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Biological activities of curcumin and its analogues (Congeners) made by man and Mother Nature

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ABSTRACT

Curcumin, a yellow pigment present in the Indian spice turmeric (associated with curry powder), has been linked with suppression of inflammation; angiogenesis; tumorigenesis; diabetes; diseases of the cardiovascular, pulmonary, and neurological systems, of skin, and of liver; loss of bone and muscle; depression; chronic fatigue; and neuropathic pain. The utility of curcumin is limited by its color, lack of water solubility, and relatively low in vivo bioavailability. Because of the multiple therapeutic activities attributed to curcumin, however, there is an intense search for a “super curcumin” without these problems. Multiple approaches are being sought to overcome these limitations. These include discovery of natural curcumin analogues from turmeric; discovery of natural curcumin analogues made by Mother Nature; synthesis of “man-made” curcumin analogues; reformulation of curcumin with various oils and with inhibitors of metabolism (e.g., piperine); development of liposomal and nanoparticle formulations of curcumin; conjugation of curcumin prodrugs; and linking curcumin with polyethylene glycol. Curcumin is a homodimer of feruloyl-methane containing a methoxy group and a hydroxyl group, a heptadiene with two Michael acceptors, and an α,β -diketone. Structural homologues involving modification of all these groups are being considered. This review focuses on the status of all these approaches in generating a “super curcumin.”

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1. Introduction

Curcumin, commonly called diferuloyl methane, is a hydrophobic polyphenol derived from the rhizome (turmeric) of the herb *Curcuma longa*. Turmeric has been used traditionally for many ailments because of its wide spectrum of pharmacological activities. Curcumin has been identified as the active principle of turmeric; chemically, it is a bis- α,β -unsaturated

β -diketone that exhibits keto-enol tautomerism. Curcumin has been shown to exhibit antioxidant, anti-inflammatory, antimicrobial, and anticarcinogenic activities. It also has hepatoprotective and nephroprotective activities, suppresses thrombosis, protects against myocardial infarction, and has hypoglycemic and antirheumatic properties. Moreover, curcumin has been shown in various animal models and human studies to be extremely safe even at very high doses [1–12]. In

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spite of its efficacy and safety, curcumin has not yet been approved as a therapeutic agent. The poor aqueous solubility, relatively low bioavailability, and intense staining color of curcumin have been highlighted as major problems; and consequently search for a “super curcumin” without these problems and with efficacy equal to or better than that of curcumin is ongoing. This review presents the current status of the efforts toward finding this “super curcumin.”

The strategies used in the search for “super curcumin” can be categorized under two broad headings, namely (1) synthetic analogues or derivatives and (2) formulations. The most explored of these two is the analogues and derivatives. The literature describes numerous synthetic curcumin analogues with a wide range of applications. This review analyzes the curcumin analogues with special reference to their biological activity. The formulation part of this review describes the adjuvant, nanoparticle, liposomal and micellar delivery systems, phospholipid complexes, prodrugs and PEGylation of curcumin.

2. Analogues and derivatives

Curcumin is a member of the linear diarylheptanoid class of natural products in which two oxy-substituted aryl moieties are linked together through a seven-carbon chain (Fig. 1). The C₇ chain of linear diarylheptanoids is known to have unsaturation, oxo functions, enone moiety, and a 1,3-diketone group. Except for the oxo and hydroxy functions, the C₇ chain is generally unsubstituted. This unsaturation in the linker unit

has an E-configuration (*trans* C=C bonds). The aryl rings may be symmetrically or unsymmetrically substituted; the most prevalent natural substituents are of the oxy type, such as hydroxy or methoxy elements. In this review, the curcumin analogues are classified in three groups: analogues from turmeric, analogues from Mother Nature, and synthetic analogues.

2.1. Natural analogues from turmeric and its metabolites

The natural analogues of curcumin from turmeric and the important metabolites of curcumin are depicted in Fig. 1. The bioactivities of these analogues are summarized in Table 1.

2.1.1. Natural analogues from turmeric

Turmeric contains three important analogues, curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC). Collectively called curcuminoids, the three compounds differ in methoxy substitution on the aromatic ring. While curcumin has two symmetric *o*-methoxy phenols linked through the α,β -unsaturated β -diketone moiety, BDMC, also symmetric, is deficient in two *o*-methoxy substitutions, and DMC has an asymmetric structure with one of the phenyl rings having *o*-methoxy substitution. Of the three curcuminoids, curcumin is the most abundant in turmeric, followed by DMC and BDMC. Commercially available curcumin mixture contain 77% curcumin, 17% DMC, and 3% BDMC.

A lesser known curcuminoid from turmeric is cyclocurcumin, first isolated and characterized by Kiuchi et al. [13]. Structurally, cyclocurcumin differs from curcumin in the β -

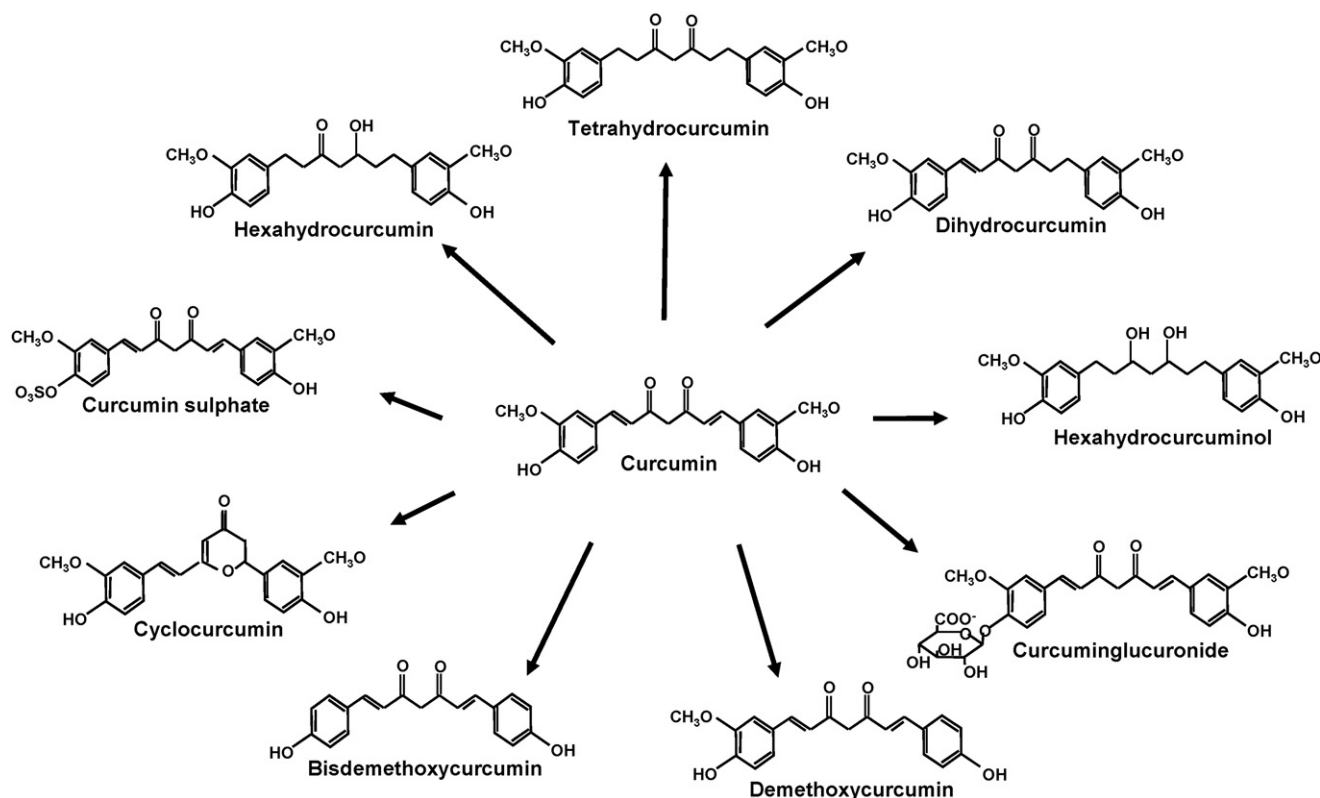


Fig. 1 – Natural analogues from turmeric and curcumin metabolites.

Table 1 – Activities of curcumin analogues derived from turmeric and of curcumin metabolites

- BDMC is more active than DMC or curcumin for cytotoxicity against ovarian cancer cells [32]
- BDMC is less active than curcumin or DMC as an antioxidant and as an oxidative DNA cleaving agent [15]
- BDMC is less active than curcumin or DMC as an inhibitor of peroxynitrite scavenger [16]
- BDMC was most active when compared with DMC or curcumin for antimutagenic and anticarcinogenic activity [31]
- BDMC is more active than curcumin or DMC for antitumor and antioxidant activity [24]
- BDMC is more active than curcumin or DMC for suppression of carcinogenesis [31]
- BDMC was more active than curcumin for reducing nicotine-induced oxidative stress [121]
- BDMC improved innate immunity and transcription of MGAT-III and Toll-like receptors in AD pts [29]
- BDMC is more active than curcumin for modulation of MDR1 gene [58]
- BDMC is less active than curcumin or DMC in inhibiting singlet oxygen-induced DNA damage [18]
- BDMC is less active than curcumin or DMC in binding and inhibiting Pgp and sensitizing cells to vinblastin [35]
- BDMC is less active than curcumin or DMC in binding and inhibiting MRP1 and sensitizing cells to etoposide [37]
- BDMC was more active than curcumin or DMC in protecting nerve and endothelial cells from beta amyloid-induced oxidative stress [27]
- BDMC prevents DMH induced colon carcinogenesis [67]
- BDMC is as active as curcumin in preventing DMH induced colon carcinogenesis [36]
- BDMC is more active than curcumin in preventing alcohol and PUFA-induced oxidative stress [99]
- BDMC is more active than curcumin in preventing CCL4-induced hepatotoxicity in rats [122]
- BDMC is more active than curcumin in preventing alcohol and PUFA-induced cholesterol, TGs, PLs and FFA [104]
- BDMC, curcumin, and DMC exhibit equivalent activity in suppression of blood glucose levels in diabetic mice through binding to PPAR- γ [25]
- BDMC is less active than curcumin and DMC in protecting rats from lead-induced neurotoxicity [28]
- BDMC is less active than curcumin and DMC in suppressing NF- κ B activation [30]
- BDMC is more active than DMC or curcumin in inducing NRF2-mediated induction of heme oxygenase-1 [36]
- BDMC is least active than DMC or curcumin in inducing p38 MAPK mediated induction of heme oxygenase-1 [23]
- BDMC is least active than DMC or curcumin in inhibiting H₂O₂-induced lipid peroxidation and hemolysis of erythrocytes [21]
- BDMC is least active than DMC or curcumin in inhibiting the proliferation of VSMC induced by ox-LDL and induction of LDL-R [21]
- BDMC is least active than DMC or curcumin in inhibiting the liposomal peroxidation; and of COX1 and COX2 activity [20]
- DMC is more potent than curcumin, BDMC and cyclocurcumin in inhibiting proliferation of breast cancer cells [14]
- DMC is more potent than curcumin and BDMC in inducing nematocidal activity [13]
- THC is less potent than curcumin in inhibiting the activity of 5-LOX; but more potent than curcumin in inhibiting COX-dependent arachidonic acid metabolism [60]
- THC is more active than curcumin in preventing DMH-induced ACF formation in mice [61]
- THC does not induces ROS production and membrane mobility coefficient but curcumin does [185]
- THC is less active than curcumin in preventing PMA-induced skin tumor promotion in mice [33]
- THC is more active than curcumin as an antioxidant [39]
- THC is less active than curcumin as an antioxidant [186]
- THC is less active under aerated condition than curcumin but under N₂O purged conditions, THC is more active than curcumin in suppressing radiation-induced lipid peroxidation [41]
- THC was less active than curcumin, DMC or BDMC in suppressing NF- κ B activation [30]
- THC, HHC, OHC are less active than curcumin in suppressing NF- κ B activation [59]
- THC is more active than curcumin in suppressing nitrilotriacetate-induced oxidative renal damage [43]
- THC is more active than curcumin in protecting from chloroquine-induced hepatotoxicity in rats [45]
- THC is more active than curcumin in preventing brain lipid peroxidation in diabetic rats [51]
- THC is more potent than curcumin for antioxidant and antidiabetic effects in rats [48]
- THC is more potent than curcumin for modulation of renal and hepatic functional markers in diabetic rats [56]
- THC is more potent than curcumin for modulation of blood glucose, plasma insulin and erythrocyte TBARS in diabetic rats [55]
- THC is more potent than curcumin in decreasing blood glucose and increasing plasma insulin in diabetic rats [50]
- THC is less potent than curcumin in modulation of ABC drug transporters [58]
- THC's effect was comparable with curcumin on reduction of accumulation and cross-linking of collagen in diabetic rats [53]
- THC exhibits stronger antioxidant activity than HHC=OHC > curcumin > DMC > BDMC [17]
- THC was more potent than curcumin in suppressing LDL oxidation [42]
- THC is more active than curcumin in suppressing lipid peroxidation of erythrocyte membrane ghosts [40]
- Cyclocur exhibits weak anticancer activity [14]

Note: BDMC, bisdemethoxycurcumin; COX, cyclooxygenase; DMC, demethoxycurcumin; HHC, hexahydrocurcumin; LDL, low-density lipoproteins; NF- κ B, nuclear factor kappa B; OHC, octahydrocurcumin; ROS, reactive oxygen species; THC, tetrahydrocurcumin.

diketone link. In this molecule, the α,β -unsaturated β -diketone moiety of curcumin is replaced by an α,β -unsaturated dihydropyranone moiety. To date, not many biological studies on cyclocurcumin have been reported; in one study, Simon et al. [14] reported that this analogue was ineffective in inhibiting MCF-7 tumor cell proliferation and arrest of cell cycle progression.

In the last few decades, efforts have been made to isolate curcuminoids from different sources, including *Curcuma longa*,

Curcuma zedoaria, and *Curcuma aromatica*. Several research groups have investigated and compared their antioxidant, cardioprotective, neuroprotective, antidiabetic, antitumor, and chemopreventive activities, employing them either individually or as mixtures. The curcuminoids have been shown to be scavengers of free radicals and reactive oxygen species (ROS), such as hydroxyl radicals, superoxide radicals, singlet oxygen, peroxy radicals, and peroxynitrite, whose production is implicated in the induction of oxidative stress

[15–19]. They efficiently neutralized the stable free radical 1,1-diphenyl-2-picryl-hydrazyl (DPPH), and this reaction is often used in comparing the antioxidant activities of different compounds [16,17]. Although all three are highly reactive in these scavenging reactions, curcumin is more efficient than DMC or BDMC.

Curcuminoids exhibit differential antioxidant activity in several *in vitro* and *in vivo* models. They inhibited lipid peroxidation in a variety of models such as rat brain homogenates, rat liver microsomes, erythrocytes, liposomes, and macrophages, where peroxidation is induced by Fenton reagent, as well as metals, H_2O_2 , and 2,2'-azo-bis(2-amidino-propane) hydrochloride (AAPH) [15,17,18,20–22]. They prevented singlet oxygen-stimulated DNA cleavage in plasmid pBR322 DNA [18], significantly reduced H_2O_2 - and AAPH-induced hemolysis of erythrocytes [17], and attenuated H_2O_2 -mediated endothelial cell viability [23]. Curcuminoids were able to inhibit cyclo-oxygenase (COX)-1 and (COX)-2 enzymes [20] and reduce AAPH-induced conjugated diene formation during linoleic acid oxidation [17]. In most of these actions, BDMC was less active than the other two, and curcumin was the most potent of the three.

In a different *in vivo* study, BDMC was found to be more effective than curcumin and DMC in increasing the life span of Swiss albino mice bearing Ehrlich ascites and in reducing lipid peroxidation and superoxide generation in their macrophages [24]. Interestingly, curcuminoids could also act as pro-oxidants. A report by Ahsan et al. [15] compared pro-oxidant activities of the curcuminoids by measuring their abilities to enhance Cu(II)-induced cleavage of plasmid pBR322 DNA through production of ROS. Of the three curcuminoids examined, curcumin was more effective than DMC and BDMC in inducing DNA cleavage.

