Perspectives on New Synthetic Curcumin Analogs and their Potential Anticancer Properties

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Abstract

Curcumin is the active component of dried rhizome of *Curcuma longa*, a perennial herb belonging to ginger family, cultivated extensively in south and southeastern tropical Asia. It is widely consumed in the Indian subcontinent, south Asia and Japan in traditional food recipes. Extensive research over last few decades has shown that curcumin is a potent anti-inflammatory agent with powerful therapeutic potential against a variety of cancers. It suppresses proliferation and metastasis of human tumors through regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases and other enzymes. It induces apoptotic cell death and also inhibits proliferation of cancer cells by cell cycle arrest. Pharmacokinetic data has shown that curcumin undergoes rapid metabolism leading to glucuronidation and sulfation in the liver and excretion in the feces, which accounts for its poor systemic bioavailability. The compound has, therefore, been formulated and administered using different drug delivery systems such as liposomes, micelles, polysaccharides, phospholipid complexes and nanoparticles that can overcome the limitation of bioavailability to some extent. Attempts to avoid rapid metabolism of curcumin until now have been met with limited success. This has prompted researchers to look for new synthetic curcumin analogs in order to overcome the drawbacks of limited bioavailability and rapid metabolism, and gain efficacy with reduced toxicity. In this review we provide a summarized account of novel synthetic curcumin formulations and analogs, and the recent progress in the field of cancer prevention and treatment.

Keywords

Curcumin; curcumin analogs; anticancer; novel formulations

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

1. INTRODUCTION

Phytochemicals are a broad variety of biologically active compounds produced by plants usually as secondary metabolites that possess either antioxidant or hormone-like actions. They are generally found in fruits, vegetables, beans or grains. Diets rich in fruits, vegetables or whole grains have been shown to reduce the risk of certain cancers, heart diseases, diabetes and other health disorders, and hence there is a continual attempt to identify specific compounds in these foods that may account for their beneficial effects in humans. Since phytochemicals help prevent formation of potential cancer-causing moieties by blocking their action, they are also viewed as chemopreventive agents against cancers [1].

Among many such agents, Curcumin has attracted increased attention. This is a phytochemical which is derived from turmeric (*Curcumin longa*) and has been used for thousands of years as a healing agent in Indian and Chinese systems of medicine for variety of illnesses. Several research reports over the last few decades have established that curcumin is a potent anti-inflammatory agent [2–6] with powerful therapeutic potential against a variety of cancers [7–11]. It has been shown to suppress transformation, proliferation, and metastasis of tumors [12]. These effects are mediated through regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases and other enzymes [13]. Curcumin also inhibits proliferation of cancer cells by arresting them in various phases of the cell cycle and by inducing apoptosis [14]. The compound has the ability to inhibit carcinogen bioactivities via suppression of specific cytochrome P450 enzymes, and to induce the activity or expression of phase II carcinogen detoxifying enzymes, which may account for its cancer chemopreventive effects [15].

Although curcumin has been successfully evaluated for wide ranging biological activities, the two main concerns related to its poor bioavailability and rapid metabolism have prompted researchers to look for novel drug delivery systems, and new synthetic curcumin analogs in order to overcome these drawbacks and gain in efficacy with reduced toxicity. In the present review, we provide a short account of some of the new curcumin analogs reported since 2005 which have shown enhanced anticancer activities than curcumin against certain cancers, and hence offer hope for clinical benefits. A summarized account of the reports published earlier is provided in our earlier review published in 2010 [16].

2. CHEMISTRY OF CURCUMIN

Curcumin is an orange–yellow crystalline powder practically insoluble in water and ether but soluble in ethanol, dimethylsulfoxide and acetone. It was first isolated in 1815 by Vogel and Pelletier, while it was isolated in crystalline form in 1870, and identified as 1, 6-heptadiene-3, 5-dione1,7-bis(4-hydroxy-3-methoxyphenyl)-(1E, 6E) or Diferuloylmethane. The feruloylmethane skeleton of curcumin was confirmed in 1910 by Lampe [17, 18]. Chemically, curcumin is a bis-α, β-unsaturated β-diketone and exists in equilibrium with its enol tautomer (Fig. 1). The bis-keto form predominates in acidic and neutral aqueous solutions as well as in the cell membrane due to the heptadienone linkage between two methoxyphenol rings containing a highly activated carbon atom.

