 4, 5-dihydroxybisabola-2, 10-diene, (4) turmeronol A, (5) bisacurone, (6) bisacurone A, (7) bisacurone B, (8) bisacurone C, (9) dehydrozingerone, and (10) zingerone. Compounds 1, 6, 7, 8, 9, and 10 (listed above) were isolated for the first time from this plant.

Another group investigated the ethanolic extract of *C. longa* rhizomes [11]. They isolated two new sesquiterpenes: 2-methoxy-5-hydroxybisabola-3,10-diene-9-one, and 2,8-epoxy-5-hydroxybisabola-3,10-diene-9-one; one new monoterpene: 2-(2,5-dihydroxy-4-methylcyclohex-3-enyl) propanoic acid; as well as five known sesquiterpenes. Among the known compounds, bisacurone A was isolated from *C. longa* and 4-methylene-5-hydroxybisabola-2,10-diene-9-one from the genus *Curcuma* for the first time.

Perhaps another important component of turmeric is turmeric oil, which is responsible for the spice's aromatic taste and smell. Dried turmeric usually contains 1.5–5% essential oils [12], which are dominated by sesquiterpenes. One kilogram of turmeric root may contain as much as 7–8 g (0.7–0.8%) of turmeric oil. Bisabolanes are the most abundant sesquiterpenes in turmeric [13, 14]. As many as 109 sesquiterpenes have been identified in turmeric oil, including 54 bisabolanes, 6 germacrones, 7 guaianes, 4 selinanes, 3 santalanes, 2 caryophyllanes, 2 elemenes, as well as following: acorane, aristolene, bergamotane, carbrane, cedrane, himachalene, and sesquisabinane.

Besides sesquiterpenes, five diterpenes, three triterpenoids [15, 16], and four steroids [7] have been identified in turmeric. Some of the major compounds of turmeric oil include aromatic (*ar*)-turmerone (28%), α-turmerone (17%), β-turmerone, curlone (14%), 2-carene (5%), zingiberene (4.37%), sesquiphellandrene (6%), *ar*-curcumene (3%), and linoleic acid (5%) [17, 18]. Interestingly, the compound allantone is found only in turmeric from Brazil. In addition to the above components, turmeric has been shown to contain a novel water-soluble antioxidant peptide named turmerin that is known to possess anticancer and anti-inflammatory activities.

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Table 1. Curcumin-free turmeric compounds exhibit anticancer activities

Turmerones

(1) Inhibited the growth of cancer cells [53].
(2) Suppressed TPA-induced invasion, migration, and colony formation in human breast cancer cells [57].
(3) Inhibited the growth, induced apoptotic bodies and DNA fragmentation in leukemia cells [56].
(4) Induced expression of bax, p53, cytochrome c, and caspase-3 in leukemia cells [62].
(5) Induced DNA fragmentation and caspase activation in human breast cancer cells [63].
(6) Stimulated the proliferation of normal human peripheral blood lymphocytes [63].
(7) Induced apoptosis in human hepatocellular carcinoma cells through ROS-mediated activation of ERK and JNK kinases [64].
(8) Prevented inflammation-induced carcinogenesis in a mouse model [65].

Elemene

(1) Enhanced the radiosensitivity of lung adenocarcinoma xenograft through downregulation of survivin and HIF-1α [74].
(2) Restored the sensitivity of NSCLC to gefitinib through elevation of p21 levels [75].
(3) Induced apoptosis in human lung carcinoma cells by increasing p38 MAPK and iNOS levels [76].
(4) Exhibited antiproliferative effects against chemoresistant ovarian carcinoma cells through G2/M cell cycle arrest [78].
(5) Inhibited the growth, induced apoptosis, and suppressed the expression of eIFs, bFGF, and VEGF in laryngeal cancer cells [79].
(6) Exhibited antiproliferative activities against human cervix epitheloid carcinoma, gastric carcinoma, and leukemia cells [80].
(7) Exhibited antiproliferative activities, decreased Bcl-2, increased cytochrome c, and activated PARP and caspases in prostate cancer cells [81].
(8) Induced apoptosis in glioblastoma cells [85].
(9) Induced apoptosis in human leukemia cells through downregulation of c-FLIP and generation of ROS [86].
(10) Induced apoptosis in colorectal adenocarcinoma cells via a mitochondria-mediated pathway [91].
(11) Inhibited brain tumor growth in mice [92].
(12) Inhibited the growth of hepatocellular carcinoma by enhancing the expression of histone H1 [93].

Furanodiene

(1) Induced G2/M cell cycle arrest and apoptosis in human hepatocellular carcinoma cells through MAPK and caspase pathway [101].
(2) Induced apoptosis in leukemia cells through activation of TNFR1 [102].
(3) Inhibited the growth of uterine cervical and sarcoma tumors in mice [103].
(4) Inhibited proliferation of breast cancer cells by increasing ROS formation, decreasing mitochondrial membrane potential, and by activating caspases [104].
(5) Inhibited proliferation and increased lactate dehydrogenase release in breast cancer cells [105].
(6) Exhibited strong anti-angiogenic activity on endothelial cells [106].

Cyclocurcumin

(1) Inhibited the proliferation of human breast cancer cells [110].