Curcumin, DMC, and BDMC exhibit cardioprotective, antidiabetic, and nematocidal activities. The three compounds inhibited proliferation of bovine vascular smooth muscle cells stimulated by oxidized low-density lipoproteins (LDL) and delayed development of arteriosclerosis [25]. Again, curcumin was the most efficient cardioprotective agent of the three. Turmeric extract containing the three curcuminoids could cause lowering of the blood glucose level in type 2 diabetic KK-A^y mice, and its hypoglycemic effect improved when administered in combination with sesquiterpenes [26]. It is the binding of curcuminoids to peroxisome proliferator-activated receptor- γ (PPAR- γ) and their acting as PPAR- γ agonists that are responsible for their hypoglycemic effect. The three curcuminoids individually did not show nematocidal activity against *Toxocara canis*, but their nematocidal activity increased remarkably when they were combined, suggesting a synergistic action [13].

The neuroprotective effects of curcuminoids have been investigated by various groups. Curcumin, DMC, and BDMC protected PC12 rat pheochromocytoma and normal human umbilical vein endothelial cells against β -amyloid-induced oxidative stress even better than α -tocopherol [27]. Curcuminoids have been found to be inhibitors of lead acetate (Pb(II))-induced neurotoxicity in primary hippocampal neurons [28]. They decreased lipid peroxidation, improved neuron viability, and prevented decrease in glutathione levels in rat brain. Under similar treatment concentrations, curcumin was the

most effective, DMC moderately effective, and BDMC the least effective. Curcumin and DMC, but not BDMC, reduced Pb(II)-induced memory deficits in rats. BDMC, on the other hand, exhibited potent immunostimulatory effects and was able to correct immune defects of Alzheimer's disease patients by enhancing phagocytosis of β -amyloid and regulation of the transcription of β -1,4-mannosyl-glycoprotein 4- β -N-acetylglucosaminyl transferase and toll-like receptors [29].

Several *in vitro* and *in vivo* comparisons of the anti-inflammatory and antitumor properties of curcuminoids have been reported. The activities varied depending on the type of tumor and carcinogen employed. Curcumin, DMC, BDMC, and a curcumin mix inhibited proliferation of a wide variety of tumor cells, including leukemia, lung cancer, head and neck cancer, pancreatic cancer, breast cancer, and prostate cancer [30]. Under identical experimental conditions, individual curcuminoids exhibited similar antiproliferative effects in all these cell lines [30]. In a separate study, however, DMC was found to be more potent than curcumin or BDMC in inhibiting proliferation of MCF-7 breast cancer cells [14].

Curcuminoids show antimutagenic and anticarcinogenic activity. They inhibited the mutagenic activity of 2-acetamidofluorene and prevented croton oil-induced skin tumor and papilloma formation in mice [31]. They significantly reduced tumor size in Swiss albino mice implanted with solid tumors [24]. Under identical treatment conditions, BDMC showed greater antitumor, antipromoter, and anticarcinogenic activities than curcumin or DMC. Similarly, in another study, the cytotoxicity of BDMC against human ovarian cancer cell line OVCAR-3 was more pronounced than that of curcumin or DMC [32]. Curcumin and DMC had approximately the same potency in inhibiting 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation of mouse ears as well as TPA-induced transformation of cultured JB6 (P+) cells, while the activity of BDMC was less [33].

P-glycoprotein (Pgp) is a member of the ATP-dependent drug efflux protein pump (ABC transporter protein) superfamily, linked to multidrug resistance (MDR) in cancer cells. Curcumin, DMC, and BDMC had the ability to modulate the function of Pgp in multidrug-resistant human cervical carcinoma cell line KB-V1. The three curcuminoids were not effluxed by the Pgp transporter protein. At non-toxic doses, the curcuminoids increased the sensitivity of cells to the chemotherapeutic agent vinblastine. Of the three, curcumin was the most effective in retaining the drug [34]; it also is an effective MDR modulator [35]. The few and mild side effects associated with curcuminoids make them attractive alternatives for better MDR modulation. Current research is investigating how these structurally related curcuminoids modulate antioxidant, anti-inflammatory, and antiproliferative responses, with the principal aim of evaluating their mechanisms of action.

Curcumin and DMC were more effective than BDMC in inducing p38 MAPK-mediated heme oxygenase-1 (HO-1) expression and activity in human endothelial cells [23]. On the other hand, another related study reported that BDMC was more active than either curcumin or DMC in inducing NRF-2-mediated induction of HO-1 [38].

A recent study by Sandur et al. [30] reported that curcumin, DMC, and BDMC exhibited differential abilities in regulation of

anti-inflammatory and antiproliferative responses and ROS generation in chronic myeloid leukemia cell line KBM-5. Their relative potencies for suppression of tumor necrosis factor (TNF)-mediated nuclear factor- κ B (NF- κ B) activation are curcumin > DMC > BDMC. Under similar experimental conditions, a mixture of curcuminoids showed better activity than any of the individual curcuminoids. However, the ROS-generating ability of curcuminoids in the same cells did not correlate with either anti-inflammatory or antioxidant activity, and BDMC generated the highest quantities of ROS. Curcumin and DMC induced glutathione level to a similar extent, whereas BDMC was the least effective in inducing glutathione, indicating that the anti-inflammatory and antiproliferative activities of curcuminoids are independent of their redox-modulatory property.

2.1.2. Curcumin metabolites

Various metabolites of curcumin have been reported, including dihydrocurcumin (DHC), tetrahydrocurcumin (THC), hexahydrocurcumin (HHC), octahydrocurcumin (OHC), curcumin glucuronide, and curcumin sulfate (see Fig. 1). THC, a partially reduced derivative of curcumin not found in turmeric, is one of the major metabolites of curcumin. Other reduced forms of curcumin, HHC and OHC, have also been considered curcumin metabolites, but have not been examined as extensively as THC. THC is obtained by partial hydrogenation of curcumin; it is colorless and more hydrophilic than curcumin. THC exhibits greater antioxidant potential than curcumin in most models and presently is considered to be one of the factors responsible for the *in vivo* antioxidant activity of curcumin (see Table 1).

THC scavenged several free radicals, such as *t*-butoxyl radicals, peroxy radicals, and DPPH radical, better than the curcuminoids and was more effective in inhibiting AAPH-induced red blood cell hemolysis and lipid peroxidation in rabbit erythrocyte membrane ghosts and rat liver microsomes [39,40]. The relative activities of THC and curcumin in inhibiting gamma radiation-induced lipid peroxidation in rat liver microsomes varied depending on the level of oxygen present [41]. THC is useful as a functional food factor because of its cardioprotective ability, which is even greater than that of curcumin [42]. It inhibited oxidative modification of LDL and showed protective effects against oxidative stress in cholesterol-fed rats [42]. The ability of THC to suppress nitrolotriacetate-induced oxidative renal damage was greater than that of curcumin [43].

Administration of THC to mice at an oral dose of 80 mg/kg body weight for nearly 15 days reduced hepatotoxicity induced by the commonly used antibiotic erythromycin estolate and the antimalarial drug chloroquine [44–47]. At the same dose for nearly 45 days, THC showed an antihyperlipidemic effect in streptozotocin-nicotinamide-induced oxidative stress in diabetic rats [48–54]. The membrane-bound antioxidant enzymes, which were decreased in these mice, increased significantly on THC treatment. Oral administration of THC also prevented changes in the levels of fatty acids, glucose, and insulin in the blood of diabetic rats [55,56]. These studies reported that THC significantly decreased lipid peroxidation in different tissues of these rats. All these studies confirmed that THC, when compared with similar treatment doses of curcumin, had much greater antidiabetic effects.

THC was ineffective in producing intracellular ROS in human gingival fibroblasts, human submandibular gland carcinoma cells [57], and KBM-5 cells [30]. THC is less potent than curcumin in modulating ABC drug transporters [58]. It failed to inhibit TNF-induced NF- κ B activation in KBM-5 and RAW cells [30,59]. THC is less active than the curcuminoids in preventing TPA-induced tumor promotion in mouse skin and inflammation of mouse ears and less active than curcumin in preventing phorbol 12-myristate 13-acetate (PMA)-induced skin tumor promotion in mice [33]. On the other hand, THC was as effective as curcumin in inhibiting the release of arachidonic acid and its metabolites, formation of prostaglandin E₂, and lipopolysaccharide (LPS)-induced COX-2 expression in RAW cells [60]. THC exhibited chemopreventive activity by inhibiting 1,3-dimethylhydrazine-induced putative preneoplastic aberrant crypt foci development in colons of mice [61].

2.1.3. Structure-activity correlation

Although curcumin, DMC, and BDMC differ in their chemical structures only with regard to methoxy substitution, they exhibit significantly different antioxidant, antitumor, and anti-inflammatory activities. To date there has been no systematic study that clearly correlates the physicochemical and molecular properties of the three curcuminoids with their biological activities. However, the existing literature provides some clues to understanding which group is actually responsible for a given biological activity of the curcuminoids.

Since many reports suggest that curcumin has better radical scavenging and antioxidant ability than the other two, and that DMC is superior to BDMC in this activity, the *o*-methoxy substitutions are certainly involved in this activity. The hydrogen bonding interaction between the phenolic OH and the *o*-methoxy groups in curcumin markedly influences the O–H bond energy and H-atom abstraction by free radicals, thus making it a better free radical scavenger than BDMC [17]. The ability of curcuminoids to act as antioxidants or pro-oxidants in the presence of metals such as Cu(II), Fe(II), or Pb(II) arises mainly from their chelating power [15,28]. Although transition metal-chelation by curcumin can take place through either the diketone moiety or the *o*-methoxy phenol moiety, in most cases chelation is observed only through the diketone group. Since the three curcuminoids possess similar diketone moieties, their effects on metal-induced toxicity should be similar. The *o*-methoxy group may influence the electron density on the diketo group, however, which in turn can affect their chelating ability.

The α,β -unsaturated diketone moiety in the curcuminoids is a Michael reaction acceptor, which belongs to the major class of phase-II enzyme inducers [23]. Therefore, this property may be responsible for inducing HO-1 and NF- κ B suppression in cells by curcuminoids. Methoxy substitution on the aromatic ring can significantly influence the interactions of curcuminoids with nucleophiles in the Michael reaction. The reasons and the actual mechanism of the antitumor activities of the curcuminoids are still far from understood. It is still not known why the *o*-methoxy-deficient BDMC is a more potent ROS inducer and the *o*-methoxy-substituted curcumin is a more potent suppressor of NF- κ B activation [30]. The effect of change in the lipophilicity of the

curcuminoids with methoxy substitution in influencing some of these activities also cannot be ignored.

Hydrogenation of the heptadiene moiety in curcumin to produce THC markedly increased the antioxidant activity but significantly reduced the antitumor and anti-inflammatory abilities. It is clear that the *o*-methoxy phenol groups, when not linked through conjugation with the β -diketone moiety, make the molecule a better antioxidant. This lack of conjugation in THC also can cause C–C bond cleavage at the active methylene carbon of the β -diketone group during oxidation, yielding smaller *o*-methoxy phenol derivatives that also act as antioxidants [40]. Lack of NF- κ B activity and ROS-generating ability [30] in THC clearly confirms that the α,β -unsaturated β -diketone moiety in conjugation with the aromatic rings is definitely involved in these activities.

2.2. Natural analogues made by Mother Nature

Structural variations in any lead compound are important for its physiological activity, especially if these affect its receptor-binding interactions. Structural variations also alter its pharmacokinetics, i.e., how easily the drug is absorbed, distributed, metabolized, and excreted. Extensive structure-activity relationship studies have been carried out on

the curcumin molecule, and a large number of synthetic analogues are known. The curcumin molecule is unique in its physiological effects, however, having a greater number of molecular targets than any other molecule so far reported. In order to define a drug profile of this “wonder” molecule, it is necessary that, along with its synthetic analogues, its naturally occurring analogues should be analyzed exhaustively. Fig. 2 shows a number of naturally occurring bioactive compounds having some structural similarity to the curcumin molecule, or at least having a pharmacophore containing one aryl function with 3,4 substitution, i.e., either a methoxylated phenol or catechol. These include ferulic acid, cinnamic acid, caffeic acid, chlorogenic acid, capsaicin, gingerol, paradol, zingerone, eugenol, dibenzoylmethane, dehydrozingerone, cassumuin and yakuchinone.

Although no comparative studies on the antioxidant potential of different naturally occurring analogues of curcumin are available, a look at Table 2 and Fig. 2 indicates that an ortho-methoxylated phenolic chromophore is desirable [62–64], which may be present in a single aromatic ring (e.g., ferulic acid, caffeic acid, chlorogenic acid, capsaicin, gingerols, zingerone, eugenols) or in two aromatic rings (e.g., oregonin, the potent nitric oxide synthase (iNOS) inhibitor, dehydroguaiaretic acid, yakuchinones, cassumunins). The same chro-

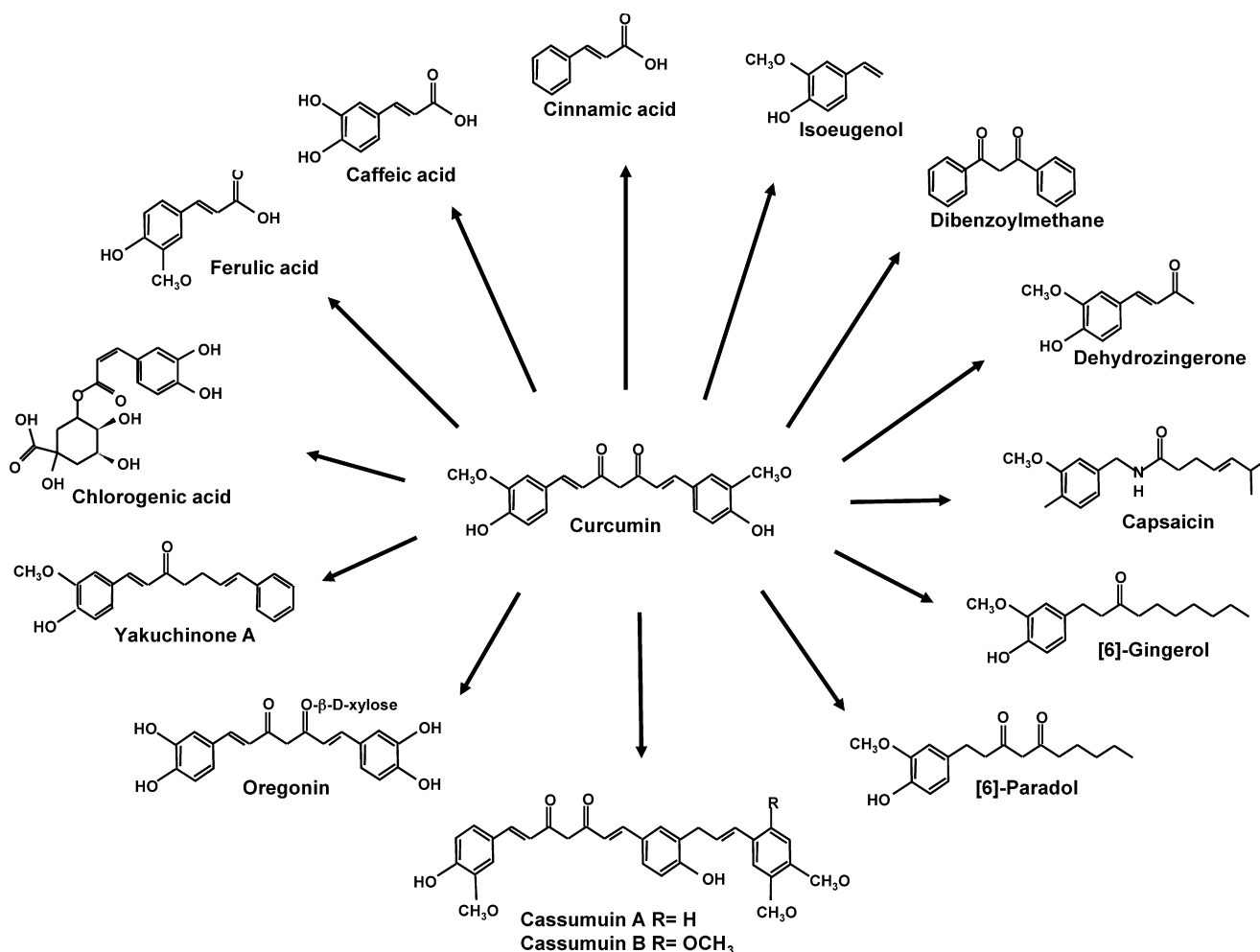


Fig. 2 – Curcumin analogues from Mother Nature.