Tonnesen and Karlsen [19] have studied the hydrolytic degradative reaction kinetics of curcumin over the rage of pH 1–11 by using HPLC and found that at pH < 1, curcumin aqueous solution exhibits red color which is indicative of the protonated form (**2**). At a pH range 1–7, curcumin molecules are in the neutral state (**3**) with yellow color and low water solubility, while at pH>7.5 this color turns to red (Fig. 2). In the keto form of curcumin, the heptadienone linkage between the two methoxyphenol rings contains a highly activated

carbon atom and the C–H bonds on this carbon are very weak due to delocalization of the unpaired electron on the adjacent oxygen atoms. Curcumin possesses three protons that are ionizable in water, Viz. the enolic proton with a pKa of approximately 8.5 and two phenolic protons with pKa of 10 – 10.5 (in mixed alcoholic/water solvent). The pKa values for the dissociation of the three acidic protons in curcumin (forms **4**, **5** and **6**) have been determined to be 7.8, 8.5 and 9.0, respectively (Fig. 3). Between the acidic range of pH 3–7, curcumin acts as a potent H-atom donor, while above pH 8 (basic condition), the enolate form of the heptadienone chain predominates and the compound acts mainly as an electron donor similar to many phenolic antioxidants [19]. Tonnesen and Karlsen [19] have further found that the main degradation products of curcumin are ferulic acid and feruloylmethane and have investigated their kinetics of degradation in a MeOH/aqueous buffer medium (1: 9), with phosphate buffer (pH 6 – 9) or carbonate buffer (pH 9 – 10), wherein the rate of degradation was found to be second order for curcumin. It was found that curcumin decomposed 90% within 30 min in 0.1 M phosphate buffer at pH 7.2 at 37°C, while the tentatively identified intermediate decomposition product, viz.trans-6-(4-hydroxy-3-methoxyphenyl)-2,4-dioxo-5-hexenal, decomposed further to yield vanillin as a final product (Fig. 4) along with ferulic acid and feruloylmethane respectively [20].

Bernabe-Pineda *et al.* [21] have shown that curcumin exhibits a pseudo-zero-order kinetics of decomposition in non-buffered aqueous medium of pH 10–13.5, with a rate constant of 1.39×10^{-9} M/min. Several *in vivo* studies have identified number of intestinal metabolites (Fig. 5) in human and rats including curcumin glucuronide (**7**), curcumin sulfate (**8**), tetrahydrocurcumin (**9**) and hexahydrocurcumin (**10**) [22]. Hence, both metabolic conjugation and reduction were observed along with traces of the aforementioned decomposition products of dihydroferulic acid and ferulic acid as biliary metabolites of oral curcumin administration in rats [23].

3. STRATEGIES FOR IMPROVING CURCUMIN AS THERAPEUTIC AGENT

Curcumin has been reported to be very safe because it does not cause any adverse effects, even up to doses as high as 8 g per day in humans and no resistance against curcumin has been reported. However, the bioavailability of Curcumin is a major concern limiting its therapeutic utility, since as much as 75% of Curcumin gets excreted in the feces, indicating its poor absorption in the gut. This suggests that in order to make Curcumin as a viable therapeutic agent one needs to address two shortcomings of Curcumin, one being its low bioavailability and the other concerning its rapid metabolism. This has been tackled by adopting two strategies: (a) Employing novel drug delivery systems and (b) Synthesizing its analogs through modification of its structural motif. Attempts avoiding rapid metabolism until now have been met with limited success except in case of difluorocurcumin (CDF), a novel synthetic analog of curcumin described recently by us [24]. In the discussion below we have summarized a brief account of both.

3.1. Novel Drug Delivery Systems

In an attempt to stabilize curcumin, Wang and co-workers have developed curcumin micelles by aggregation of surfactant molecules, like sodium dodecyl sulfate, cetyltrimethylammonium bromide (CTAB), Tween 80, Triton X-100 and pluronic polymers [25]. Stable self-emulsifying curcumin formulations having particles size of approximately 30 nm and approximately 99% curcumin loading have successfully been developed [26] which showed 10–14-fold greater absorption rate in male Wistarstrain rats.