Calebin A

(1) Inhibited growth and induced apoptosis in drug-resistant human gastric cancer cells [112].

Germacrone

(1) Inhibited the proliferation of breast cancer cells by inducing cell cycle arrest and promoting apoptosis [114].
(2) Inhibited proliferation of breast cancer cells by increasing ROS formation, decreasing mitochondrial membrane potential, and by activating caspases [104].
(3) Inhibited the growth of human hepatoma cells by inducing G2/M cell cycle arrest and apoptosis [115].
(4) Exhibited anti-androgenic activities in prostate cancer cells [116].

Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma-2; bFGF, basic fibroblast growth factor; eIFs, eukaryotic initiation factors; ERK, extracellular signal-regulated kinase; FLIP, FLICE/caspase-8 inhibitory protein; HIF-1α, hypoxia-inducible factor-1 alpha; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; NSCLC, non small cell lung cancer; PARP, poly ADP ribose polymerase; ROS, reactive oxygen species; TNFR1, TNF receptor 1; TPA, 12-O-tetradecanoylphorbol-13-acetate; VEGF, vascular endothelial growth factor.

3 Anti-inflammatory and anticancer activities of noncurcumin compounds of turmeric

3.1 Anti-inflammatory and anticancer activities of CFT

Although initially the anti-inflammatory and anticancer activities of turmeric were believed to be due to curcumin, recent research has identified numerous other chemical entities with similar activities in turmeric [2]. Cell-based assays conducted in our laboratory have indicated that curcumin is less potent in inhibiting cancer cell growth than is turmeric containing an equivalent amount of curcumin [19]. Likewise, whole turmeric had higher peroxisomal proliferator-activated receptor (PPAR)-γ ligand-binding activity than did pure curcumin [20]. Moreover, increasing evidence over the

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Table 2. Curcumin-free turmeric compounds exhibit anti-inflammatory activities

Turmerones

(1) Suppressed LPS-induced expression of COX-2 and iNOS in macrophages [54].
(2) Inhibited expression of MMP-9, COX-2, and NF-κB in breast cancer cells [57].
(3) Inhibited the LPS-induced expression of pro-inflammatory cytokines and chemokines, and activities of PGE2, NO, and MMP-9 in microglial cells [58].
(4) Found to be more potent than aspirin in inhibiting platelet aggregation induced by collagen and arachidonic acid [59].
(5) Reduced paw thickness in carrageenan- and dextran-induced acute inflammation, and formalin-induced chronic inflammation in mice [48].
(6) Suppressed TNF-induced adhesion of inflammatory cells to endothelial cells [65].

Elemene

(1) Downregulated IL-17 and IFN-γ in experimental autoimmune encephalomyelitis [96].
(2) Downregulated serum TNF-α levels and hepatic CD14 expression in rats with liver fibrosis [98].

Furanodiene

(1) Suppressed TPA-induced inflammation of mouse ears [100].

Curdione

(1) Inhibited the production of PGE2 in LPS-stimulated mouse macrophages through the suppression of COX-2 [108].

Bisacurone

(1) Downregulated TNF-induced VCAM-1 expression in HUVECs [109].

Germacrone

(1) Exhibited anti-inflammatory activity in carrageenin-induced edema in rats [119].
(2) Exhibited anti-inflammatory activity in carrageenin-induced hind paw edema in rats [120].
(3) Inhibited LPS-induced NO production in cultured mouse peritoneal macrophages [121].

COX-2, cyclooxygenase-2; HUVECs, human umbilical vein endothelial cells; IFN-γ, interferon-gamma; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MMP, matrix metalloproteinase; NF-κB, nucler factor-kappaB; NO, nitric oxide; PGE2, prostoglandin E2; STAT, signal transducers and activators of transcription protein; TNF, tumor necrosis factor; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; VCAM-1, vascular cell adhesion molecule-1.

past decade has suggested that aqueous extracts of turmeric that lack curcumin exhibit antioxidant [21] and corneal wound healing [22] activities, suppress hepatitis B virus replication by enhancing p53 levels [23], exhibit anti-*Helicobacter pylori* activity [24], stimulate insulin release and mimic insulin action [25], and exhibit antidepressant activity in mice [26]. In addition, these aqueous extracts were found to be effective against cancer as indicated by suppression of smoke-induced DNA damage of human lymphocytes [27–29] and induction of apoptosis and G2/M arrest in human colon carcinoma [30]. In addition, CFT has been reported to inhibit benzo[a]pyrene (BP)-induced genotoxicity and carcinogenicity [31], downregulate BP-induced forestomach papillomas in mice [32], and suppress 7,12-dimethylbenz[a]anthracene–induced rat mammary tumorigenesis [33]. Azuine et al. [31] reported that curcumin-free aqueous extracts of turmeric were as potent as curcumin-containing turmeric or curcumin alone in suppressing BP-induced forestomach tumors in female Swiss mice. Furthermore, curcumin-free aqueous extracts of turmeric have been shown to protect against DNA damage induced by fuel smoke condensate in human lymphocytes [28].