Table 2 – Relative potency of curcumin and its analogues made by Mother Nature

- Caffeic acid and ferulic acid but not cinnamic acid are more potent than curcumin in inhibiting lipid peroxidation [65]
- Caffeic acid, ferulic acid, and chlorogenic acid are less potent than curcumin in inhibiting TPA-induced inflammation and promotion of skin tumors [66]
- Dibenzoylmethane is several times more potent (10-fold) than curcumin in inducing phase II enzymes, in inhibiting DMBA-induced mammary tumors in rodents and in inhibiting TPA-induced skin inflammation and tumor promotion [66–68,187]
- 6-gingerol is more potent (10⁷-fold) mutagen than curcumin whereas less potent in inhibiting TPA-induced inflammation, epidermal ornithine decarboxylase activity, and skin tumor promotion in mice [69,70]
- Capsaicin is more potent than curcumin in lowering acidic glycoprotein and inflammation in arthritic rats [71]
- Capsaicin and curcumin are more potent (1000-fold) than eugenol in inhibiting superoxide radical generation [72]
- Capsaicin and curcumin are equally potent in inhibiting arachidonic acid metabolism [73]
- Dehydrozingerone is less active than curcumin in inhibiting formation of conjugated dienes and spontaneous lipid peroxidation [74]
- Dehydrozingerone is as active as curcumin but less active than isoeugenol in inhibiting Epstein–Barr virus antigen early antigen activation [75]
- Yakuchinone A and B are as potent as curcumin in inhibiting LPS-induced nitric oxide production, TPA-induced superoxide production and lipid peroxidation [76,77]
- Cassumunins A and B are more active than curcumin in protecting thymocytes from H₂O₂-induced toxicity [188]

Note: DMBA: 7,12-dimethylbenz[*a*]anthracene; H₂O₂, hydrogen peroxide; LPS, lipopolysachharide; TPA, 12-O-tetradecanoylphorbol-13-acetate.

mophore is responsible for both the antioxidant and pro-oxidant properties of curcumin and its analogues, which may be due to its radical-generating or hydrogen bond donor/acceptor properties.

2.3. Synthetic analogues made by man

Curcumin and its analogues have been the subject of computational studies, mostly with the intention of unraveling its unique structural features and exploiting the information for further molecular design. Fig. 3 depicts the representative members of synthetic curcumin analogues and Table 3 summarizes the relative bioactivities of synthetic curcumin analogues. Recent high-level, *ab initio*, and computationally intensive calculations have shown that the optimized structure of curcumin is planar and linear [123]. The enol form has been found to be the stable ground state, and in the optimized structure the methoxy groups are seen pointing in the opposite direction with respect to the 1,3-keto-enol group, as shown in Scheme 1 (Fig. 3A). This study showed that the phenolic and enolic groups provide areas of high polarity and the C₇ bridge region is quite hydrophobic. Suggestions based upon computational chemistry regarding redesign of curcumin to enhance its bioactivities have appeared in the literature [124]. In several recent studies that involve computations of energy-minimized structures and subsequent docking studies, only the β -diketo form has been investigated, despite the fact that curcumin exists mostly in the enol form.

The single crystal X-ray diffraction studies on curcumin and its derivatives reported by several groups indicate the enol form as the preferred tautomer. The crystal structure studies show that curcumin in solid state has a perfectly delocalized central keto-enol unit coplanar with one *trans*-Ar-CH=CH-moiety. The plane of the second *trans*-CH=CH-unit is twisted about 17° with respect to the former, planar, Ar-CH=CH-unit. This second unit is also not coplanar with its attached aryl unit. Thus the computationally derived structure differs somewhat with that seen in the solid state [125–127].

The characteristic structural features of curcumin include two *o*-methoxy phenol units, two enone moieties, and a 1,3-diketone $\rightleftharpoons$ 1,3-keto-enol system. The possibilities for struc-

tural alteration on curcumin are shown in Scheme 1. Alterations of structure at all these molecular architectural sites have been attempted. The modification of the basic structure of curcumin to access related compounds by chemical synthesis may be classified into three broad groups. These are termed “curcumin derivatives,” “curcumin analogues,” and “metal complexes of curcumin” in this review. Compounds that retain the basic structural features of curcumin, such as the two dioxy-substituted benzene rings, the –C=C–CO–CH₂–CO–C=C–linker, and the oxy substituents on the benzene rings, are designated as curcumin derivatives. The second group, the curcumin analogues, which encompass all other compounds with some perceived or claimed structural analogy to curcumin, now vastly outnumber the first group. The members of the third group are metal complexes of curcumin and its analogues.

The curcumin derivatives are generally synthesized by derivatization, starting from curcumin. For example, the phenolic hydroxy group may be acylated, alkylated, glycosylated, and amino acylated (Scheme 2, Fig. 3B) [78–81,128–138]. The methoxy groups may be demethylated to hydroxy groups [65]. The reactive methylene group of the linker may be acylated or alkylated or substituted by an arylidene group (Ar-CH=) [81], thereby introducing substituents on the C₇ chain.

A battery of molecular tinkering has been applied to curcumin with a view to preparing analogues. The more common strategies are indicated in Scheme 3 (Fig. 3C). The so-called analogues of curcumin vary on a wide scale in their structural resemblance to curcumin, spanning a spectrum from structures such as (ferrocenyl-CH=CH-CO)₂ CH₂ to methyl ferulate.

The hydrogenation of the C₇ linker double bonds and the carbonyl groups affords the simplest of the analogues, such as DHC, THC, HHC, and OHC, which are obtained by the reduction of curcumin (Scheme 4, Fig. 3D) [17,59,60,80,139].

Analogues that are sourced from curcumin also include those obtained by exploiting the reactivity of the central β -diketone unit with hydrazine, its substituted derivatives, and hydroxylamine. Such heterocyclizations lead to bisstyrylpyrazoles and isoxazoles in which the central 1,3-diketone $\rightleftharpoons$ 1,3-keto-enol system has been masked and rigidized (Scheme 5, Fig. 3E) [81–84,139–141]. More recently, monosemicarbazone

Table 3 – Relative activities of man-made curcumin analogues

- Diacetyl, diglycinoyl, diglycinoyl-di-piperoyl, dipiperoyl, and dialanoyl derivatives and curcumin-4,40-di-O-b-D glucopyranoside have more potent antibacterial and antifungal activities than curcumin [78–80]
- Pyrazole analogues and a curcumin Knoevenagel condensate have more potent antimalarial, antioxidant and COX-1- and COX-2-inhibitory activities than curcumin [81,82]
- Hydrazinocurcumin is a more potent inhibitor of endothelial cell proliferation than curcumin and it inhibits the cell cycle progression of colon cancer cells via antagonism of Ca2/CaM functions [83,84]
- Semicarbazone of curcumin has greater antioxidant and antiproliferative activities but less antiradical activity than curcumin [85]
- Compounds with ortho-diphenoxyl functionality exhibit greater antioxidant activity than curcumin [86]
- Cinnamoyl derivatives are more active than curcumin in inhibiting p300 enzyme [144]
- Symmetrical curcuminoids BJC005 and CHC002 have greater potency than curcumin in inhibiting Fos-Jun, tumor-induced angiogenesis, migration, and invasion [87,88]
- Synthetic analogues with a modified aromatic ring and/or modified enone/dienone bridge between rings have more potent antiangiogenic and COX-1 inhibiting activity than curcumin [89,90]
- Curcumin analogues that retain the 7-carbon spacer between the aryl rings, with a 5-carbon spacer and with a 3-carbon spacer, are more active than curcumin in inhibiting TPA-induced AP-1 and TNF-induced NF-κB activation and are more active antioxidants than curcumin [91–93]
- Cyclic curcumin analogues have more potent cytostatic, antitumor and radical-scavenging activities than curcumin [94–96]
- Synthesized EF24 and other related compounds have greater anticancer and antiangiogenic activities than curcumin [97,98]
- Fused pyridine analogues of curcumin have more potent antioxidant activity than curcumin [99]
- 2,6-dibenzylidenecyclohexanone, 2,5-dibenzylidenecyclopentanone, and 1,4-pentadiene-3-one substituted analogues of curcumin have more potent human cytochrome P450-inhibitory activity than curcumin [100]
- Cinnamoyl derivatives of curcumin are more potent than curcumin in inhibiting HIV-1 integrase [101]
- Mono-carbonyl analogues have the same or greater anti-inflammatory and antibacterial activity than curcumin [102,103]
- Symmetrical analogues with aromatic rings having an alkoxy substitution are more potent in suppressing tumor growth than curcumin [104]
- Aromatic enonic analogues are as or more potent than curcumin in inhibiting cell growth and proliferation [105,107]
- Synthetic analogues with asymmetrical units such as a phenyl group with alkyl amide, chloro-substituted benzamide, or heteroaromatic amide moieties are more potent inhibitors of growth and tube formation than curcumin [106]
- Symmetrical bis-alkynyl or alkyl pyridine and thiophene derivatives have more potent antiangiogenic activities than curcumin [108]
- Curcumin-boron complexes are more potent than curcumin in inhibiting HIV-1 and HIV-2 proteases [104]
- Synthetic copper(II)-curcumin complexes have greater SOD mimicking, radiation-induced lipid peroxidation, and radical-scavenging activities than curcumin [109]
- Manganese complexes of curcumin and diacetylcurcumin are more potent in preventing excitotoxicity and kainic acid-induced nitric oxide levels and neuronal cell damage in rats and are more potent nitric oxide radical scavengers and neuroprotectors than curcumin [110–113]
- Copper(II) conjugate of a synthetic analogue with non-enolizable diketone is more potent than curcumin in inhibiting TNF-induced NF-κB activation and proliferation [114]
- Cyclopalladated complexes of curcumin have more potent antiproliferative effects than curcumin [115]
- Vanadium complex of curcumin has antidiabetic and hypolipidemic effects and improves the cardiovascular complications associated with diabetes [116]
- Vanadium, gallium, and indium complexes of curcumin and its derivatives have more potent cytotoxic activity than curcumin [117]
- Curcumin derivatives with a modified aromatic ring and a cyclohexanone bridge between rings are more potent than curcumin in increasing mitochondrial membrane permeability [118]
- Glycosylated derivatives of curcumin have more potent water-solubility and iron-chelating properties than curcumin [119]
- BDMC-A is more active than curcumin in suppressing nicotine, alcohol and polyunsaturated fatty acid-induced oxidative stress, CCl₄-induced hepatotoxicity and alcohol- and polyunsaturated fatty acid hyperlipidemia in rats [120–122]

Note: AP-1, activator protein-1; BDMC, bisdemethoxycurcumin; BJC005, 1,7-bis(4-hydroxy-5-methoxy-3-nitrophenyl)-1,6-heptadiene-3,5-dione; Ca2/CaM, calcium 2+/calmodulin; CHC002, 1,7-bis(3,4,5-trimethoxyphenyl)-1,6-heptadiene-3,5-dione; COX, cyclooxygenase; EF24, 2,6-bis(2-fluorobenzylidene)piperidone; HIV, human immunodeficiency virus; NF-κB, nuclear factor kappa B; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF, tumor necrosis.

[85], bisthiosemicarbazone [114], and an ethylene diamine adduct [142] of curcumin have also appeared in the literature.

Most of the analogues of curcumin are not obtained from curcumin but rather have been synthesized from smaller synthons. Curcumins are usually assembled from araldehydes and acetylacetone, and this route enables synthesis of a diverse set of curcumin analogues starting from araldehydes; a few typical examples are shown in Scheme 6 (Fig. 3F). This assembly of curcuminoids from araldehydes and acetylacetone has produced a large number of analogues. The use of acetylacetone derivatives bearing substituents on the central carbon further extends this route, leading to analogues with alkyl substituents on the middle carbon of

the C₇ linker moiety (Scheme 7, Fig. 3G) [86–89,91–93,97–101,139,140,143–148].

A further elaboration of this approach involves the use of β-diketones other than acetylacetone derivatives. For example, the use of 2-acetylcycloalkanones has afforded analogues that are conformation restricted. The C₇ linker unit in these analogues now bears a cyclic structure (Scheme 8, Fig. 3H) [94,149].

Yet another strategy has been alteration of the number of the carbons in the middle linker chain, resulting in analogues that are further removed from the native curcumin structure. Reports show that deletion of one or both of the C=C bonds in the parent structure, omission of one C=C and C=O group

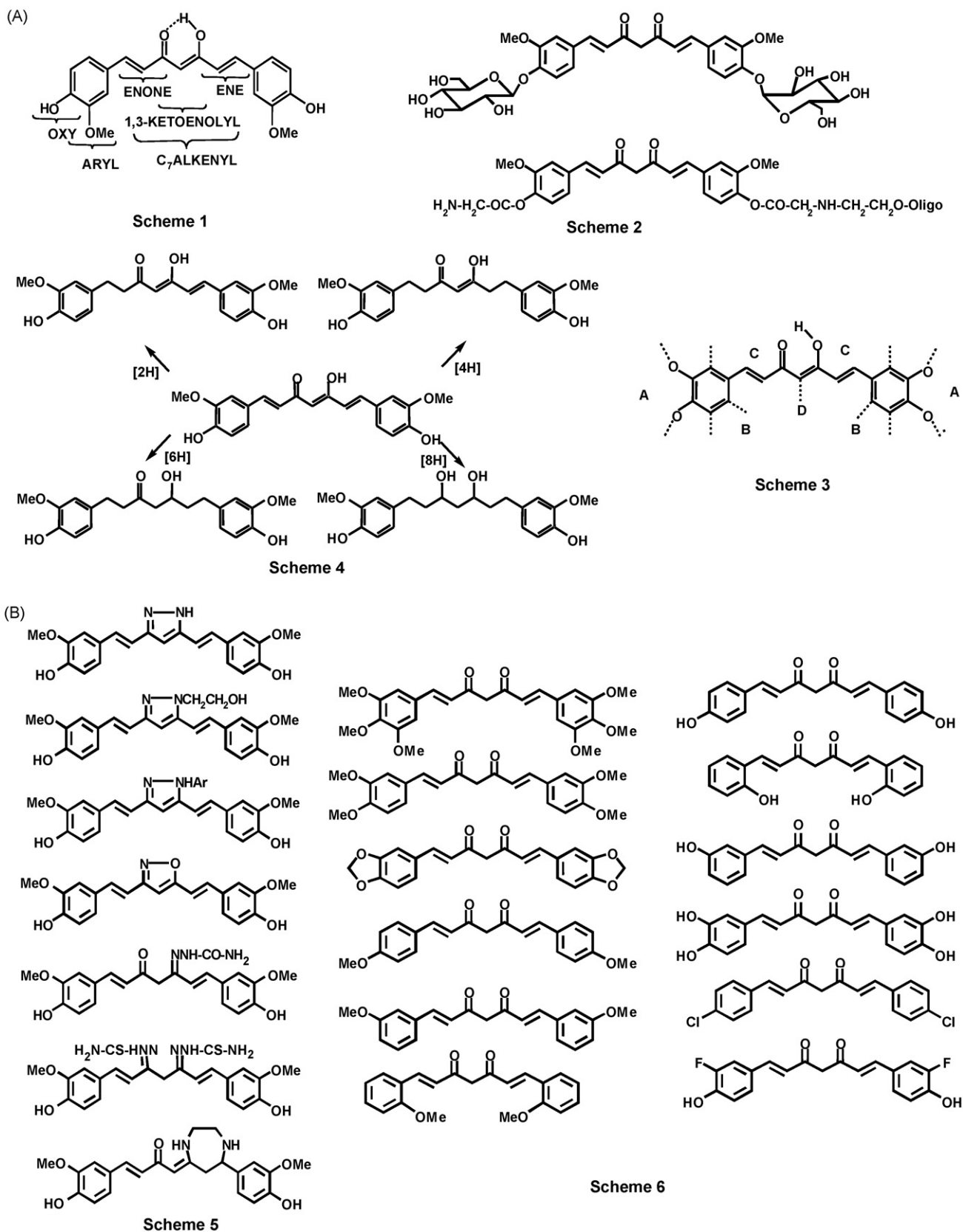


Fig. 3 – Curcumin analogues made by man. (A) Scheme 1: possible sites for structural modifications on curcumin; (B) Scheme 2: curcumin derivatives; (C) Scheme 3: strategies for curcumin analogue preparation. (A) Modify –OMe and –OH groups; remove oxy groups; replace oxy groups. (B) Introduce/remove atoms/groups on aromatic rings; replace aromatic ring by hetero aromatic rings; or by multirings. (C) Alter number of –C=C– and C=O; incorporate –C=C– in cyclic structure. (D) Replace 1,3-diketone by ketone; alter number of enone units; mask 1,3-diketone; convert 1,3-diketone to cyclic structures