Curcumin nanosuspension (CUR-NS) was stabilized by d- tocopheryl polyethylene glycol 1000 succinate (TPGS), which has been examined for its pharmacokinetics after intravenous administration to rabbits and mice [27]. It was interesting to observe that these formulations

increased the plasma concentration of curcumin by 3.8 times, thus increasing its bioavailability. In another study, Pandey *et al.* [28] developed novel polyethylene glycosylated (PE-Gylated) curcumin analogs for potent nuclear factor erythroid-2 related factor 2 (Nrf2) activators, which positively regulated the antioxidant defense system and could decrease inflammation. These analogs improved curcumin solubility from 0.6×10^{-6} to 0.98×10^{-6} g/ml. This formulation exhibited growth inhibitory effects on a panel of human pancreatic cancer cell lines. Another report has indicated that polyacetal-based curcumin polymers (PCurc 8) are highly cytotoxic to SKOV-3 and OVCAR-3 ovarian cancers, and MCF-7 breast cancer cell lines. These conjugates were selectively taken up by cancer cells, hydrolyzed and released an active form of curcumin in lysosomes. The mechanistic study revealed that inhibition of cancer cell growth was predominant in G (0)/G (1) phase and occurred through induced apoptosis by caspase-3 activation [29]. Another strategy of increasing bioavailability was to prepare micro-emulsions of curcumin which are isotropic nanostructures and stable solutions comprising of surfactant, oil and water. In another study, Ganta and co-workers [30] have reported that curcumin nanoemulsion increases the bioavailability of paclitaxel up to 5.2-fold, and there was a 3.2-fold increase in its accumulation at the tumor site in an oral administration to SKOV-3 tumor-bearing xenografts mice models. This was possible due to down-regulation of intestinal cytochrome P450 3A2 (CYP3A2) protein levels.

Li *et al.* [31] have evaluated the anticancer efficacy of liposomes of curcumin on various pancreatic carcinoma cell lines, including ASPC-1, BxPC-3, Capan-1, Capan-2, HS766-T and Mia-paCa-2, respectively. The study revealed that this liposomal formulation could inhibit cancer cells at IC_{50} values in the range of 2.0–37.8 μM. Nano-formulations based on dextransulfate–chitosan combinations are widely accepted for oral, intravenous and controlled delivery purposes. In a study by Anitha *et al.* [32], the authors quantified the cellular uptake of curcumin encapsulated in dextransulfate–chitosan NPs using a spectrophotometric method in a panel of cancer cells including L929, MCF-7, PC-3 and MG 63 cells. The results revealed that the anticancer efficacy of this formulation was greater in MCF-7 cells. Another method employed for curcumin formulation was to generate self-assembly complexes with βcyclodextrin and their derivatives. Such complexes helped in the suppression of curcumin degradation and consequently increased the stability and bioavailability [33, 34]. Employing this strategy, Yadav and co-workers [35] have developed cyclodextrin–curcumin self-assembly, which exhibited higher efficacy compared to curcumin in inhibiting tumor necrosis factor (TNF)-induced expression of NF-κB regulated genes (VEGF, MMP-9 and cyclin D1) and up-regulation of death receptors (DR4 and DR5) in KBM-5 cancer cells. Similar studies by Yallapu *et al.* [36] showed that self-assembled complex of curcumin with poly-βcyclodextrin showed anti-proliferative properties against prostate cancer cells. It is presumable that the presence of curcumin in the complex results in down-regulation of anti-apoptotic Bcl-2 and Bcl-xL, and induction of pro-apoptotic Bax family proteins thereby inducing apoptosis. Our group has recently reported a new difluoro curcumin analog commonly referred to as **CDF** (**139**) with superior anticancer activity. The CDF conjugate with βcyclodextrin (**CDFCD**) [37] in 1: 2 proportions exhibited significantly lower IC_{50} values when tested against a panel of BXPC-3, MDA-MB-231 and PC-3 cancer cell lines compared to CDF alone. *In vivo* studies revealed that the conjugate preferentially accumulated in the pancreas and the levels of CDF-βcyclodextrin conjugate in mice were 10 times higher than in serum, following intravenous administration of an aqueous CDF-βcyclodextrin preparation. These studies indicated that the self-assembly of βcyclodextrin and CDF may provide a crucial breakthrough in enhancing the bioavailability and tissue distribution of such analogs.