The volatile terpenes and phenolic curcuminoids that constitute hydrophobic turmeric oil appear to differ in their anti-inflammatory activities. Turmeric oil was found to be more effective than curcumin when examined for suppression of LPS-induced prostaglandin E2 (PGE2) production in leukemia cells [34]. The dose of turmeric oil required to inhibit PGE2 production by 50% was comparable to that of indomethacin, a well-known nonsteroidal anti-inflammatory drug (84 ng/mL versus 52 ng/mL). Of interest, the authors also showed that curcumin inhibited cyclooxygenase-2 (COX-2) expression, whereas turmeric oil had no effect on COX-2 mRNA, even when tested at 20-fold higher doses, suggesting that the various components of turmeric mediate their effects through different mechanisms.

Naganuma et al. [35] showed that turmeric and curcumin differ in conjugation reaction linked to activation of procarcinogens. Turmeric was found to exhibit inhibitory activity toward both sulfo conjugation and glucuronosyl conjugations of 1-naphthol at approximately the same levels, but curcumin inhibited sulfo conjugation at lower concentrations and showed only weak inhibition toward glucuronosyl conjugation of 1-naphthol in Caco-2 cells. Another study indicated that the anti-inflammatory activity of turmeric against adjuvant arthritis in mice is independent of curcumin [36]. Turmeric was also found to be more effective than curcumin in suppressing streptozotocin-induced diabetic cataracts in rats [37] and in reducing blood glucose levels in type 2 diabetic KK-A mice [20].

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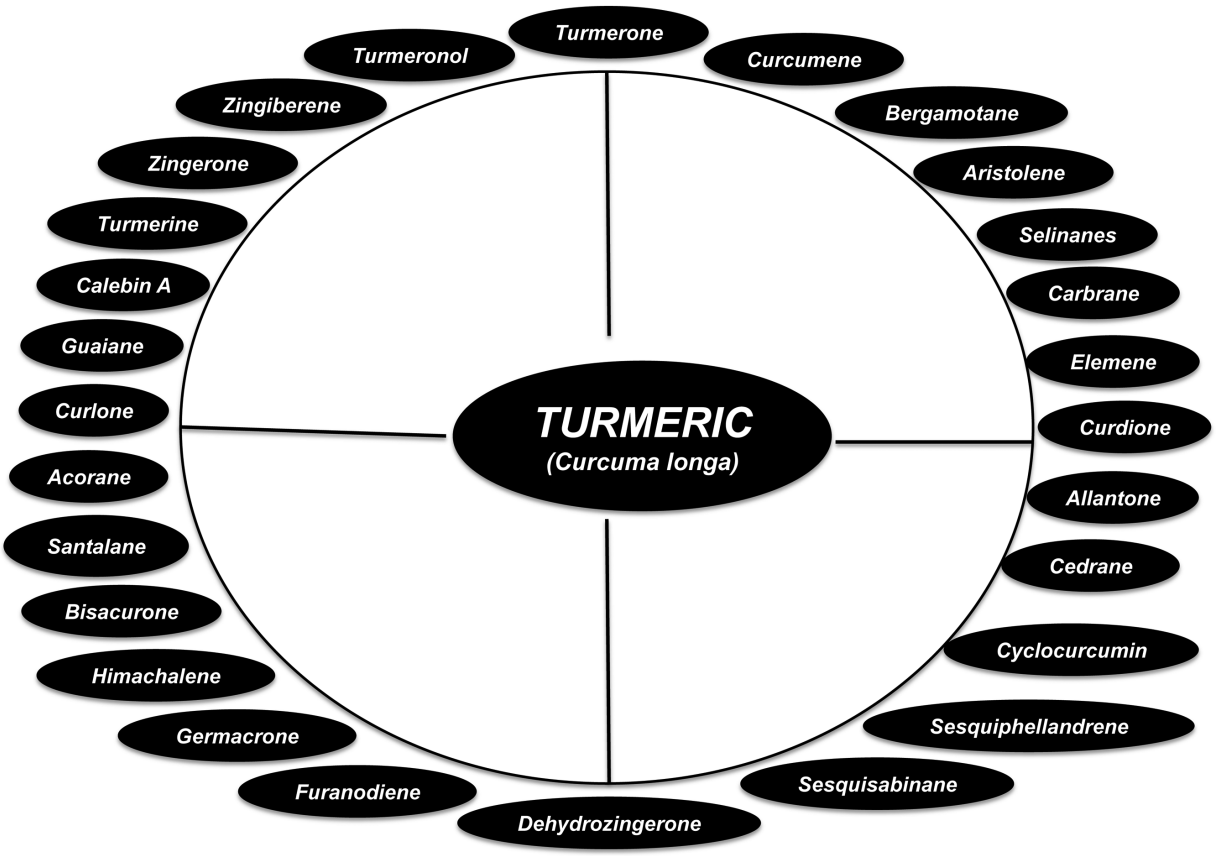

Figure 1. The noncurcumin compounds of turmeric.