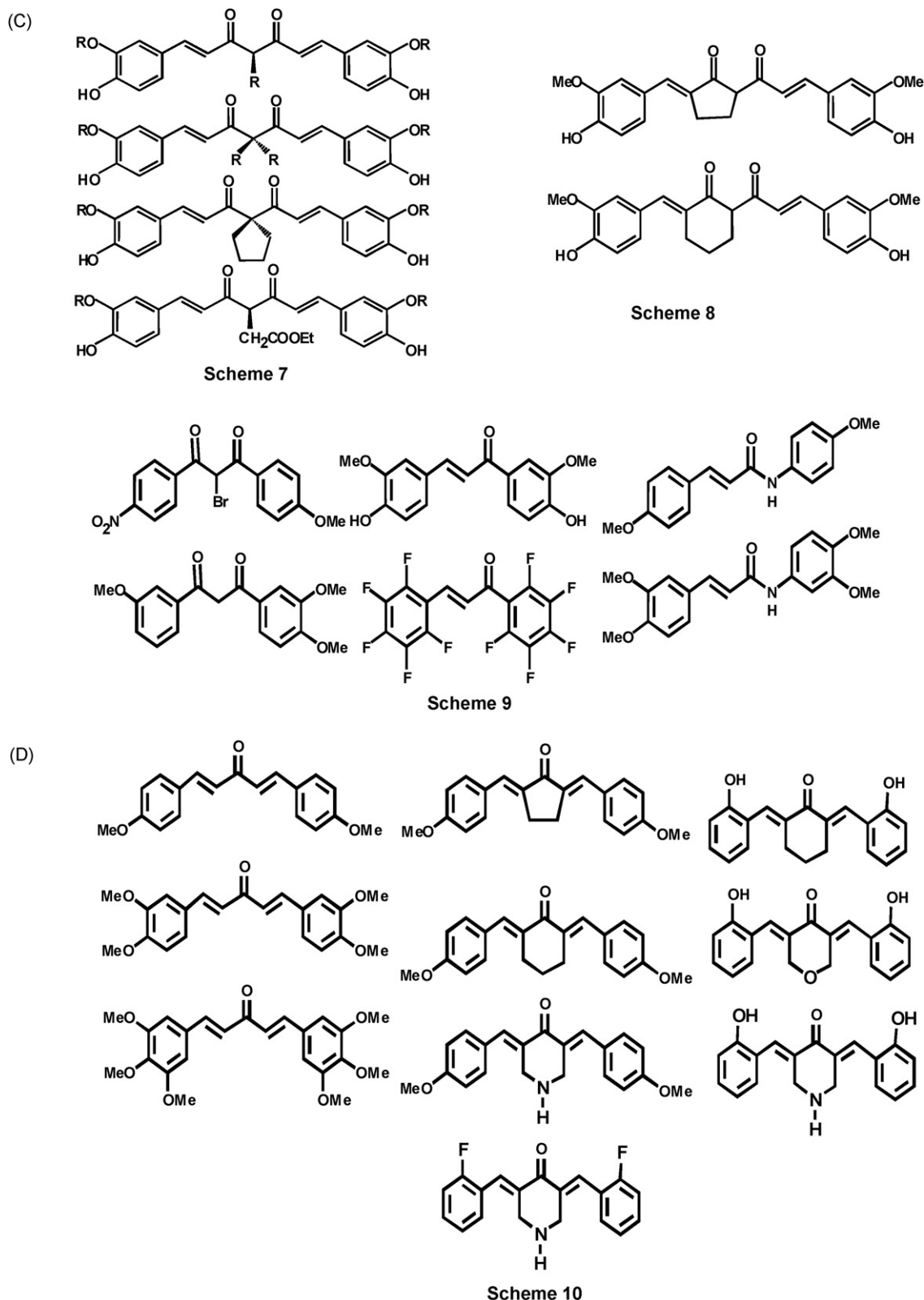


Fig. 3. (Continued).

like pyrazole or isoxazole. (D) Scheme 4: analogues synthesized by reduction of curcumin; (E) Scheme 5: analogues synthesized by masking the central 3-diketone unit; (F) Scheme 6: typical examples of analogues from araldehydes; (G) Scheme 7: Typical examples of analogues from substituted acetylacetones; (H) Scheme 8: conformationally restricted analogues; (I) Scheme 9: C3 bridged analogues; (J) Scheme 10: C5 bridged analogues; (K) Scheme 11: C7, C9, C11, and longer bridged analogues. (L) Scheme 12: exotic analogues.

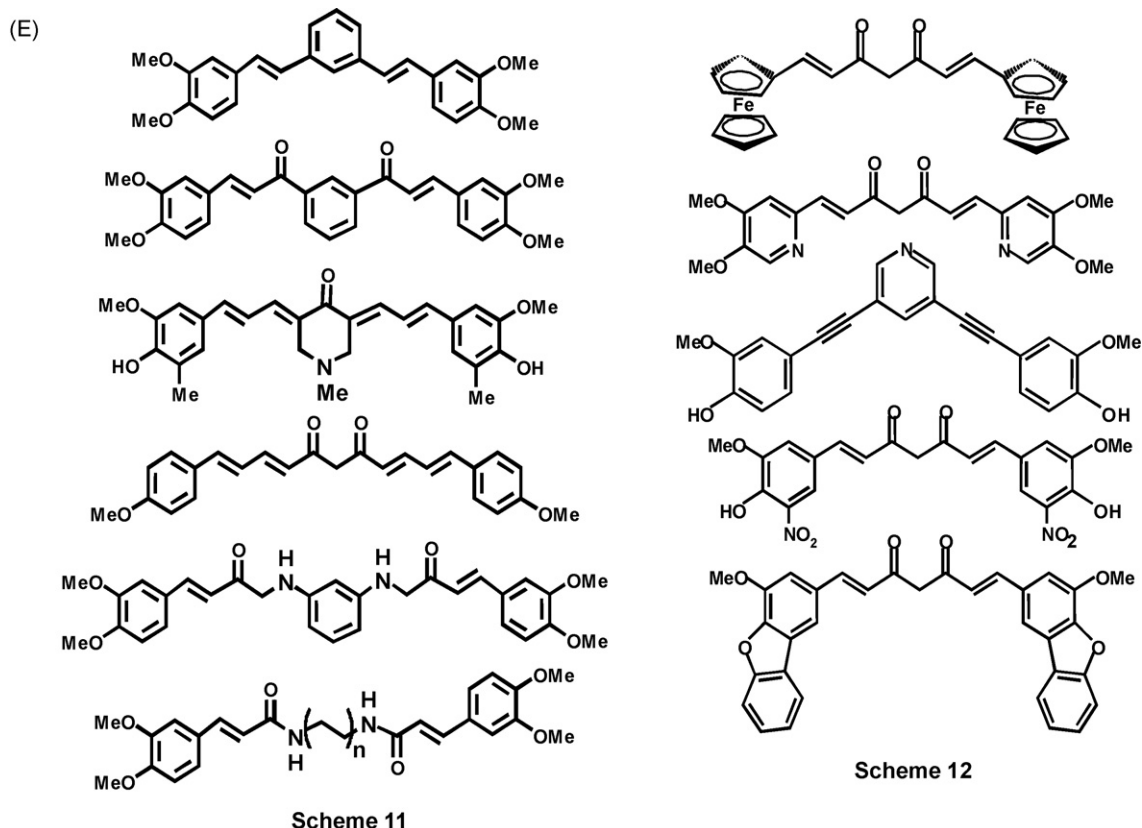


Fig. 3. (Continued).

each (Scheme 9, Fig. 3I), avoidance of the $-\text{CH}_2-\text{CO}-$ unit (Scheme 10, Fig. 3J), or addition of two more $\text{C}=\text{C}$ bonds (Scheme 11, Fig. 3K) all have been attempted, leading to C_3 , C_5 , C_9 , C_{11} or longer linkers in addition to the natural C_7 linker unit. A few randomly selected, nonprioritized, representative structures are shown in Fig. 3, as the total numbers of such analogues now synthesized are too many to depict conveniently [60,64,67,89–91,93,95–97,100,102,103,105,106,139,140,144,146,150–164]. Incorporation of the shortened linker unit carbons in carbocyclic rings has been attempted [107].

Analogues with only one-half of the basic curcumin skeleton embedded in the structure also have been synthesized. These include esters and amides of ferulic acid [165] and other similar cinnamic acids (Fig. 3I). Further structural alterations based on exotic modifications and more drastic molecular surgery of curcumin appear in the literature (Scheme 12, Fig. 3L) [89,108,140,145,148].

Several metal complexes of curcumin, derivatives of curcumin, and analogues of curcumin have been reported. These have generally been obtained by the reaction of curcumin or one of its analogues with a metal salt. Boron has long been known to form a complex with curcumin [104]. The complex resulting from combination of a molecule of curcumin, oxalic acid, and a boron atom, sourced from boric oxide or acid, is known as rubrocurcumin. The complexation of two curcumin molecules with a boron atom affords rosocyanin. Complexes of copper [109,114,166], iron, manganese [110–113,142], palladium [115], vanadyl [118], gallium, and indium [116,117] have been reported.

2.3.1. Antioxidant activity

The antioxidant activities of curcumin and related compounds have been investigated by a variety of assay systems, in both *in vitro* and *in vivo* conditions. The disparity in assay conditions makes exact comparisons rather difficult. The general trends that emerge are discussed in this section.

In one of the early papers on the antioxidant activity of curcumin and its derivatives, Sharma observed that the phenolic hydroxyl groups are needed for antioxidant activity and that the presence of more than one of these groups, as in the curcumin derivative bis(3,4-dihydroxycinnamoyl)-methane, confers better activity than that of curcumin itself [65]. The mechanistic aspects of curcumin antioxidant activity have been more recently investigated at length, and the recent studies by Wright [124], Sun et al. [167], Priyadarsini et al. [168], Ligeret et al. [158], Suzuki et al. [136], and Chen et al. [86] seem to suggest that the phenolic OH groups are important in the antioxidant activity, as was earlier surmised by Barclay et al. [169] and Venkatesan and Rao [143]. A possible role for the β -diketone moiety was suggested by Sugiyama et al. [40] based on their observations using dimethyltetrahydrocurcumin and further advocated by the work of Jovanovic et al. [170].

The presence of an ortho alkoxy group seems to potentiate the antioxidant activity [143,158], as does an additional hydroxy group as in bis(3,4-dihydroxycinnamoyl)methane [86,147]. The effect of the position of the hydroxy group has been investigated under *in vivo* conditions [99], and it seems that the 2-hydroxyphenyl group, as seen in bis(2-hydroxycinnamoyl)-methane, yields better antioxidant activity than the 4-hydro-

xyphenyl group, as present in curcumin. The reduction of the C=C bonds of the C₇ linker leading to THC is apparently not deleterious to antioxidant activity [91]. Telomere repeat amplification protocol assays have shown that, though phenolic hydroxy groups are desirable, the enone and β -diketone moieties are not unavoidable [91]. The desirability of the β -diketo unit has been studied by Sardijiman et al. [100] using bis(4-hydroxybenzylidene)acetones, 2,6-bis-benzylidenecyclohexanones, and cyclopentanones having a C₅ linker. These workers report that the 4-hydroxyphenyl group confers potent antioxidant activity, which is much enhanced by one, or two, methoxy substituents ortho to the hydroxy group. These C₅-linked bis(4-hydroxyphenyl)-1,4-pentadien-3-ones showed greater antioxidant activity than curcumin. In a similar observation among 2,6-bis-benzylidenepiperidones, cycloheptanones and acetones, Youssef et al. demonstrated greater antioxidant activity in those examples that bear a 3-alkoxy-4-hydroxyphenyl unit [95]. The enhancement of antioxidant activity offered by additional hydroxy substituents on the phenyl rings of curcumin-type compounds has been further demonstrated by Venkateswarlu et al. [64].

The antioxidant potential of curcumin complexes has been investigated by another approach. The manganese complexes of curcumin and its diacetyl derivative were found to show greater superoxide dismutase (SOD) activity [83], HO radical-scavenging activity [136], and nitric oxide radical-scavenging activity [110] than the parent molecules. The copper complex of curcumin also has been found to exhibit antioxidant, superoxide-scavenging, and SOD enzyme-mimicking activities superior to those of curcumin itself [109]. In an investigation based on the trolox-equivalent antioxidant capacity assay, Mohammadi et al. [117] found that the vandyl, indium, and gallium complexes of curcumin I and curcumin III were more potent than the respective ligands. In summary, antioxidant activity seems to require, minimally, two hydroxyphenyl units connected together through a linker unit, and the activity increases with additional oxy groups, especially if these are adjacent to one another. Whether the linker unit should contain an unsaturation and/or an oxo group has not been conclusively established yet.

2.3.2. Anti-inflammatory activity

Saturation of the alkene and reduction of the carbonyl functions in the C₇ linker of curcumin appear to reduce its anti-inflammatory activity by suppressing activation of NF- κ B through inhibition of I κ B kinase activity [59]. An early study pointed to the fact that the hydroxyphenyl unit in curcumin confers anti-inflammatory activity since acylation and alkylation of the phenolic hydroxy group of curcumin were found to drastically reduce its anti-inflammatory activity [80]. Nurfina et al. suggested that the presence of a 4-hydroxyphenyl unit is required for anti-inflammatory activity and that this activity seems to increase if additional small-sized alkyl or methoxy groups are present on the adjacent 3- and 5-positions on the phenyl ring [148]. Hong et al. [60] found that the phenolic hydroxyl groups are required for inhibition of COX-1 activity. However, Handler et al. [89] recently observed that many analogues of curcumin that lack a 4-hydroxyphenyl unit, such as 1,7-di-(2,3,4-trimethoxyphenyl)-1,6-heptadien-3,5-dione and 4-[7-(4-methoxycarbonyl)phenyl]-3,5-dioxo-1,6-heptadie-

nyl]benzoate dimethyl ester, were more potent COX-1 inhibitors than curcumin. Even the presence of the β -diketone moiety per se was not a must; its replacement by a pyrazole or isoxazole unit did not abolish the COX-inhibitory activity of curcumin. Further, the pyrazole replacement provides better COX-1/COX-2 selectivity [82]. The architectural change of the “ene-[1,3-dioxo]-ene” C₇ linker in curcumin to a C₅ “ene-oxo-ene,” as in 1,4-pentadiene-3-ones and their cyclopenta- and cyclohexa-analogues, has been reported to improve the inhibition of LPS-induced TNF- α and interleukin-6 expression [156].

2.3.3. Anticancer and anticarcinogenic activity

The anticarcinogenic properties of classical Michael acceptors, recognized by Talalay et al. [171], have been demonstrated in curcumin [67], and it has been suggested that the presence of a hydroxyphenyl group in compounds analogous to curcumin, especially in the 2-position, is supportive of the chemoprotective activity through the ability to induce Phase II detoxification enzymes. The necessity of the “ene-[1,3-dioxo]-ene” C₇ linker, however, could not be firmly established; Dinkova-Kostova et al. observed activity in dibenzoyl and di(2-hydroxybenzoyl)methanes, which are not examples of classic Michael acceptors. An early report by Markaverich et al. [160] suggests that the Michael acceptor type 2,6-bis(3,4-dihydroxy or 4-hydroxy-3-methoxybenzylidene)cyclohexanones, having only a “ene-oxo-ene” motif, could inhibit cancer cell proliferation *in vitro* and *in vivo*. Dinkova-Kostova et al. [67] investigated a large set of Michael acceptors and concluded that the shortened C₅ “ene-oxo-ene” version, as present in 2,6-bis(2-hydroxybenzylidene)cyclopentanone as a typical example, is sufficient to confer potent quinone reductase inducer activity, and the presence of a 2-hydroxyphenyl unit in the bisbenzylidenealkanones and biscycloalkanones profoundly increases inducer potency. In a study of the inhibition of formation of the Fos-Jun-DNA complex, the presence of a 4-hydroxyphenyl, flanked by an adjacent methoxy or nitro group on the phenyl ring in curcumin analogues, conferred better potency [87]. Interestingly, the 4-nitrophenyl analogue also was active. It is tempting to speculate that the ability of the phenyl ring substituent to accept hydrogen bonds, either intramolecularly or intermolecularly, is a structural factor possibly leading to bioactivity.