Although survey of available literature on curcumin-based nano-particulate formulations suggests that this strategy holds some promise in the use of curcumin in cancer therapeutics, the issue of rapid metabolism of curcumin remains a matter of concern.

3.2. Novel Curcumin analogs through Structural modifications

Curcumin is a simple symmetrical β-diketone and incorporates several functional groups. The two aromatic rings containing phenolic groups are connected by two α, β-unsaturated carbonyl groups. These carbonyl groups form a diketone moiety which exists in keto-enolic tautomeric forms, where energetically more stable enol-form exists in the solid phase and in acidic solutions. It can be easily deprotonated under mild alkaline condition to yield enolate moiety. Such facile tautomeric conversions are suspected to contribute to the rapid metabolism of curcumin. In its unmodified form α, β-unsaturated carbonyls in curcumin play the role of a good Michael acceptor and can undergo nucleophilic additions under biological conditions which may enhance its bioavailability. Exploiting this strategy led to limited success in terms of modulating Curcumin's metabolism, resulting in ill-defined and unstable products. In view of this several research groups have attempted to modify structural motif of Curcumin in order to slow down its metabolism and improvements in its potency and efficacy of anticancer activity. In (Fig. 6), we have summarized the sites used by these workers for structural modifications of curcumin. These include aryl side chain modification (Fig. 7A), modification of diketo functionality (Fig. 7B), modification of double bond (Fig. 7C), modification of active methylene functionality (Fig. 7D), metal complexes of curcumin (Fig. 7E) and structural analogs of curcumin (Fig. 8). Most of these modifications were made on the basis of what was achievable chemically and for tailoring the biological space and hence has remained partially successful. Following is the brief account of each modification and resulting changes in terms of specificity and efficacy for different cancers.

3.2.1. Modifications of Aryl Side Chain—Aggarwal and coworkers [38] have synthesized a bioconjugate of Luteinizing Hormone Releasing Hormone (LHRH)) and Curcumin as shown in **11**. The work revealed that MIAPaCa-2, Panc-1 and BxPC-3 pancreatic cancer cell lines express LHRH receptors and consequently the conjugate inhibited cell proliferation and induced apoptotic cell death. Apoptosis was induced by cleavage of polyadenosine-5-diphosphate-ribose-polymerase and caspase-3. Unlike curcumin, the conjugate is water soluble which allows its intravenous administration. Under *in vivo* conditions, the conjugate brought about significant reduction in tumor weight and volume (compared to free curcumin), in the nude mouse pancreatic cancer model. Al-Hujaily *et al*. [39] have investigated the anticancer activities of two novel curcumin analogs **EAC (12)** and **PAC (13)** against normal and breast cancer cells wherein the latter was found to be five times more efficient than curcumin in inducing apoptosis at 40 μM dose. This effect was 10-fold higher against ER-negative as compared to ER-positive breast cancer cells. In addition, **PAC** delayed the cell cycle at G2/M phase with a stronger effect on ER-negative cells. The compound exhibited higher stability in blood and greater bio-distribution and bioavailability than curcumin in mice. Al-Wabli *et al*. [40] have synthesized and evaluated new curcumin and ethyl-curcumin bioconjugates with various functionalities which are more active than the parent compounds. Many of these compounds are non-toxic to non-cancerous cells. Compound **14** exerted cytotoxicity against SK-MEL (human malignant melanoma) and BT-549 (breast ductal carcinoma) with IC_{50} values of 12.5 and 10 μM, respectively. The compound **15** showed highest cytotoxic activity against SK-MEL and SK-OV-3 (human ovary carcinoma) cancer cells with IC_{50} values 4.75 and 2.8 μM, respectively.

Devasena *et al.* [41] have studied the protective effect of a salicylcurcumin (**16**) on hepatic lipid peroxidation (LPO) and antioxidant status during 1, 2-dimethylhydrazine (DMH)-induced colon carcinogenesis in male wistar rats. Intra-gastric administration of curcumin and salicylcurcumin (80 mg/kg body weight) to DMH-injected rats significantly reduced the number and size of tumors in the colon, lowered lipid peroxidation and enhanced the activities of GPx, GST, SOD and CAT in the liver. The mechanism of this action was shown to be the modulation of hepatic biotransformation enzymes and antioxidant status which was similar and comparable with that of curcumin. This suggests that the hydroxyl group in the aromatic ring is responsible for the protective effect of these compounds rather than the methoxy group as thought previously [41, 42].