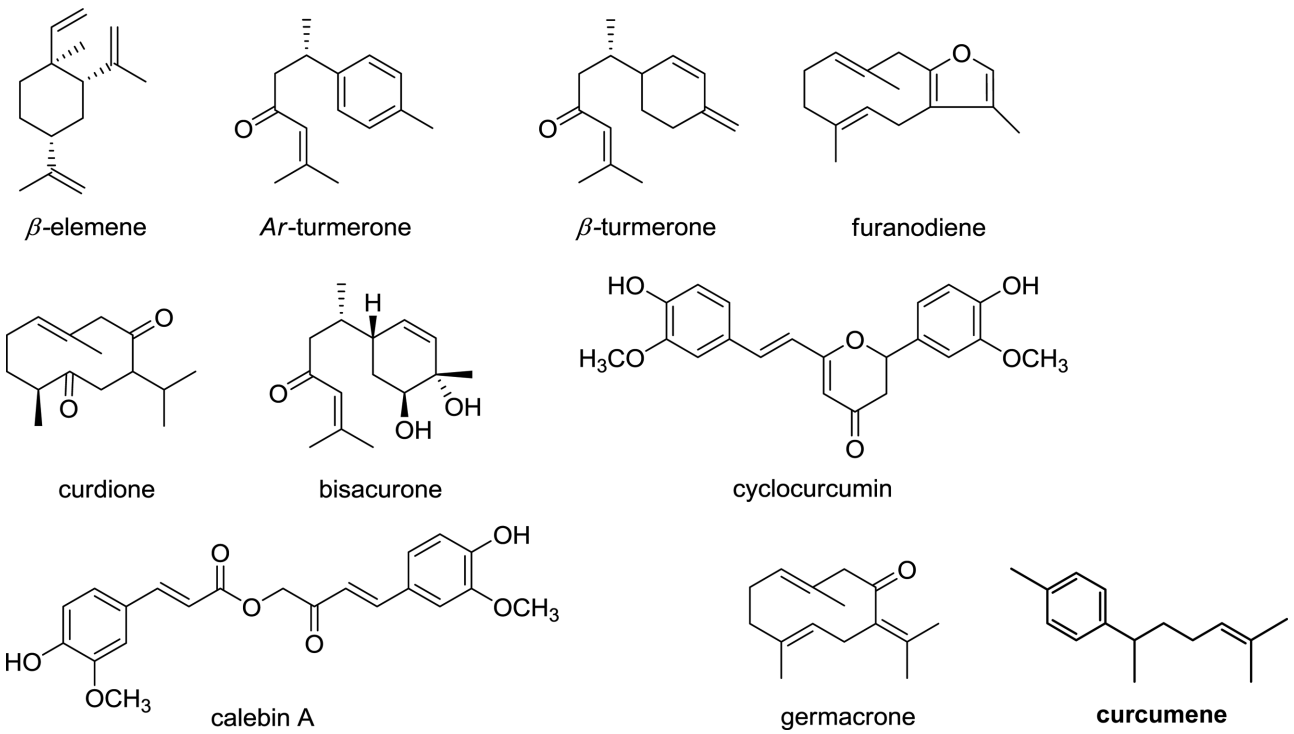

Figure 2. Chemical structure of the common components of turmeric, other than curcumin.

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3.2 Anti-inflammatory and anticancer activities of turmerines

Besides small molecules, turmeric has been shown to contain a novel water-soluble antioxidant peptide named turmerin [38]. Turmerin, a heat-stable noncyclic peptide containing 40 amino acid residues with a molecular mass of 5 kDa, was found to be an efficient antioxidant/DNA-protectant/antimutagen [39]. Turmerines constitutes 0.1% of the dry weight of turmeric and is obtained in a crystalline form. It is insensitive to trypsin, pepsin, heat, and UV radiation. Turmerin contains three residues of methionine that are partly responsible for its antioxidant activity. Turmerin at a 183 nM concentration offered 80% protection to membranes and DNA against oxidative injury [38]. Turmerin also inhibited reactive oxygen species (ROS)-induced arachidonate release and the mutagenic activity of t-butyl hydroperoxide. When examined on human lymphocytes, turmerin was found to be noncytotoxic up to milligram concentrations [38]. The same group more recently reported that turmerin had a relative molecular mass of 14 kDa [40]. The difference in molecular mass of turmerin between the two studies is unclear. However, the authors of this study believe that 5 kDa and 14 kDa turmerines in two different publications should be referred as turmerin I and turmerin II, respectively. The group showed that turmerin inhibits enzymatic activity and neutralizes pharmacological properties such as cytotoxicity, edema, and myotoxicity of multitoxic phospholipase A2. Turmerin has also been linked with anti-HIV activity [41].

Another heat-stable protein with antioxidant properties, turmeric antioxidant protein (TAP), was identified in the aqueous extracts of turmeric [21]. This protein has a molecular weight of 24 kDa, and its antioxidant activity is abolished by trypsin. The thiol groups of the protein were found to contribute to its antioxidant activity. In a subsequent report, the group reported the purification and characterization of a ~34 kDa antioxidant glycoprotein (β-turmerin) from turmeric waste grits [42]. Whether any structural relationship between α- and β-turmerin exists is unclear. β-turmerin, however, was found to inhibit lipid peroxidation with a potency 3200 times higher than that of butylated hydroxyanisole (BHA) or α-tocopherol. β-turmerin also effectively scavenges hydroxyl radicals compared with BHA and α-tocopherol. β-turmerin further inhibits the activation of polymorphonuclear leukocytes mediated by *N*-formyl methionyl leucinyl phenylalanine more efficiently than BHA or mannitol does. β-turmerin prevented tertiary butylated hydroperoxide-induced cell death and was nontoxic to lymphocytes. Neither pepsin nor trypsin treatment had any effect on the antioxidant activity of this protein, but activity was destroyed by nonspecific protease.