In a study encompassing a large collection of curcumin analogues of diverse structural types, Ishida et al. [139] observed that diarylheptanoids of curcumin type with 3,4-dihydroxyphenyl, 3,4-dimethoxyphenyl, 2-fluorophenyl, and the pyrazole analogue of curcumin-I were cytotoxic, whereas the reduced curcumin types were inactive. These workers also examined a panel of 1,3-diarylpropan-1,3-diones that are examples of the C₃ linker type, and the most active compound happens to be a -CO-CHBr-CO- derivative whose structure, by virtue of the very reactive bromo substituent, is quite remote from that of curcumin. Other work done in the same laboratories showed that bis(3,4-dimethoxyphenyl) units and the “ene-[1,3-dioxo]-ene” segment in curcumin analogues are important structural factors that confer antiandrogenic activity, with possible application in prostate cancer therapy [140]. The observation of Shim et al. [83,84] that the so-called hydrazinocurcumin analogues, which are formulated more correctly as 3,5-bisstyrylpyrazoles, are more antiangiogenic

than curcumin also seems to point to the importance of the 1,3-diketo unit or its masked version as a pyrazole or isoxazole moiety. Extension of this work to more curcumin analogues has been reported by Ohtsu et al. [140] who found that the presence of a methoxyphenyl or fluorophenyl and introduction of a $\text{CH}_2\text{CH}_2\text{COOEt}$ group into the 1,3-diketo unit affords a novel set of curcuminoid-type antiandrogens. More recently, Dutta et al. [85] showed that the monosemicarbazone of curcumin has greater cytotoxic activity than curcumin itself.

In one of the more significant findings on the anticancer activity of compounds inspired by curcumin, Adams et al. [102,150] announced the superior activity of 2,6-bis(2-fluorobenzylidene)piperidone (EF24) in antiangiogenesis, cell cycle arrest, and apoptosis of cancer cells. These authors observed that the bis-benzylidenepiperidone, pyrone, and cyclohexanone derivatives, containing the α,β -unsaturated ketone unit, exhibit much greater anticancer and antiangiogenesis activities than curcumin, with its 1,3-diketone unit. They also observed that hydroxyl substituent in position 2 generally confers good activity, and concluded that incorporation of the α,β -unsaturated keto group into a heteroatom-containing ring was desirable. The improved cytotoxicity of bis-(3-alkoxy-4-hydroxybenzylidene) piperidones has been reported by Youssef and El-Sherbeny [96]. In this connection, it is notable that the increased cytotoxicity provided by more than one hydroxyl substituent on the phenyl ring of curcuminoids is further exemplified by the analogues reported by Venkateswarlu et al. [64].

The question of the essentiality of the β -keto unit in the bioactivity of curcuminoids has been addressed recently by Lin et al. [97,159]. Their work seems to suggest that the enol-keto moiety is responsible for the antiandrogenic activity and that the di-keto form probably is not an active form. In an ambitious study, Weber et al. [93] investigated the inhibition of TNF- α -induced activation of NF- κ B by a large collection of curcumin analogues, including those with C_7 , C_5 , or C_3 linkers between the aromatic rings. They observed that activity did not depend on linker length, except that compounds with the α,β -unsaturated keto unit were more generally active, 1,5-bis(3-pyridyl)-1,4-pentadien-3-one being the most active among the 72 compounds tested. Those without the enone unit also exhibited activity, however, and the inhibitory activity of the activation of NF- κ B did not correlate with the antioxidant activity of the compounds tested. Many of the active compounds bore hydroxyl and/or methoxyphenyl groups, including the simple 4-hydroxy-3-methoxybenzalacetophenone. Extending their search for a compound with better antiandrogen activity, Lin et al. [159] examined a set of 50 curcumin analogues, encompassing monophenyl and heteroaryl curcumin analogues, curcumin analogues diversely substituted on the phenyl rings, and curcumin analogues with various linkers. Most of the active compounds had methoxy substituents and several were C_7 curcumin analogues with a substituted methylene carbon of the 1,3-diketo moiety.

Overall, it seems that shortening of the C_7 linker to a C_5 linker results in compounds that are more active than curcumin, with the caveat that the substituent groups and their distribution pattern on the phenyl ring should be kept in view. Alkoxy and hydroxy substituents are, in general, activity promoting, and the presence of unsaturation and an oxo group

seems to be desirable. The recent report by Ohori et al. [161] seems to support this very general surmise. The presence of a halo substituent such as F does not provide much enhancement, the case of EF24 being a very successful exception.

3. Formulations

Apart from the synthetic analogues, several other strategies have been evaluated to enhance the biological activity of curcumin. These strategies include adjuvants, nanoparticles, liposomes, micelles, and phospholipid complexes. The adjuvants were selected on the basis of their ability to prevent the rapid metabolism of curcumin by interfering with the enzymes that catalyze the metabolism of curcumin. All other formulations mentioned are designed primarily to increase absorption of curcumin into tissues. Nanoparticles can provide more penetration to membrane barriers because of their small size. Besides their size, their potential for modification for targeting specific organs makes them excellent drug carriers. Liposomes, micelles, and phospholipid complexes can reduce the hydrophobicity of curcumin; these carriers also can increase the permeability of membrane barriers by interacting with the membrane components. Recently it was also reported that the water solubility of curcumin could be 12-fold by the use of heat [172].

3.1. Adjuvants

Piperine is known to inhibit hepatic and intestinal glucuronidation. When combined with piperine, the elimination half-life and clearance of curcumin were significantly decreased, resulting in an increase of bioavailability to 154% that of curcumin alone in rats. In contrast, the increase in bioavailability was 2000% in humans, clearly showing that the effect of piperine on bioavailability of curcumin is much greater in humans than in rats. A human volunteer trial conducted by our group revealed the enhancing effect of piperine on serum curcumin level. Six healthy adult male human volunteers took 2 g of curcumin with or without 5 mg piperine (as Bioperine®) in this cross-over design study. Three subjects were randomized to receive curcumin only, while the remaining three received the curcumin + piperine combination. One week following initial drug administration, volunteers were crossed over to the other therapy and blood samples were obtained for evaluation. The presence of piperine was found to double the absorption of curcumin [7].

The effect of piperine on tissue uptake of a radiolabeled fluoropropyl-substituted curcumin was evaluated in mice. Mice that received piperine had 48% greater brain uptake of curcumin after 2 min than mice that did not receive piperine. However, the uptake in other organs was not found to be significantly improved by piperine in this study; the authors think this observation can be explained by the poor solubility of piperine in 10% ethanolic saline (injection medium) [7].

Some other agents that showed a synergistic effect when used in combination with curcumin in various *in vitro* studies look promising for further evaluation. Five patients with familial adenomatous polyposis who had undergone colectomy received curcumin 480 mg and quercetin 20 mg orally 3

times a day. The number and size of polyps were assessed at baseline and after therapy. All five patients had decreases in polyp number and size, 60.4% and 50.9%, respectively, from baseline after a mean of 6 months of this treatment. Though the authors did not compare the effects of this combination treatment with those of the single agents, this study at least throws light on the therapeutic value of this combination [7].

The synergistic inhibitory effect of curcumin and genistein against pesticide-induced growth of estrogen-dependent MCF-7 breast carcinoma cells has been reported. It was showed that a combination of curcumin and genistein completely inhibited the cellular proliferation induced by an individual pesticide or a mixture of pesticides, and that the inhibitory effect was superior to the individual effects of either curcumin or genistein. Curcumin uptake within rat skin after topical application of a curcumin hydrogel, with or without eugenol or terpenol pretreatment, was evaluated in an *in vivo* study. The effects of eugenol and terpenol as enhancers of skin curcumin absorption were demonstrated; 8 h after application, curcumin levels in skin were 2.2- and 2.5-fold greater, respectively, in mice that received eugenol or terpenol pretreatment than in mice that received curcumin alone. These observations indicate that these absorption-enhancing agents may also be effective as adjuvants. Epigallocatechin-3-gallate, a component of green tea, could counteract certain activities attributed to curcumin. BCM-95 (also called Biocurcunmax) curcuminoids combined with turmeric oil (turmerons) in a specific proportion enhanced the bioavailability and showed better absorption into blood and had longer retention time than curcumin alone. Currently a multicenter, phase II, randomized, double-blinded, placebo-controlled clinical study is ongoing to assess the efficacy and safety of BCM-95 in oral premalignant lesions or cervical cancer [7].

3.2. Nanoparticles

Targeted and triggered drug delivery systems employing nanoparticle technology have emerged as solutions to the problems of enhancing the bioavailability of therapeutic agents and reducing their unwanted side effects. The synthesis, physicochemical characterization, and cancer-related applications of a polymer-based nanoparticle of curcumin named “nanocurcumin” was reported recently. Nanocurcumin was found to have *in vitro* activity similar to that of free curcumin in pancreatic cancer cell lines, inhibiting activation of the transcription factor NF- κ B and reducing steady-state levels of pro-inflammatory cytokines such as interleukins and TNF- α . The authors determined neither the *in vivo* effect of nanocurcumin in mice nor its biodistribution, which would show any potential increase of *in vivo* efficacy of nanocurcumin over that of free curcumin. Curcuminoid-loaded solid lipid nanoparticles for topical application were found to be stable for 6 months at room temperature and gave prolonged *in vitro* release of curcuminoids for up to 12 h. Furthermore, the light and oxygen sensitivities of curcuminoids were strongly reduced by their incorporation into this unique type of formulation. An *in vivo* study revealed the improved efficiency of this topical cream containing curcuminoid-loaded solid lipid nanoparticles over

that containing free curcuminoids [7]. Sou et al. [173] very recently reported that lipid-based nanoparticles provide improved intravenous delivery of curcumin to tissue macrophages. At 6 h after intravenous injection in rats via the tail vein, curcumin in a nanoparticle delivery system was massively distributed in macrophages of the bone marrow and spleen. Overall, nanoparticle-based systems for curcumin delivery are still in their infancy, and much progress is expected in this area.

3.3. Liposomes, micelles, and other delivery systems

Liposomes are excellent drug delivery systems since they can carry both hydrophilic and hydrophobic molecules. The *in vitro* and *in vivo* antitumor activity of liposomal curcumin against human pancreatic carcinoma cells was evaluated and demonstrated that liposomal curcumin not only inhibited pancreatic carcinoma growth but also exhibited antiangiogenic effects. Liposomal curcumin suppressed pancreatic carcinoma growth in murine xenograft models and inhibited tumor angiogenesis. In the *in vivo* part of this study, the effect of liposomal curcumin was evaluated in comparison to no treatment or to treatment with a liposomal vehicle in mice. Comparison of the effects of liposomal curcumin with those of free curcumin and biodistribution profiles of liposomal curcumin and free curcumin have yet to be reported.

The preclinical anticancer activity of a liposomal curcumin formulation in colorectal cancer was recently evaluated. This study also compared the efficacy of liposomal curcumin with that of oxaliplatin, a standard chemotherapeutic agent for colorectal cancer. There was synergism between liposomal curcumin and oxaliplatin at a ratio of 4:1 in LoVo cells *in vitro*. *In vivo*, significant tumor growth inhibition was observed in Colo205 and LoVo xenografts, and the growth inhibition by liposomal curcumin was greater than that by oxaliplatin in Colo205 cells. This study established that liposomal curcumin has comparable or greater growth-inhibitory and apoptotic effects than oxaliplatin in colorectal cancer both *in vitro* and *in vivo*. This group is currently developing liposomal curcumin for introduction into the clinical setting [7].

Ruby et al. [24] reported the antitumor and antioxidant activities of neutral unilamellar liposomal curcuminoids in mice. The *in vitro* cellular uptake studies of liposomal and albumin-loaded curcumin showed that liposomal vehicle is capable of loading more curcumin into cells than either human serum albumin or aqueous dimethyl sulfoxide, and lymphoma cells showed greater uptake of curcumin than lymphocytes. Nevertheless, *in vivo* preclinical studies are warranted to verify that liposomal curcumin has greater bioavailability and efficacy than free curcumin. A 13×10^5 -fold greater solubility of curcumin in a polymeric micellar formulation containing methoxy poly(ethylene glycol)-block-polycaprolactone diblock copolymers (MePEG-b-PCL) was also reported indicating the possibility of further exploration on this micellar formulation [7].

Another study compared the phototoxic effects of curcumin formulations in cyclodextrin and liposomes. Liposomes were proved to be a more suitable curcumin carrier system,

since as much as 30% of the phototoxic effect caused by curcumin in cyclodextrin was obtained with about 1/30 of the curcumin concentration in liposomes. Furthermore, curcumin prepared in cyclodextrin yielded a significantly greater rate of cell death than curcumin alone [174].

The intestinal absorption of curcumin and a micellar curcumin formulation with phospholipid and a bile salt was evaluated using an *in vitro* model consisting of everted rat intestinal sacs. This study suggested that curcumin is biologically transformed during absorption. Further, the *in vitro* intestinal absorption of curcumin was found to increase from 47% to 56% when it was prepared in micelles. Pharmacokinetic studies demonstrated that curcumin in a polymeric micellar formulation had a 60-fold higher biological half-life in rats than curcumin solubilized in a mixture of dimethylacetamide, polyethylene glycol (PEG), and dextrose [7].

Monoesters of curcumin with valine and glycine and diesters with valine, glutamic acid, and demethylenated piperic acid have been prepared and assessed for their antimicrobial and anticancer activities. The results of this study suggested that diesters of curcumin are relatively more active than curcumin itself because of their increased solubility, slow metabolism, and better cellular uptake. Moreover, monoesters of curcumin had better antimicrobial activity than their corresponding diesters, indicating the significant role of a free phenolic group [175].

In an attempt to reduce the color staining effect and enhance the stability of curcumin, which are its principal limitations in dermatological applications, the curcumin was microencapsulated in gelatin. The results of this study revealed that microencapsulation resolved the color-staining problem and enhanced the flow properties and photostability of curcumin [176].

Gal et al. [177] demonstrated the antioxidant effect of liposomal curcumin against copper-induced lipid peroxidation. Very recently, the feasibility of a curcumin microemulsion containing ethyl oleate, lecithin, and Tween80 as an ultrasonic drug delivery carrier was evaluated [178]. Furthermore, Thangapazham et al. [179] reported that a liposomal curcumin formulation had 10-fold higher antiproliferative activity in human prostate cancer cell lines than free curcumin.

3.4. Phospholipid complexes

In a study, curcumin (100 mg/kg) or curcumin–phospholipid complex (corresponding to 100 mg/kg curcumin) was administered orally to rats. Curcumin–phospholipid complex produced a maximum plasma curcumin level of 600 ng/ml 2.33 h after oral administration, while free curcumin yielded a maximum plasma concentration of 267 ng/ml 1.62 h after oral administration. The curcumin–phospholipid complex yielded a curcumin half-life about 1.5-fold greater than that yielded by free curcumin. These results indicate that a curcumin–phospholipid complex can significantly increase circulating levels of presumably active curcumin in rats. Another study showed that a curcumin–phospholipid complex yielded a threefold greater aqueous solubility and a better hepatoprotective effect than free curcumin.

Curcumin–phospholipid complex significantly protected the liver from carbon tetrachloride-induced acute liver damage in rats by restoring levels of the enzymes of the liver glutathione system and of SOD, catalase, and thiobarbituric acid reactive substances. Yet another study explored whether formulation with phosphatidylcholine increases the oral bioavailability or affects the metabolite profile of curcumin *in vivo*. Male Wistar rats received 340 mg/kg of either unformulated curcumin or curcumin formulated with phosphatidylcholine (Meriva) by oral gavage. Curcumin, the accompanying curcuminoids desmethoxycurcumin and bis-desmethoxycurcumin, and the metabolites THC, HHC, curcumin glucuronide, and curcumin sulfate were identified in plasma, intestinal mucosa, and liver of rats that had received Meriva. Peak plasma levels for parent curcumin after administration of Meriva were fivefold higher than those after administration of unformulated curcumin. Similarly, liver levels of curcumin were higher after administration of Meriva than after administration of unformulated curcumin. In contrast, curcumin concentrations in the gastrointestinal mucosa after ingestion of Meriva were somewhat lower than those observed after administration of unformulated curcumin. These results suggest that curcumin formulated with phosphatidylcholine furnishes higher systemic levels of the parent agent than unformulated curcumin [7].

3.5. Curcumin prodrugs

Two curcumin prodrugs, *N*-maleoyl-*L*-valine-curcumin and *N*-maleoyl-glycine-curcumin, were synthesized and evaluated for the selective inhibition of growth of bladder cancer cell lines. This study revealed that activation of curcumin prodrugs via hydrolysis functions of cellular esterase could inhibit the growth of tumor cells and reduce the side effects of these drugs on normal diploid cells [180].

A DNA-curcumin-tetraglycine was prepared by a deoxy 11-mer oligonucleotide, 5'-GTTAGGGTTAG-3', complementary to a repeat sequence of human telomerase RNA template and linked through phosphate and a C-2 linker to a bioactive tetraglycine conjugate of curcumin. This molecule, targeted by an antisense mechanism to telomerase, has been found to act as a prodrug affecting cell growth [131,181].