More recently, turmerin has been shown to exhibit antihyperglycemic activity [43]. It inhibited α-amylase and α-glucosidase activities with IC_{50} values of 31 and 192 μg/mL, respectively. The authors suggested that the antidiabetic activity of turmeric is due to the ability of turmerin to inhibit enzymes linked to type 2 diabetes and its antioxidant capacity.

3.3 Anti-inflammatory and anticancer activities of turmerones

The major components in turmeric oil are *ar*-turmerones. As much as 60% of turmeric oil consists of turmerone (15%), *ar*-turmerones (31%), and curlone (10%) [44–46]. These turmerones have been linked with numerous biological activities. They exhibit antimutagenic activity, as indicated by the Ames test, and antioxidant activity [45–48]. Perhaps one of the first activities to be attributed to *ar*-turmerone is antivenom activity against snakebite [49]. Another report showed that *ar*-turmerone exhibits antifungal activity against *Candida albicans* [50]. Potent antibacterial activity has also been assigned to this turmerone [51]. *Ar*-turmerone was found to be a potent inhibitor of acetylcholine esterase as well [52].

Our laboratory has found that turmerones exhibit a profile of activity against cancer cells that is different from that of curcuminoids [53]. Curcumin and bisdemethoxycurcumin inhibited tumor necrosis factor (TNF)-induced nuclear factor-κB (NF-κB) activation, but turmerones failed to inhibit NF-κB activation. However, like curcuminoids, turmerones were found to be active in suppression of cancer cell growth. Interestingly, suppression of cancer cell growth by curcuminoids and turmerones did not correlate with their ability to modulate ROS production.

Ar-turmerone, β-turmerone, and curlone isolated from turmeric have been shown to exhibit potent anticancer and anti-inflammatory activities [54–56]. *Ar*-turmerone was found to suppress LPS-induced expression of COX-2 and iNOS in macrophages [54]. Recently, Park et al. [57] examined the effects of *ar*-turmerone on 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced expression of matrix metalloproteinase (MMP)-9 and COX-2 in breast cancer cells. *Ar*-turmerone inhibited expression of MMP-9 as well as activation of COX-2 and NF-κB, but did not affect AP-1 activation. As revealed by ChIP assay, in vivo binding activities of NF-κB to the MMP-9 and COX-2 promoter were significantly inhibited by *ar*-turmerone. In addition, *ar*-turmerone reduced the phosphorylation of PI3K/Akt and extracellular signal-regulated kinase (ERK)1/2 signaling. TPA-induced invasion, migration, and colony formation in human breast cancer cells was also inhibited by turmerone.

In cultured LPS-activated mouse macrophages, β-turmerone and *ar*-turmerone exhibited potent COX-2 (β-turmerone, IC_{50}: 1.6 μg/mL; *ar*-turmerone, IC_{50}: 5.2 μg/mL) and iNOS (β-turmerone, IC_{50}: 4.6 μg/mL; *ar*-turmerone, IC_{50}: 3.2 μg/mL) inhibitory activity at a concentration comparable to that of curcumin [54]. In one study, the antineuroinflammatory properties of *ar*-turmerone in LPS-stimulated BV-2 microglial cells were investigated [58]. *Ar*-turmerone inhibited the LPS-induced expression of proinflammatory cytokines and chemokines, PGE_2, NO, and

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ROS production and MMP-9 enzymatic activity in microglial cells through modulation of c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK), and NF-κB activation. *Ar*-turmerone induced HO-1 and Nrf-2 activation and phosphorylation of CREB by upregulating cAMP levels in microglial cells.

Interestingly, *ar*-turmerone was found to be more potent than was aspirin in inhibiting platelet aggregation induced by collagen and arachidonic acid [59]. Antiplatelet activity of turmerones was also independently confirmed by another group in a myocardial-ischemia-reperfusion model [60]. In animal models, anti-inflammatory activity of *ar*-turmerone was examined by Liju et al. [48]. They showed significant reduction in paw thickness in carrageenan, dextran-induced acute inflammation, and formalin-induced chronic inflammation in mice.

Besides the above activities, *ar*-turmerone has shown anticancer activity as indicated by its ability to inhibit the growth of human leukemia cells [56]. *Ar*-turmerone induced apoptotic body formation and DNA fragmentation in leukemia cells but not in cells from human gastric cancer cell lines. Why this turmerone selectively kills leukemic cells but not gastric cancer cells, however, is unclear. That *ar*-turmerone can induce apoptosis in various leukemic cell lines was also independently reported by another group [61]. Other reports showed that these apoptotic effects of *ar*-turmerone are mediated through induction of bax and p53 and activation of mitochondrial cytochrome C and caspase-3 [62]. Besides leukemia, *ar*-turmerones have also been shown to suppress the proliferation of human breast cancer cells [63], while stimulating the proliferation of normal human peripheral blood lymphocytes. Apoptosis in breast cancer cells was confirmed by DNA fragmentation and caspase activation.