3.6. PEGylation

PEGylation is used mainly to increase the solubility and decrease the degradation of drug molecules. The aqueous solubility of curcumin was increased by formulating it with MePEG-b-PCL [182]. A recent study by Salmaso et al. [183] reported significant increase in solubility of curcumin in a bioconjugate with PEG and cyclodextrin. A bioconjugate with beta-cyclodextrin and PEG was prepared and folic acid was incorporated for targeting purposes. This bioconjugate, CD-(C6-PEG)5-FA, formed a complex with curcumin and increased curcumin solubility by about 3200-fold as compared to native beta-cyclodextrins; this bioconjugation reduced the degradation rates of curcumin at pH 6.5 and 7.2 by 10- and 45-fold, respectively. *In vitro* studies using folic acid receptor-

overexpressing and -non-expressing cells demonstrated that the new carrier possesses potential selectivity for the folic acid receptor-overexpressing tumor cells. Two conjugates of curcumin with PEGs of different molecular weights exhibited greater cytotoxicity than unconjugated curcumin [184]. Although not meant to evaluate the effect of PEGylation, researchers used a PEG derivative to make nanocurcumin, which is described in section D2 of this review.

4. Conclusion

The fast growing research on curcumin, curcuminoids, and natural and synthetic curcumin analogues clearly confirms the versatility and flexibility of curcumin for structural modifications. However the actual role of different functionalities in curcumin in influencing its special physico-chemical properties and pleiotropic effects of natural and synthetic curcuminoids is far from understood. Such structure-activity studies are still rewarding and would definitely provide a proper basis for unraveling the wide variety of biological actions of the age old spice.

This review describes various approaches that have been undertaken to solve the problems associated with curcumin by searching for molecules that are better than curcumin in bioactivity, solubility, bioavailability and being non-staining. Overall, one finds a complex structural variations either among the natural analogues from turmeric and curcumin metabolites or among the analogues made by Mother Nature and man. Surveying this large collection of molecules and the associated reports on bioactivities, a few generalizations can be made regarding the design of a molecule mimicking the curcumin scaffold and emulating its bioactivities. Albeit with some exceptions, curcumin in general appears to be better than either DMC or BDMC in many bioactivity related screens. The antioxidant activity seems to require one or more oxy substituents on aryl rings, preferably in an ortho orientation, adjacent to or connected by a carbon–carbon unit to a carbonyl function, flanking the latter. A similar conclusion seems warranted in the case of antidiabetic activity, though such studies are not as numerous as antioxidant studies. The picture regarding antitumor and cancer cell cytotoxic activities are much more diffuse. In general, oxyaryl substituent with an adjacent, unsaturated –C=C–CO–unit seems to offer antitumor and cancer cell cytotoxicity. Antiinflammatory activity also seems to be better with the presence of such a molecular unit. The C7 linker unit connecting the two oxyaryl rings in an “ene-[1,3-dioxo]-ene” fashion appears to be replaceable with a smaller carbon bridge such as “ene-oxo-ene” or “ene-oxo-aryl” motifs. Further, the incorporation of the linker unit between the aryl moieties into a cyclic structure does not extinguish activity.

Whether using structural analogues or reformulations of curcumin, most studies have been done *in vitro*. Unlike native curcumin, these novel preparations have been subjected to very few animal studies. Whether these analogues have the same molecular targets as curcumin is also not clear at present. Thus neither the bioavailability nor their activity in animal models is known. Future studies are expected to

unravel curcumin analogues that would be more suitable for human clinical trials.

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REFERENCES

- [1] Aggarwal BB, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. *Anticancer Res* 2003;23:363–98.
- [2] Jagetia GC, Aggarwal BB. “Spicing up” of the immune system by curcumin. *J Clin Immunol* 2007;27:19–35.
- [3] Aggarwal BB, Sundaram C, Malani N, Ichikawa H. Curcumin: the Indian solid gold. *Adv Exp Med Biol* 2007;595:1–75.
- [4] Shishodia S, Chaturvedi MM, Aggarwal BB. Role of curcumin in cancer therapy. *Curr Problems Cancer* 2007;31:243–305.
- [5] Shishodia S, Sethi G, Aggarwal BB. Curcumin: getting back to the roots. *Ann NY Acad Sci* 2005;1056:206–17.
- [6] Goel A, Kunnumakkara AB, Aggarwal BB. Curcumin as “Curecumin”: from kitchen to clinic. *Biochem Pharmacol* 2008;75:787–809.
- [7] Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. *Mol Pharm* 2007;4:807–18.
- [8] Aggarwal BB, Harikumar KB. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. *Int J Biochem Cell Biol* 2008.
- [9] Kunnumakkara AB, Anand P, Aggarwal BB. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. *Cancer Lett* 2008.
- [10] Kunnumakkara AB, Diagaradjane P, Guha S, Deorukhkar A, Shentu S, Aggarwal BB, et al. Curcumin sensitizes human colorectal cancer xenografts in nude mice to gamma-radiation by targeting nuclear factor-kappaB-regulated gene products. *Clin Cancer Res* 2008;14: 2128–36.
- [11] Anand P, Sundaram C, Jhurani S, Kunnumakkara AB, Aggarwal BB. Curcumin and cancer: an “old-age” disease with an “age-old” solution. *Cancer Lett* 2008;267:133–64.
- [12] Goel A, Jhurani S, Aggarwal BB. Multi-targeted therapy by curcumin: how spicy is it? *Mol Nutr Food Res* 2008.
- [13] Kiuchi F, Goto Y, Sugimoto N, Akao N, Kondo K, Tsuda Y. Nematocidal activity of turmeric: synergistic action of curcuminoids. *Chem Pharm Bull (Tokyo)* 1993;41: 1640–3.
- [14] Simon A, Allais DP, Duroux JL, Basly JP, Durand-Fontanier S, Delage C. Inhibitory effect of curcuminoids on MCF-7 cell proliferation and structure-activity relationships. *Cancer Lett* 1998;129:111–6.
- [15] Ahsan H, Parveen N, Khan NU, Hadi SM. Pro-oxidant, anti-oxidant and cleavage activities on DNA of curcumin and its derivatives demethoxycurcumin and bisdemethoxycurcumin. *Chem Biol Interact* 1999;121: 161–75.

- [16] Kim JE, Kim AR, Chung HY, Han SY, Kim BS, Choi JS. In vitro peroxynitrite scavenging activity of diarylheptanoids from *Curcuma longa*. *Phytother Res* 2003;17:481–4.
- [17] Somporn P, Phisalaphong C, Nakornchai S, Unchern S, Morales NP. Comparative antioxidant activities of curcumin and its demethoxy and hydrogenated derivatives. *Biol Pharm Bull* 2007;30:74–8.
- [18] Subramanian M, Sreejayan, Rao MN, Devasagayam TP, Singh BB. Diminution of singlet oxygen-induced DNA damage by curcumin and related antioxidants. *Mutation Res* 1994;311:249–55.
- [19] Sreejayan N, Rao MN. Free radical scavenging activity of curcuminoids. *Arzneimittelforschung* 1996;46:169–71.
- [20] Ramsewak RS, DeWitt DL, Nair MG. Cytotoxicity, antioxidant and anti-inflammatory activities of curcumins I–III from *Curcuma longa*. *Phytomedicine* 2000;7:303–8.
- [21] Toda S, Ohnishi M, Kimura M, Nakashima K. Action of curcuminoids on the hemolysis and lipid peroxidation of mouse erythrocytes induced by hydrogen peroxide. *J Ethnopharmacol* 1988;23:105–8.
- [22] Sreejayan, Rao MN. Curcuminoids as potent inhibitors of lipid peroxidation. *J Pharm Pharmacol* 1994;46:1013–6.
- [23] Jeong GS, Oh GS, Pae HO, Jeong SO, Kim YC, Shin MK, et al. Comparative effects of curcuminoids on endothelial heme oxygenase-1 expression: ortho-methoxy groups are essential to enhance heme oxygenase activity and protection. *Exp Mol Med* 2006;38:393–400.
- [24] Ruby AJ, Kuttan G, Babu KD, Rajasekharan KN, Kuttan R. Anti-tumour and antioxidant activity of natural curcuminoids. *Cancer Lett* 1995;94:79–83.
- [25] Liu Y, Hong XQ. Effect of three different curcumin pigments on the proliferation of vascular smooth muscle cells by ox-LDL and the expression of LDL-R. *Zhongguo Zhong Yao Za Zhi* 2006;31:500–3.
- [26] Nishiyama T, Mae T, Kishida H, Tsukagawa M, Mimaki Y, Kuroda M, et al. Curcuminoids and sesquiterpenoids in turmeric (*Curcuma longa* L.) suppress an increase in blood glucose level in type 2 diabetic KK-Ay mice. *J Agric Food Chem* 2005;53:959–63.
- [27] Kim DS, Park SY, Kim JK. Curcuminoids from *Curcuma longa* L. (Zingiberaceae) that protect PC12 rat pheochromocytoma and normal human umbilical vein endothelial cells from betaA(1–42) insult. *Neurosci Lett* 2001;303:57–61.
- [28] Dairam A, Limson JL, Watkins GM, Antunes E, Daya S. Curcuminoids, curcumin, and demethoxycurcumin reduce lead-induced memory deficits in male Wistar rats. *J Agric Food Chem* 2007;55:1039–44.
- [29] Fiala M, Liu PT, Espinosa-Jeffrey A, Rosenthal MJ, Bernard G, Ringman JM, et al. Innate immunity and transcription of MGAT-III and Toll-like receptors in Alzheimer's disease patients are improved by bisdemethoxycurcumin. *Proc Natl Acad Sci USA* 2007;104:12849–54.
- [30] Sandur SK, Pandey MK, Sung B, Ahn KS, Murakami A, Sethi G, et al. Curcumin, demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin and turmerones differentially regulate anti-inflammatory and anti-proliferative responses through a ROS-independent mechanism. *Carcinogenesis* 2007;28:1765–73.
- [31] Anto RJ, George J, Babu KV, Rajasekharan KN, Kuttan R. Antimutagenic and anticarcinogenic activity of natural and synthetic curcuminoids. *Mutation Res* 1996;370:127–31.
- [32] Syu WJ, Shen CC, Don MJ, Ou JC, Lee GH, Sun CM. Cytotoxicity of curcuminoids and some novel compounds from *Curcuma zedoaria*. *J Nat Prod* 1998;61:1531–4.
- [33] Huang MT, Ma W, Lu YP, Chang RL, Fisher C, Manchand PS, et al. Effects of curcumin, demethoxycurcumin, bisdemethoxycurcumin and tetrahydrocurcumin on 12-O-tetradecanoylphorbol-13-acetate-induced tumor promotion. *Carcinogenesis* 1995;16:2493–7.
- [34] Bonte F, Noel-Hudson MS, Wepierre J, Meybeck A. Protective effect of curcuminoids on epidermal skin cells under free oxygen radical stress. *Planta Med* 1997;63:265–6.
- [35] Chearwae W, Anuchapreeda S, Nandigama K, Ambudkar SV, Limtrakul P. Biochemical mechanism of modulation of human P-glycoprotein (ABCB1) by curcumin I, II, and III purified from Turmeric powder. *Biochem Pharmacol* 2004;68:2043–52.
- [36] Devasena T, Rajasekaran KN, Gunasekaran G, Viswanathan P, Menon VP. Anticarcinogenic effect of bis-1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5-dione a curcumin analog on DMH-induced colon cancer model. *Pharmacol Res* 2003;47:133–40.
- [37] Chearwae W, Wu CP, Chu HY, Lee TR, Ambudkar SV, Limtrakul P. Curcuminoids purified from turmeric powder modulate the function of human multidrug resistance protein 1 (ABCC1). *Cancer Chemother Pharmacol* 2006;57:376–88.
- [38] Pugazhenth S, Akhoy L, Selvaraj G, Wang M, Alam J. Regulation of heme oxygenase-1 expression by demethoxy curcuminoids through Nrf2 by a PI3-kinase/Akt-mediated pathway in mouse beta-cells. *Am J Physiol Endocrinol Metab* 2007;293:E645–55.
- [39] Osawa T, Sugiyama Y, Inayoshi M, Kawakishi S. Antioxidative activity of tetrahydrocurcuminoids. *Biosci Biotechnol Biochem* 1995;59:1609–12.
- [40] Sugiyama Y, Kawakishi S, Osawa T. Involvement of the beta-diketone moiety in the antioxidative mechanism of tetrahydrocurcumin. *Biochem Pharmacol* 1996;52:519–25.
- [41] Khopde SM, Priyadarsini KI, Guha SN, Satav JG, Venkatesan P, Rao MN. Inhibition of radiation-induced lipid peroxidation by tetrahydrocurcumin: possible mechanisms by pulse radiolysis. *Biosci Biotechnol Biochem* 2000;64:503–9.
- [42] Naito M, Wu X, Nomura H, Kodama M, Kato Y, Kato Y, et al. The protective effects of tetrahydrocurcumin on oxidative stress in cholesterol-fed rabbits. *J Atheroscler Thromb* 2002;9:243–50.
- [43] Okada K, Wangpoengtrakul C, Tanaka T, Toyokuni S, Uchida K, Osawa T. Curcumin and especially tetrahydrocurcumin ameliorate oxidative stress-induced renal injury in mice. *J Nutr* 2001;131:2090–5.
- [44] Murugan P, Pari L. Effect of tetrahydrocurcumin on erythromycin estolate-induced lipid peroxidation in rats. *J Basic Clin Physiol Pharmacol* 2005;16:1–15.
- [45] Pari L, Amali DR. Protective role of tetrahydrocurcumin (THC) an active principle of turmeric on chloroquine induced hepatotoxicity in rats. *J Pharm Pharm Sci* 2005;8:115–23.
- [46] Pari L, Murugan P. Protective role of tetrahydrocurcumin against erythromycin estolate-induced hepatotoxicity. *Pharmacol Res* 2004;49:481–6.
- [47] Pari L, Murugan P. Tetrahydrocurcumin: effect on chloroquine-mediated oxidative damage in rat kidney. *Basic Clin Pharmacol Toxicol* 2006;99:329–34.
- [48] Murugan P, Pari L. Antioxidant effect of tetrahydrocurcumin in streptozotocin-nicotinamide induced diabetic rats. *Life Sci* 2006;79:1720–8.
- [49] Murugan P, Pari L. Effect of tetrahydrocurcumin on lipid peroxidation and lipids in streptozotocin-nicotinamide-induced diabetic rats. *Basic Clin Pharmacol Toxicol* 2006;99:122–7.
- [50] Murugan P, Pari L. Effect of tetrahydrocurcumin on plasma antioxidants in streptozotocin-nicotinamide experimental diabetes. *J Basic Clin Physiol Pharmacol* 2006;17:231–44.

- [51] Pari L, Murugan P. Antihyperlipidemic effect of curcumin and tetrahydrocurcumin in experimental type 2 diabetic rats. *Ren Fail* 2007;29:881–9.
- [52] Pari L, Murugan P. Changes in glycoprotein components in streptozotocin–nicotinamide induced type 2 diabetes: influence of tetrahydrocurcumin from *Curcuma longa*. *Plant Foods Hum Nutr* 2007;62:25–9.
- [53] Pari L, Murugan P. Influence of tetrahydrocurcumin on tail tendon collagen contents and its properties in rats with streptozotocin–nicotinamide-induced type 2 diabetes. *Fundam Clin Pharmacol* 2007;21:665–71.
- [54] Pari L, Murugan P. Tetrahydrocurcumin prevents brain lipid peroxidation in streptozotocin-induced diabetic rats. *J Med Food* 2007;10:323–9.
- [55] Murugan P, Pari L. Influence of tetrahydrocurcumin on erythrocyte membrane bound enzymes and antioxidant status in experimental type 2 diabetic rats. *J Ethnopharmacol* 2007;113:479–86.
- [56] Murugan P, Pari L. Influence of tetrahydrocurcumin on hepatic and renal functional markers and protein levels in experimental type 2 diabetic rats. *Basic Clin Pharmacol Toxicol* 2007;101:241–5.
- [57] Atsumi T, Tonosaki K, Fujisawa S. Comparative cytotoxicity and ROS generation by curcumin and tetrahydrocurcumin following visible-light irradiation or treatment with horseradish peroxidase. *Anticancer Res* 2007;27:363–71.
- [58] Limtrakul P, Chearwae W, Shukla S, Phisalpong C, Ambudkar SV. Modulation of function of three ABC drug transporters, P-glycoprotein (ABCB1), mitoxantrone resistance protein (ABCG2) and multidrug resistance protein 1 (ABCC1) by tetrahydrocurcumin, a major metabolite of curcumin. *Mol Cell Biochem* 2007;296:85–95.
- [59] Pan MH, Lin-Shiau SY, Lin JK. Comparative studies on the suppression of nitric oxide synthase by curcumin and its hydrogenated metabolites through down-regulation of IkappaB kinase and NFkappaB activation in macrophages. *Biochem Pharmacol* 2000;60:1665–76.
- [60] Hong J, Bose M, Ju J, Ryu JH, Chen X, Sang S, et al. Modulation of arachidonic acid metabolism by curcumin and related beta-diketone derivatives: effects on cytosolic phospholipase A(2), cyclooxygenases and 5-lipoxygenase. *Carcinogenesis* 2004;25:1671–9.
- [61] Kim JM, Araki S, Kim DJ, Park CB, Takasuka N, Baba-Toriyama H, et al. Chemopreventive effects of carotenoids and curcumins on mouse colon carcinogenesis after 1,2-dimethylhydrazine initiation. *Carcinogenesis* 1998;19:81–5.
- [62] Shoskes D, Lapierre C, Cruz-Correa M, Muruve N, Rosario R, Fromkin B, et al. Beneficial effects of the bioflavonoids curcumin and quercetin on early function in cadaveric renal transplantation: a randomized placebo controlled trial. *Transplantation* 2005;80:1556–9.
- [63] Fujisawa S, Kadoma Y. Anti- and pro-oxidant effects of oxidized quercetin, curcumin or curcumin-related compounds with thiols or ascorbate as measured by the induction period method. *In Vivo* 2006;20:39–44.
- [64] Venkateswarlu S, Ramachandra MS, Subbaraju GV. Synthesis and biological evaluation of polyhydroxycurcuminoids. *Bioorg Med Chem* 2005;13:6374–80.
- [65] Sharma OP. Antioxidant activity of curcumin and related compounds. *Biochem Pharmacol* 1976;25:1811–2.
- [66] Conney AH, Lysz T, Ferraro T, Abidi TF, Manchand PS, Laskin JD, et al. Inhibitory effect of curcumin and some related dietary compounds on tumor promotion and arachidonic acid metabolism in mouse skin. *Adv Enzyme Regul* 1991;31:385–96.
- [67] Dinkova-Kostova AT, Talalay P. Relation of structure of curcumin analogs to their potencies as inducers of Phase 2 detoxification enzymes. *Carcinogenesis* 1999;20:911–4.
- [68] Lin CC, Lu YP, Lou YR, Ho CT, Newmark HH, MacDonald C, et al. Inhibition by dietary dibenzoylmethane of mammary gland proliferation, formation of DMBA-DNA adducts in mammary glands, and mammary tumorigenesis in Sencar mice. *Cancer Lett* 2001;168:125–32.
- [69] Nakamura H, Yamamoto T. The active part of the [6]-gingerol molecule in mutagenesis. *Mutation Res* 1983;122:87–94.
- [70] Park KK, Chun KS, Lee JM, Lee SS, Surh YJ. Inhibitory effects of [6]-gingerol, a major pungent principle of ginger, on phorbol ester-induced inflammation, epidermal ornithine decarboxylase activity and skin tumor promotion in ICR mice. *Cancer Lett* 1998;129:139–44.
- [71] Joe B, Rao UJ, Lokesh BR. Presence of an acidic glycoprotein in the serum of arthritic rats: modulation by capsaicin and curcumin. *Mol Cell Biochem* 1997;169:125–34.
- [72] Joe B, Lokesh BR. Role of capsaicin, curcumin and dietary n – 3 fatty acids in lowering the generation of reactive oxygen species in rat peritoneal macrophages. *Biochim Biophys Acta* 1994;1224:255–63.
- [73] Joe B, Lokesh BR. Effect of curcumin and capsaicin on arachidonic acid metabolism and lysosomal enzyme secretion by rat peritoneal macrophages. *Lipids* 1997;32:1173–80.
- [74] Rajakumar DV, Rao MN. Antioxidant properties of dehydrozingerone and curcumin in rat brain homogenates. *Mol Cell Biochem* 1994;140:73–9.
- [75] Motohashi N, Yamagami C, Tokuda H, Konoshima T, Okuda Y, Okuda M, et al. Inhibitory effects of dehydrozingerone and related compounds on 12-O-tetradecanoylphorbol-13-acetate induced Epstein-Barr virus early antigen activation. *Cancer Lett* 1998;134:37–42.
- [76] Oh S, Jang S, Kim D, Han IO, Jung JC. Synthesis and evaluation of biological properties of benzylideneacetophenone derivatives. *Arch Pharmacol Res* 2006;29:469–75.
- [77] Chun KS, Sohn Y, Kim HS, Kim OH, Park KK, Lee JM, et al. Anti-tumor promoting potential of naturally occurring diarylheptanoids structurally related to curcumin. *Mutation Res* 1999;428:49–57.
- [78] Kumar S, Dubey KK, Tripathi S, Fujii M, Misra K. Design and synthesis of curcumin-bioconjugates to improve systemic delivery. *Nucl Acids Symp Ser* 2000;75–6.
- [79] Mishra S, Kapoor N, Mubarak Ali A, Pardhasaradhi BV, Kumari AL, Khar A, et al. Differential apoptotic and redox regulatory activities of curcumin and its derivatives. *Free Radic Biol Med* 2005;38:1353–60.
- [80] Mukhopadhyay A, Basu N, Ghatak N, Gujral PK. Anti-inflammatory and irritant activities of curcumin analogues in rats. *Agents Actions* 1982;12:508–15.
- [81] Mishra S, Karmodiya K, Suroliya N, Suroliya A. Synthesis and exploration of novel curcumin analogues as anti-malarial agents. *Bioorg Med Chem* 2008;16:2894–902.
- [82] Selvam C, Jachak SM, Thilagavathi R, Chakraborti AK. Design, synthesis, biological evaluation and molecular docking of curcumin analogues as antioxidant, cyclooxygenase inhibitory and anti-inflammatory agents. *Bioorg Med Chem Lett* 2005;15:1793–7.
- [83] Shim JS, Kim DH, Jung HJ, Kim JH, Lim D, Lee SK, et al. Hydrazinocurcumin, a novel synthetic curcumin derivative, is a potent inhibitor of endothelial cell proliferation. *Bioorg Med Chem* 2002;10:2987–92.
- [84] Shim JS, Lee J, Park HJ, Park SJ, Kwon HJ. A new curcumin derivative, HBC, interferes with the cell cycle progression

- of colon cancer cells via antagonization of the Ca²⁺/calmodulin function. *Chem Biol* 2004;11:1455–63.
- [85] Dutta S, Padhye S, Priyadarsini KI, Newton C. Antioxidant and antiproliferative activity of curcumin semicarbazone. *Bioorg Med Chem Lett* 2005;15:2738–44.
 - [86] Chen WF, Deng SL, Zhou B, Yang L, Liu ZL. Curcumin and its analogues as potent inhibitors of low density lipoprotein oxidation: H-atom abstraction from the phenolic groups and possible involvement of the 4-hydroxy-3-methoxyphenyl groups. *Free Radic Biol Med* 2006;40:526–35.
 - [87] Hahm ER, Cheon G, Lee J, Kim B, Park C, Yang CH. New and known symmetrical curcumin derivatives inhibit the formation of Fos-Jun-DNA complex. *Cancer Lett* 2002;184:89–96.
 - [88] Hahm ER, Gho YS, Park S, Park C, Kim KW, Yang CH. Synthetic curcumin analogs inhibit activator protein-1 transcription and tumor-induced angiogenesis. *Biochem Biophys Res Commun* 2004;321:337–44.
 - [89] Handler N, Jaeger W, Puschacher H, Leisser K, Erker T. Synthesis of novel curcumin analogues and their evaluation as selective cyclooxygenase-1 (COX-1) inhibitors. *Chem Pharm Bull (Tokyo)* 2007;55:64–71.
 - [90] Furness MS, Robinson TP, Ehlers T, Hubbard RB, Arbiser JL, Goldsmith DJ, et al. Antiangiogenic agents: studies on fumagillin and curcumin analogs. *Curr Pharm Des* 2005;11:357–73.
 - [91] Weber WM, Hunsaker LA, Abcouwer SF, Deck LM, Vander Jagt DL. Anti-oxidant activities of curcumin and related enones. *Bioorg Med Chem* 2005;13:3811–20.
 - [92] Weber WM, Hunsaker LA, Gonzales AM, Heynekamp JJ, Orlando RA, Deck LM, et al. TPA-induced up-regulation of activator protein-1 can be inhibited or enhanced by analogs of the natural product curcumin. *Biochem Pharmacol* 2006;72:928–40.
 - [93] Weber WM, Hunsaker LA, Roybal CN, Bobrovnikova-Marjon EV, Abcouwer SF, Royer RE, et al. Activation of NFκB is inhibited by curcumin and related enones. *Bioorg Med Chem* 2006;14:2450–61.
 - [94] Youssef D, Nichols CE, Cameron TS, Balzarini J, De Clercq E, Jha A. Design, synthesis, and cytostatic activity of novel cyclic curcumin analogues. *Bioorg Med Chem Lett* 2007;17:5624–9.
 - [95] Youssef KM, El-Sherbeny MA, El-Shafie FS, Farag HA, Al-Deeb OA, Awadalla SA. Synthesis of curcumin analogues as potential antioxidant, cancer chemopreventive agents. *Arch Pharm (Weinheim)* 2004;337:42–54.
 - [96] Youssef KM, El-Sherbeny MA. Synthesis and antitumor activity of some curcumin analogs. *Arch Pharm (Weinheim)* 2005;338:181–9.
 - [97] Lin L, Shi Q, Nyarko AK, Bastow KF, Wu CC, Su CY. Antitumor agents. 250. Design and synthesis of new curcumin analogues as potential anti-prostate cancer agents. *J Med Chem* 2006;49:3963–72.
 - [98] Mazumder A, Neamati N, Sunder S, Schulz J, Pertz H, Eich E, et al. Curcumin analogs with altered potencies against HIV-1 integrase as probes for biochemical mechanisms of drug action. *J Med Chem* 1997;40:3057–63.
 - [99] Rukkumani R, Aruna K, Varma PS, Rajasekaran KN, Menon VP. Comparative effects of curcumin and an analog of curcumin on alcohol and PUFA induced oxidative stress. *J Pharm Pharm Sci* 2004;7:274–83.
 - [100] Sardijman SS, Reksahadiprodjo MS, van der Groot H, Timmerman H. 1,5-Diphenyl-1,4-pentadiene-3-ones and cyclic analogues as antioxidative agents. Synthesis and structure activity relationships. *Eur J Med Chem* 1997;32:625–30.
 - [101] Srinivasan A, Menon VP, Periaswamy V, Rajasekaran KN. Protection of pancreatic beta-cells by the potential antioxidant bis-o-hydroxycinnamoyl methane, analogue of natural curcuminoid in experimental diabetes. *J Pharm Pharm Sci* 2003;6:327–33.
 - [102] Adams BK, Cai J, Armstrong J, Herold M, Lu YJ, Sun A, et al. EF24, a novel synthetic curcumin analog, induces apoptosis in cancer cells via a redox-dependent mechanism. *Anticancer Drugs* 2005;16:263–75.
 - [103] Al-Omar MA, Youssef KM, El-Sherbeny MA, Awadalla SA, El-Subbagh HI. Synthesis and in vitro antioxidant activity of some new fused pyridine analogs. *Arch Pharm (Weinheim)* 2005;338:175–80.
 - [104] Sui Z, Salto R, Li J, Craik C, Ortiz de Montellano PR. Inhibition of the HIV-1 and HIV-2 proteases by curcumin and curcumin boron complexes. *Bioorg Med Chem* 1993;1:415–22.
 - [105] Robinson TP, Ehlers T, Hubbard IR, Bai X, Arbiser JL, Goldsmith DJ, et al. Design, synthesis, and biological evaluation of angiogenesis inhibitors: aromatic enone and dienone analogues of curcumin. *Bioorg Med Chem Lett* 2003;13:115–7.
 - [106] Woo HB, Shin WS, Lee S, Ahn CM. Synthesis of novel curcumin mimics with asymmetrical units and their anti-angiogenic activity. *Bioorg Med Chem Lett* 2005;15:3782–6.
 - [107] Robinson TP, Hubbard RB, Ehlers TJ, Arbiser JL, Goldsmith DJ, Bowen JP. Synthesis and biological evaluation of aromatic enones related to curcumin. *Bioorg Med Chem* 2005;13:4007–13.
 - [108] Ahn CM, Shin WS, Bum Woo H, Lee S, Lee HW. Synthesis of symmetrical bis-alkynyl or alkyl pyridine and thiophene derivatives and their antiangiogenic activities. *Bioorg Med Chem Lett* 2004;14:3893–6.
 - [109] Barik A, Mishra B, Shen L, Mohan H, Kadam RM, Dutta S, et al. Evaluation of a new copper(II)-curcumin complex as superoxide dismutase mimic and its free radical reactions. *Free Radic Biol Med* 2005;39:811–22.
 - [110] Sumanont Y, Murakami Y, Tohda M, Vajragupta O, Matsumoto K, Watanabe H. Evaluation of the nitric oxide radical scavenging activity of manganese complexes of curcumin and its derivative. *Biol Pharm Bull* 2004;27:170–3.
 - [111] Sumanont Y, Murakami Y, Tohda M, Vajragupta O, Watanabe H, Matsumoto K. Prevention of kainic acid-induced changes in nitric oxide level and neuronal cell damage in the rat hippocampus by manganese complexes of curcumin and diacetylcurcumin. *Life Sci* 2006;78:1884–91.
 - [112] Sumanont Y, Murakami Y, Tohda M, Vajragupta O, Watanabe H, Matsumoto K. Effects of manganese complexes of curcumin and diacetylcurcumin on kainic acid-induced neurotoxic responses in the rat hippocampus. *Biol Pharm Bull* 2007;30:1732–9.
 - [113] Vajragupta O, Boonchoong P, Berliner LJ. Manganese complexes of curcumin analogues: evaluation of hydroxyl radical scavenging ability, superoxide dismutase activity and stability towards hydrolysis. *Free Radic Res* 2004;38:303–14.
 - [114] Zambre AP, Kulkarni VM, Padhye S, Sandur SK, Aggarwal BB. Novel curcumin analogs targeting TNF-induced NF-κB activation and proliferation in human leukemic KBM-5 cells. *Bioorg Med Chem* 2006;14:7196–204.
 - [115] Pucci D, Bloise R, Bellusci A, Bernardini S, Ghedini M, Pirillo S, et al. Curcumin and cyclopalladated complexes: a recipe for bifunctional biomaterials. *J Inorg Biochem* 2007;101:1013–22.
 - [116] Majithiya JB, Balaraman R, Giridhar R, Yadav MR. Effect of bis[curcumin]oxovanadium complex on non-diabetic and streptozotocin-induced diabetic rats. *J Trace Elem Med Biol* 2005;18:211–7.