Ar-turmerone was also found to induce apoptosis in human hepatocellular carcinoma cells [64]. *Ar*-turmerone induced apoptosis through ROS production, mitochondrial membrane potential dissipation, increased Bax and p53 upregulated modulator of apoptosis (PUMA) levels, Bax mitochondrial translocation, cytochrome c release, Fas and death receptor 4 (DR4) augmentation, and caspase-3, caspase-8, and caspase-9 activation. Exposure to caspase inhibitors, Fas-antagonistic antibody, DR4 antagonist, and furosemide (a blocker of Bax translocation) effectively abolished *ar*-turmerone-triggered apoptosis. Moreover, *ar*-turmerone stimulated JNK and ERK phosphorylation and activation; treatment with JNK and ERK inhibitors markedly reduced PUMA, Bax, Fas, and DR4 levels and reduced apoptosis but not ROS generation. Furthermore, antioxidants attenuated *ar*-turmerone-mediated ROS production; mitochondrial dysfunction; JNK and ERK activation; PUMA, Bax, Fas, and DR4 expression; and apoptosis. Thus *ar*-turmerone induced apoptosis in human hepatocellular carcinoma cells through ROS-mediated activation of ERK and JNK kinases.

Turmerones have also been shown to suppress TNF-induced adhesion of inflammatory cells to endothelial cells [65]. These observations formed the basis of in vivo studies in which the authors examined the effect of *ar*-turmeone on inflammation-induced carcinogenesis in mice. The group found that turmerones prevented inflammation-based carcinogenesis in a mouse model. This effect of turmerone was mediated by suppressing the infiltrating cells and expression of iNOS or by suppressing the formation of 8-hydroxy-2′-deoxyguanine (8-OHdG) in the infiltrated cells. Furthermore, turmerones sustained the reducing activity in the inflammatory lesion.

Ar-turmerones have also been found to exert positive modulation on murine dendritic cells [66]. *Ar*-turmerones induced phenotypic maturation as evidenced by increased expression of CD86, CD40, CD83, CD80, and MHC II. Functional tests showed that the activity of acidic phosphatase inside the dendritic cells was downregulated after treatment with turmerone. An increase in the production of IL-12 and TNF-α was also noted. These data suggested that *ar*-turmerones could promote phenotypic and functional maturation of dendritic cells and that this adjuvant-like activity may have potential therapeutic value.

Ar-turmerone has also been linked with antidiabetic activity in type 2 diabetic mice through its binding to and activation of PPAR-γ [20, 67]. Turmerones were also found to inhibit the key enzymes linked to type 2 diabetes [68]. The ability to inhibit glucosidase activities has been linked with antidiabetic activity, and turmerones inhibited glucosidase enzymes more effectively than the reference standard drug acarbose. Furthermore, *ar*-turmerone exhibited potent α-glucosidase (IC_{50}, 0.28 μg) and α-amylase (IC_{50}, 24.5 μg) inhibitory activities.

In addition, *ar*-turmerone was found to inhibit α-melanocyte-stimulating hormone and 3-isobutyl-1-methylxanthine-induced melanogenesis in melanoma cells [69]. Interestingly, *ar*-turmerone exhibited stronger antimelanogenic effects than curcumin. These results suggest that *ar*-turmerone may be a useful therapeutic agent for treating hyperpigmentation disorders such as freckles and melasma and a beneficial additive in whitening cosmetics.

Besides these activities, turmeric oil present in turmeric has been shown to enhance the bioavailability of curcumin almost sevenfold in humans [70]. This may be because *ar*-turmerones are known to enhance the absorption of curcumin by the cells by modulating the activity of P-glycoprotein [71].

3.4 Anti-inflammatory and anticancer activities of elemene

Numerous studies have suggested that elemenes from turmeric possess anti-inflammatory and anticancer potential. Among all the active compounds isolated from turmeric, β-elemene was the first to be linked with anticancer properties [72]. This agent can inhibit the proliferation of a wide variety of tumor cells, including those of non small cell lung cancer [73–77], ovarian carcinoma [78], laryngeal cancer [79],

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human cervix epitheloid carcinoma [80], melanoma [80], prostate cancer [81], glioblastoma [82–85], leukemia [86–89], breast cancer [90], colorectal adenocarcinoma [91], brain carcinoma [92], and hepatoma [93]. How β-elemene mediates its antitumor effects against this wide variety of cancer cells has been examined. This compound appears to modulate multiple cell signaling pathways by decreasing the expression of antiapoptotic proteins such as Bcl-2 [73, 76, 81, 87], survivin [74], cFLIP [86], VEGF [94], Hsp90/Raf-1 [85], and HIF-1α [74] and by upregulating growth inhibitory and apoptotic proteins such as MKK3, MKK6 [83], and p38 MAPK [84]. β-elemene was also found to suppress the mTOR pathway [80]. The effects of β-elemene against cancer cells was not restricted to in vitro studies; it exhibited activities in in vivo mouse models of laryngeal cancer [79], lung adenocarcinoma [74], and hepatocellular carcinoma [93].

β-elemene was also found to enhance the effect of various chemotherapeutic agents such as cisplatin [78, 82], etoposide [77], tamoxifen [90], arsenic trioxide [88], and gefitinib [75]. Interestingly, β-elemene was found to easily cross the blood–brain barrier [95] and thus can exhibit effects against brain carcinoma [92].

β-elemene was also found to exhibit anti-inflammatory activities in various systems, as indicated by its ability to downregulate IL-17 and IFN-γ in experimental autoimmune encephalomyelitis [96] and by acting as an anti-ulcer agent in gastric ulcer models of rodents [97]. β-elemene was also found to downregulate serum TNF-α levels and hepatic CD14 expression in rats with liver fibrosis [98]. Thus these studies clearly demonstrate that β-elemene exhibits both anti-inflammatory and anticancer activities. In China, elemene is approved for the treatment of cancer [99].

3.5 Anti-inflammatory and anticancer activities of furanodiene

Furanodiene is another active component of turmeric oil that exhibits anti-inflammatory activity. In one study, furanodiene and furanodienone were shown to suppress TPA-induced inflammation of mouse ears by 75 and 53%, respectively, at a dose of 1.0 μmol [100]. Interestingly, the activities of furanodiene and furanodienone were comparable to those of indomethacin, the normally used anti-inflammatory agent. Furanodienone has been shown to suppress the proliferation of a wide variety of tumor cells including hepatocellular carcinoma [101], leukemia [102], uterine cervical cancer [103], and breast cancer [104] cells. Furanodiene-induced apoptosis is mediated through caspase activation, DNA fragmentation, and p38 MAPK activation. In a recent study, furanodiene significantly inhibited proliferation and increased lactate dehydrogenase release in breast cancer cells [105]. Depolarization in mitochondrial membrane potential, chromatin condensation, and DNA fragmentation were also observed after furanodiene treatment. Furanodiene induced cell cycle arrest at the G0/G1 phase and significantly inhibited the expression of p-cyclin D1, total cyclin D1, p-CDK2, total CDK2, p-Rb, total Rb, Bcl-xL, and Akt. The protein expressions of Bad and Bax, and proteolytic cleavage of caspase-9, caspase-7, and poly ADP ribose polymerase (PARP), were dramatically increased. Furthermore, caspase inhibitor markedly reversed furanodiene-induced cell cytotoxicity, proteolytic cleavage of caspase-9, and DNA fragmentation but did not affect the proteolytic cleavage of PARP, whereas an Akt inhibitor enhanced furanodiene-induced cytotoxicity and PARP cleavage. In addition, furanodiene dose-dependently suppressed tumor growth in vivo, achieving 32 and 54% inhibition rates after intraperitoneal injection of 15 and 30 mg/kg, respectively. Furanodiene was also shown to upregulate TNFR1 [102] and exhibited strong anti-angiogenic activity on endothelial cells [106]. When examined for pharmacokinetics, it was found to be highly bioavailable, with oral bioavailability of 49% at 10 mg/kg in rats [107].

3.6 Anti-inflammatory and anticancer activities of curdione

Curdione belongs to the family of monocyclic monoterpenes with one ring in the isoprene chain. Curdione was found to inhibit the production of PGE2 in LPS-stimulated mouse macrophages through the suppression of COX-2 expression [108].

3.7 Anti-inflammatory and anticancer activities of bisacurone

Bisacurone has been found to exhibit antioxidant, anti-inflammatory, and antimetastatic activities [109]. Bisacurone downregulated TNF-induced vascular cell adhesion molecule-1 (VCAM-1) expression in human umbilical vein endothelial cells [109]. In addition, bisacurone inhibited ROS generation and NF-κB activation induced by TNF. Bisacurone also inhibited phosphorylation of Akt and PKC and decreased adhesion of human monocytes and oral cancer cells to human umbilical vein endothelial cells stimulated by TNF. All these results suggest that bisacurone may exhibit anticancer activity through the downmodulation of pro-inflammatory pathways.

3.8 Anti-inflammatory and anticancer activities of cyclocurcumin

Cyclocurcumin is a newly identified curcuminoid from the rhizome of *C. longa*. This agent exhibited synergistic activity with curcumin as a nematocidal agent [9]. Cyclocurcumin was also found to inhibit the proliferation of human breast cancer MCF-7 cells [110]. More recently light-induced *trans*-to-*cis* isomerization of cyclocurcumin was reported [111].

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3.9 Anti-inflammatory and anticancer activities of calebin A

Calebin A is a novel curcuminoid isolated from *C. longa*. Like curcumin, this compound can inhibit cell growth and induce apoptosis in drug-resistant human gastric cancer cells [112]. How calebin mediates its effects is not clear, but authors have shown that the drug efflux function of P-glycoprotein was inhibited without affecting its expression. This agent reduced S phase and G2/M phase arrest in cells and modulated the activities of JNK, ERK, and p38 MAPK. Thus, calebin A exhibits activity against human gastric and perhaps other cancers. Like curcumin, calebin A has also been shown to protect neuronal cells from β-amyloid insult [113].