- [117] Mohammadi K, Thompson KH, Patrick BO, Storr T, Martins C, Polishchuk E, et al. Synthesis and characterization of dual function vanadyl, gallium and indium curcumin complexes for medicinal applications. *J Inorg Biochem* 2005;99:2217–25.
- [118] Thompson KH, Bohmerle K, Polishchuk E, Martins C, Toleikis P, Tse J, et al. Complementary inhibition of synovocyte, smooth muscle cell or mouse lymphoma cell proliferation by a vanadyl curcumin complex compared to curcumin alone. *J Inorg Biochem* 2004;98:2063–70.
- [119] Benassi R, Ferrari E, Grandi R, Lazzari S, Saladini M. Synthesis and characterization of new beta-diketo derivatives with iron chelating ability. *J Inorg Biochem* 2007;101:203–13.
- [120] Devasena T, Rajasekaran KN, Menon VP. Bis-1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5-dione (a curcumin analog) ameliorates DMH-induced hepatic oxidative stress during colon carcinogenesis. *Pharmacol Res* 2002;46:39–45.
- [121] Kalpana C, Sudheer AR, Rajasekharan KN, Menon VP. Comparative effects of curcumin and its synthetic analogue on tissue lipid peroxidation and antioxidant status during nicotine-induced toxicity. *Singapore Med J* 2007;48:124–30.
- [122] Kamalakkannan N, Rukkumani R, Varma PS, Viswanathan P, Rajasekharan KN, Menon VP. Comparative effects of curcumin and an analogue of curcumin in carbon tetrachloride-induced hepatotoxicity in rats. *Basic Clin Pharmacol Toxicol* 2005;97:15–21.
- [123] Balasubramanian S, Eckert RL. Green tea polyphenol and curcumin inversely regulate human involucrin promoter activity via opposing effects on CCAAT/enhancer-binding protein function. *J Biol Chem* 2004;279:24007–14.
- [124] Wright JS. Predicting the antioxidant activity of curcumin and curcuminoids. *J Mol Struct* 2002;591:207–17.
- [125] Ishigami YG, Masuda M, Takizawa T, Suzuki Y. The crystal structure and the fluorescent properties of curcumin. *Shikizai Kyokaiishi* 1999;72:71–7.
- [126] Tonnesen HHK, Mostad J. Structural studies of curcuminoids. I. The crystal structure of curcumin. *Acta Chem Scand B* 1982;36:475–80.
- [127] Skrzypczak-Jankun E, Zhou K, McCabe NP, Selman SH, Jankun J. Structure of curcumin in complex with lipoxygenase and its significance in cancer. *Int J Mol Med* 2003;12:17–24.
- [128] Barthelemy S, Vergnes L, Moynier M, Guyot D, Labidalle S, Bahraoui E. Curcumin and curcumin derivatives inhibit Tat-mediated transactivation of type 1 human immunodeficiency virus long terminal repeat. *Res Virol* 1998;149:43–52.
- [129] Kumar S, Misra A, Tripathi S, Misra K. Study on curcumin-oligonucleotide conjugate as a probable anticancer agent: its hybridisation with telomere target sequence 5'-GGGATTGGGATT-3'. *Nucleic Acids Res Suppl* 2001;137–8.
- [130] Kumar S, Narain U, Tripathi S, Misra K. Syntheses of curcumin bioconjugates and study of their antibacterial activities against beta-lactamase-producing microorganisms. *Bioconjug Chem* 2001;12:464–9.
- [131] Mishra S, Tripathi S, Misra K. Synthesis of a novel anticancer prodrug designed to target telomerase sequence. *Nucleic Acids Res Suppl* 2002;277–8.
- [132] Mohri K, Watanabe Y, Yoshida Y, Satoh M, Isobe K, Sugimoto N, et al. Synthesis of glycosylcurcuminoids. *Chem Pharm Bull (Tokyo)* 2003;51:1268–72.
- [133] Mizushima Y, Ishidoh T, Takeuchi T, Shimazaki N, Koiwai O, Kuramochi K, et al. Monoacetylcurcumin: a new inhibitor of eukaryotic DNA polymerase lambda and a new ligand for inhibitor-affinity chromatography. *Biochem Biophys Res Commun* 2005;337:1288–95.
- [134] Mishra S, Narain U, Mishra R, Misra K. Design, development and synthesis of mixed bioconjugates of piperic acid-glycine, curcumin-glycine/alanine and curcumin-glycine-piperic acid and their antibacterial and antifungal properties. *Bioorg Med Chem* 2005;13:1477–86.
- [135] Shi W, Dolai S, Rizk S, Hussain A, Tariq H, Averick S, et al. Synthesis of monofunctional curcumin derivatives, clicked curcumin dimer, and a PAMAM dendrimer curcumin conjugate for therapeutic applications. *Org Lett* 2007;9:5461–4.
- [136] Suzuki M, Nakamura T, Iyoki S, Fujiwara A, Watanabe Y, Mohri K, et al. Elucidation of anti-allergic activities of curcumin-related compounds with a special reference to their anti-oxidative activities. *Biol Pharm Bull* 2005;28:1438–43.
- [137] Takeuchi T, Ishidoh T, Iijima H, Kuriyama I, Shimazaki N, Koiwai O, et al. Structural relationship of curcumin derivatives binding to the BRCT domain of human DNA polymerase lambda. *Genes Cells* 2006;11:223–35.
- [138] Tong QS, Zheng LD, Lu P, Jiang FC, Chen FM, Zeng FQ, et al. Apoptosis-inducing effects of curcumin derivatives in human bladder cancer cells. *Anticancer Drugs* 2006;17:279–87.
- [139] Ishida J, Ohtsu H, Tachibana Y, Nakanishi Y, Bastow KF, Nagai M, et al. Antitumor agents. Part 214: synthesis and evaluation of curcumin analogues as cytotoxic agents. *Bioorg Med Chem* 2002;10:3481–7.
- [140] Ohtsu H, Xiao Z, Ishida J, Nagai M, Wang HK, Itokawa H, et al. Antitumor agents. 217. Curcumin analogues as novel androgen receptor antagonists with potential as anti-prostate cancer agents. *J Med Chem* 2002;45:5037–42.
- [141] Poma P, Notarbartolo M, Labbozzetta M, Maurici A, Carina V, Alaimo A, et al. The antitumor activities of curcumin and of its isoxazole analogue are not affected by multiple gene expression changes in an MDR model of the MCF-7 breast cancer cell line: analysis of the possible molecular basis. *Int J Mol Med* 2007;20:329–35.
- [142] Vajragupta O, Boonchoong P, Watanabe H, Tohda M, Kummasud N, Sumanont Y. Manganese complexes of curcumin and its derivatives: evaluation for the radical scavenging ability and neuroprotective activity. *Free Radic Biol Med* 2003;35:1632–44.
- [143] Venkatesan P, Rao MN. Structure-activity relationships for the inhibition of lipid peroxidation and the scavenging of free radicals by synthetic symmetrical curcumin analogues. *J Pharm Pharmacol* 2000;52:1123–8.
- [144] Costi R, Di Santo R, Artico M, Miele G, Valentini P, Novellino E, et al. Cinnamoyl compounds as simple molecules that inhibit p300 histone acetyltransferase. *J Med Chem* 2007;50:1973–7.
- [145] Jankun J, Aleem AM, Malgorzewicz S, Szkudlarek M, Zawadzky MI, Dewitt DL, et al. Synthetic curcuminoids modulate the arachidonic acid metabolism of human platelet 12-lipoxygenase and reduce sprout formation of human endothelial cells. *Mol Cancer Ther* 2006;5:1371–82.
- [146] Ligeret H, Barthelemy S, Bouchard Doulakas G, Carrupt PA, Tillement JP, Labidalle S, et al. Fluoride curcumin derivatives: new mitochondrial uncoupling agents. *FEBS Lett* 2004;569:37–42.
- [147] Wei QY, Chen WF, Zhou B, Yang L, Liu ZL. Inhibition of lipid peroxidation and protein oxidation in rat liver mitochondria by curcumin and its analogues. *Biochim Biophys Acta* 2006;1760:70–7.
- [148] Nurfina AN, Reksohadiprodjo MS, Timmerman H, Jenie UA, Sugiyanto D, van der Goot H. Synthesis of some symmetrical curcumin derivatives and their antiinflammatory activity. *Eur J Med Chem* 1997;32:321–8.

- [149] Nichols CE, Youssef D, Harris RG, Jha A. Microwave-assisted synthesis of curcumin analogs. *ARKIVOC* 2006;13:64–72.
- [150] Adams BK, Ferstl EM, Davis MC, Herold M, Kurtkaya S, Camalier RF, et al. Synthesis and biological evaluation of novel curcumin analogs as anti-cancer and anti-angiogenesis agents. *Bioorg Med Chem* 2004;12:3871–83.
- [151] Appiah-Opong R, de Esch I, Commandeur JN, Andarini M, Vermeulen NP. Structure-activity relationships for the inhibition of recombinant human cytochromes P450 by curcumin analogues. *Eur J Med Chem* 2007.
- [152] Artico M, Di Santo R, Costi R, Novellino E, Greco G, Massa S, et al. Geometrically and conformationally restrained cinnamoyl compounds as inhibitors of HIV-1 integrase: synthesis, biological evaluation, and molecular modeling. *J Med Chem* 1998;41:3948–60.
- [153] Chandru H, Sharada AC, Bettadaiah BK, Kumar CS, Rangappa KS, Sunila. et al. In vivo growth inhibitory and anti-angiogenic effects of synthetic novel dienone cyclopropoxy curcumin analogs on mouse Ehrlich ascites tumor. *Bioorg Med Chem* 2007;15:7696–703.
- [154] Du ZY, Bao YD, Liu Z, Qiao W, Ma L, Huang ZS, et al. Curcumin analogs as potent aldose reductase inhibitors. *Arch Pharm (Weinheim)* 2006;339:123–8.
- [155] Du ZY, Liu RR, Shao WY, Mao XP, Ma L, Gu LQ, et al. Alpha-glucosidase inhibition of natural curcuminoids and curcumin analogs. *Eur J Med Chem* 2006;41:213–8.
- [156] Liang G, Li X, Chen L, Yang S, Wu X, Studer E, et al. Synthesis and anti-inflammatory activities of mono-carbonyl analogues of curcumin. *Bioorg Med Chem Lett* 2008;18:1525–9.
- [157] Liang G, Yang S, Jiang L, Zhao Y, Shao L, Xiao J, et al. Synthesis and anti-bacterial properties of mono-carbonyl analogues of curcumin. *Chem Pharm Bull (Tokyo)* 2008;56:162–7.
- [158] Ligeret H, Barthelemy S, Zini R, Tillement JP, Labidalle S, Morin D. Effects of curcumin and curcumin derivatives on mitochondrial permeability transition pore. *Free Radic Biol Med* 2004;36:919–29.
- [159] Lin L, Shi Q, Su CY, Shih CC, Lee KH. Antitumor agents 247. New 4-ethoxycarbonyl ethyl curcumin analogs as potential antiandrogenic agents. *Bioorg Med Chem* 2006;14:2527–34.
- [160] Markaverich BM, Schauweker TH, Gregory RR, Varma M, Kittrell FS, Medina D, et al. Nuclear type II sites and malignant cell proliferation: inhibition by 2,6-bis-benzylidenecyclohexanones. *Cancer Res* 1992;52:2482–8.
- [161] Ohori H, Yamakoshi H, Tomizawa M, Shibuya M, Kakudo Y, Takahashi A, et al. Synthesis and biological analysis of new curcumin analogues bearing an enhanced potential for the medicinal treatment of cancer. *Mol Cancer Ther* 2006;5:2563–71.
- [162] Park S, Chung S, Kim KM, Jung KC, Park C, Hahm ER, et al. Determination of binding constant of transcription factor myc-max/max-max and E-box DNA: the effect of inhibitors on the binding. *Biochim Biophys Acta* 2004;1670:217–28.
- [163] Park CH, Lee JH, Yang CH. Curcumin derivatives inhibit the formation of Jun-Fos-DNA complex independently of their conserved cysteine residues. *J Biochem Mol Biol* 2005;38:474–80.
- [164] Reinke AA, Gestwicki JE. Structure-activity relationships of amyloid beta-aggregation inhibitors based on curcumin: influence of linker length and flexibility. *Chem Biol Drug Des* 2007;70:206–15.
- [165] Kumar AP, Garcia GE, Ghosh R, Rajnarayanan RV, Alworth WL, Slaga TJ. 4-Hydroxy-3-methoxybenzoic acid methyl ester: a curcumin derivative targets Akt/NF kappa B cell survival signaling pathway: potential for prostate cancer management. *Neoplasia* 2003;5:255–66.
- [166] Annaraj J, Srinivasan S, Ponvel KM, Athappan P. Mixed ligand copper(II) complexes of phenanthroline/bipyridyl and curcumin diketimines as DNA intercalators and their electrochemical behavior under Nafion and clay modified electrodes. *J Inorg Biochem* 2005;99:669–76.
- [167] Sun YM, Zhang HY, Chen DZ, Liu CB. Theoretical elucidation on the antioxidant mechanism of curcumin: a DFT study. *Org Lett* 2002;4:2909–11.
- [168] Priyadarsini KI, Maity DK, Naik GH, Kumar MS, Unnikrishnan MK, Satav JG, et al. Role of phenolic O–H and methylene hydrogen on the free radical reactions and antioxidant activity of curcumin. *Free Radic Biol Med* 2003;35:475–84.
- [169] Barclay LR, Vinqvist MR, Mukai K, Goto H, Hashimoto Y, Tokunaga A, et al. On the antioxidant mechanism of curcumin: classical methods are needed to determine antioxidant mechanism and activity. *Org Lett* 2000;2:2841–3.
- [170] Jovanovic SV, Steenken S, Boone CW, Simic MG. H-atom transfer is a preferred antioxidant mechanism of curcumin. *J Am Chem Soc* 1999;121:9677–81.
- [171] Talalay P. The importance of using scientific principles in the development of medicinal agents from plants. *Acad Med* 2001;76:238–47.
- [172] Kurien BT, Singh A, Matsumoto H, Scofield RH. Improving the solubility and pharmacological efficacy of curcumin by heat treatment. *Assay Drug Dev Technol* 2007;5:567–76.
- [173] Sou K, Inenaga S, Takeoka S, Tsuchida E. Loading of curcumin into macrophages using lipid-based nanoparticles. *Int J Pharm* 2008;352:287–93.
- [174] Bruzell EM, Morisbak E, Tonnesen HH. Studies on curcumin and curcuminoids. XXIX. Photoinduced cytotoxicity of curcumin in selected aqueous preparations. *Photochem Photobiol Sci* 2005;4:523–30.
- [175] Dubey SK, Sharma AK, Narain U, Misra K, Pati U. Design, synthesis and characterization of some bioactive conjugates of curcumin with glycine, glutamic acid, valine and demethylenated piperic acid and study of their antimicrobial and antiproliferative properties. *Eur J Med Chem* 2007 (in press).
- [176] Aziz HA, Peh KK, Tan YT. Solubility of core materials in aqueous polymeric solution effect on microencapsulation of curcumin. *Drug Dev Ind Pharm* 2007;33:1263–72.
- [177] Gal S, Lichtenberg D, Bor A, Pinchuk I. Copper-induced peroxidation of phosphatidylserine-containing liposomes is inhibited by nanomolar concentrations of specific antioxidants. *Chem Phys Lipids* 2007;150:186–203.
- [178] Lee MH, Lin HY, Chen HC, Thomas JL. Ultrasound mediates the release of curcumin from microemulsions. *Langmuir* 2008;24:1707–13.
- [179] Thangapazham RL, Puri A, Tele S, Blumenthal R, Maheshwari RK. Evaluation of a nanotechnology-based carrier for delivery of curcumin in prostate cancer cells. *Int J Oncol* 2008;32:1119–23.
- [180] Lu P, Tong Q, Jiang F, Zheng L, Chen F, Zeng F, et al. Preparation of curcumin prodrugs and their in vitro anti-tumor activities. *J Huazhong Univ Sci Technol Med Sci* 2005;25. p. 668–70, 78.
- [181] Kapoor N, Sharma AK, Dwivedi V, Kumar A, Pati U, Misra K. Telomerase targeted anticancer bioactive prodrug by antisense-based approach. *Cancer Lett* 2007;248:245–50.
- [182] Letchford K, Liggins R, Burt H. Solubilization of hydrophobic drugs by methoxy poly(ethylene glycol)-block-polycaprolactone diblock copolymer micelles: theoretical and experimental data and correlations. *J Pharm Sci* 2008;97:1179–90.

- [183] Salmaso S, Bersani S, Semenzato A, Caliceti P. New cyclodextrin bioconjugates for active tumour targeting. *J Drug Target* 2007;15:379–90.
- [184] Safavy A, Raisch KP, Mantena S, Sanford LL, Sham SW, Krishna NR, et al. Design and development of water-soluble curcumin conjugates as potential anticancer agents. *J Med Chem* 2007;50:6284–8.
- [185] Atsumi T, Fujisawa S, Tonosaki K. Relationship between intracellular ROS production and membrane mobility in curcumin- and tetrahydrocurcumin-treated human gingival fibroblasts and human submandibular gland carcinoma cells. *Oral Dis* 2005;4:236–42.
- [186] Nakamura Y, Ohto Y, Murakami A, Osawa T, Ohigashi H. Inhibitory effects of curcumin and tetrahydrocurcuminoids on the tumorpromoter-induced reactive oxygen species generation in leukocytes in vitro and in vivo. *Jpn J Cancer Res* 1998;4:361–70.
- [187] Singletary K, MacDonald C, Iovinelli M, Fisher C, Wallig M. Effect of the beta-diketones diferuloylmethane (curcumin) and dibenzoylmethane on rat mammary DNA adducts and tumors induced by 7,12-dimethylbenz[a]anthracene. *Carcinogenesis* 1998;19:1039–43.
- [188] Nagano T, Oyama Y, Kajita N, Chikahisa L, Nakata M, Okazaki E, et al. New curcuminoids isolated from Zingiber cassumunar protect cells suffering from oxidative stress: a flow-cytometric study using rat thymocytes and H₂O₂. *Jpn J Pharmacol* 1997;75:363–70.