3.10 Anti-inflammatory and anticancer activities of germacrone

Germacrone, a volatile sesquiterpene isolated from turmeric, inhibits the growth of a variety of cancer cells. Zhong et al. [114] showed that germacrone can inhibit the proliferation of breast cancer cells by inducing cell cycle arrest and promoting apoptosis. Germacrone increased lactate dehydrogenase release and induced depolarization in mitochondrial membrane potential in both MCF-7 and MDA-MB-231 cells; it also increased Bok expression and cytochrome c release from mitochondria without affecting Bcl-2, Bcl-xL, Bax, or Bim expression. This agent also induced caspase-3, caspase-7, and caspase-9 activation and PARP cleavage. Similar results were found by another group who used a mixture of furanodienone, germacrone, and furanodiene, resulting in suppressed growth of breast cancer cells [104].

Liu et al. [115] showed that this compound can inhibit the growth of human hepatoma cells by inducing G2/M cell cycle arrest and promoting apoptosis. This activity was associated with decreased expression of cyclin B1 and its activating partner CDK1, with concomitant induction of p21, upregulation of Bax, downregulation of Bcl-2/Bcl-xL, and upregulation of p53 and ROS.

Finasterides are androgen antagonists and are used for prevention of prostate cancer. In one study, Suphrom et al. [116] examined the antiandrogenic effect of six sesquiterpenes—germacrone, zederone, dehydrocurdione, curcumenol, zedoarondiol, and isocurcumenol—in prostate cancer cells. The sesquiterpenes inhibited 5α-reductase, which converts testosterone to dihydrotestosterone. Germacrone was found to be most potent (IC_{50}, 0.42 ± 0.05 mg/mL) and exhibited antiandrogenic activities in LNCaP cells. Furthermore, the activity profile of germacrone was comparable to that of finasteride. Because germacrone did not bind to the androgen receptor, it was suggested that inhibition of 5α-reductase activity contributed to its antiandrogenic effects. Curcumenol suppressed the proliferation of liver cancer and endometrial carcinoma cells [117] and strongly inhibited CYP3A4 in vitro [118].

Germacrone exhibited anti-inflammatory activity in carrageenin-induced edema in rats and acetic acid-induced vascular permeability as well as the writhing symptom in mice [119]. An assay of carrageenin-induced hind paw edema in rats by another group revealed the anti-inflammatory activity of germacrone [120]. Matsuda et al. [121] reported the protective effect of germacrone on D-galactosamine (D-GalN)/LPS-induced acute liver injury in mice. Germacrone also inhibited D-GalN-induced cytotoxicity in primary cultured rat hepatocytes and LPS-induced NO production in cultured mouse peritoneal macrophages [121]. In a later study, the same group investigated the effect of germacrone and curcumin on liver injury induced by D-galactosamine/LPS or TNF-α [122]. Germacrone and curcumin inhibited the increase in serum aspartate aminotransaminase and alanine aminotransaminase at a dose of 50 mg/kg (p.o.). Another activity that has been assigned to turmeric is its ability to inhibit cytochrome P450 (CYP). Bamba et al. [123] showed that (4S,5S)-(+)-germacrone-4,5-epoxide inhibits certain subtypes of cytochrome P450 more potently than or at levels comparable to those of curcumin and demethoxycurcumin.

3.11 Anti-inflammatory and anticancer activities of other turmeric compounds

In addition to compounds discussed, monoterpenes from turmeric may also account for its activities. The most common of these monoterpenes are ascaridol [124], borneol [125], carvacrol [126, 127], carvone [128], cymene [129], geraniol [130], limonene [131], linalool [132], α-pinene [133], terpinolene [134], and thymol [135]. Among these monoterpenes, carvacrol, geraniol, and limonene have received considerable attention over the years. These monoterpenes are not specific to turmeric and are present in the essential oil from other plants. However, because of demonstrated potential, these monoterpenes might contribute to turmeric's anticancer and anti-inflammatory activities.

4 Conclusions

All of these studies support the fact that besides curcumin, turmeric contains numerous other compounds that exhibit anti-inflammatory and anticancer activities. CFT also possesses anti-inflammatory and anticancer activities. It is also clear that some of these compounds exhibit activities that are distinct from curcumin, whereas other compounds' activities are similar to those of curcumin. Some components of turmeric appear to be as potent as, or even more potent than, nonsteroidal anti-inflammatory drugs. Some components have been shown to act synergistically with curcumin by increasing uptake by the cells through modulation of P-glycoprotein. More than 60 different clinical trials of curcumin have been completed, and a few have also been

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done using turmeric. These clinical trials have unequivocally demonstrated the safety, tolerability, and nontoxicity of both curcumin and turmeric at gram dose levels. However, none of the clinical trials have been performed using turmeric components other than curcumin. Based on the depth of the preclinical data on turmerones, elemene, furanodiene, and germacrone, we believe that these noncurcumin components needs to be further evaluated first in preclinical setting before they can be tested in humans. Therefore, the future studies should be directed toward evaluating the clinical efficacy of noncurcumin components of turmeric.

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