The cytotoxicity of some newly synthesized glycoconjugates, including curcumin ⬚ glucoside (**17**), has been investigated by Arafa and co-workers [43] in a panel of human colon cancer cells, viz. Caco-2, HT29 and T84 cells. Curcumin- ⬚glucoside exerted cytotoxicity against Caco-2, HT29 and T84 cells with IC_{50} value of 10.3, 24.6 and 50.3 ⬚M, respectively. This sensitivity correlates well with ⬚glucosidase activity which was assessed in these cell lines. The curcumin ⬚glucoside was only cleaved by beta-glucosidases and ⬚ galactosidases, but not by pancreatic lipase or hepatic esterase, suggesting that these enzymes are crucial for the bioactivation and cytotoxicity of these glycoconjugates. Dubey *et al.* [44] have synthesized the monoesters of curcumin, a symmetric diphenol with valine (**18**) and glycine (**19**) substituents, by solid phase synthesis and its diesters by solution phase method. The assessment of their anti-proliferative activities suggested that the diesters are relatively more active than curcumin itself against KB and HeLa cell lines probably due to their increased solubility, slow metabolism and better cellular uptake.

Ferrari *et al.* [45] have synthesized some new curcumin derivatives (**20–21**) in order to improve chemical properties of curcumin. The aromatic ring glycosylation of curcumin provides more water-soluble compounds with greater kinetic stability which is a fundamental feature for drug bioavailability. The acyl-derivative of curcumin (**20**) and glycosyl-curcuminoid (**21**) exhibited cytotoxicity against cisplatin (cDDP)-sensitive human ovarian carcinoma cell line and its resistant counterpart, C13* cancer cells, as compared to curcumin. Although binding of glucose to curcumin reduces the cytotoxicity of the derivatives towards cisplatin (cDDP)-sensitive/resistant human ovarian cancer cell lines, the compounds display a good selectivity since they are much less toxic to non-tumorigenic Vero cells. The combination of cDDP with the most active glycosyl-curcuminoid drug against both cDDP-sensitive and -resistant as well as against Vero cell lines showed an improvement of cDDP efficacy with higher selectivity towards cancer cells than non-cancer cells. These studies indicate further need for developing new valid components for drug treatment protocols to cDDP-resistant cells as well. Fuchs and coworkers [46] have synthesized a library of curcumin analogs and evaluated them against prostate and breast cancer cell lines. Compounds **22–26** were the most potent analogs which exerted cytotoxicity against androgen-dependent LNCaP as well as androgen-independent prostate cancer PC-3 cell line. The compounds were also inhibitory against estrogen-dependent MCF-7, and estrogen-independent MDA-MB-231 breast cancer cell lines. The compound **26** was found to be most cytotoxic compound against LNCaP, PC-3, MCF-7 and MDA-MB-231 cancer cell lines. Goto and group [47] have synthesized a novel curcumin conjugate of taxoid and have evaluated its cytotoxic activity against a panel of cancer cell line including A549 (human lung carcinoma), 1A9 (human ovarian carcinoma), HCT-8 (colon adeno-carcinoma), A431 (epidermoid skin carcinoma), KB (human epidermoid carcinoma of the nasopharynx) and multi-drug resistant KB variant expressing P-glycoprotein (KB-VIN) cancer cell lines. The compound was found to be cytotoxic to all cell lines except HCT-8 colon cancer cell line. Han *et al.* [48] have synthesized 2-hydroxycurcuminoid (HCC-7, **27**) based on the structural motif of 2-hydroxy-cinnamaldehyde which strongly

inhibited the growth of SW620 colon tumor cells while the parent compounds, HCA and curcumin displayed higher inhibitory concentraions. HCC-7 was found to induce apoptosis through reactive oxygen species–mitochondria pathway and cell cycle arrest at G2/M phase. The compound also exhibited cytotoxicity against other cancer cell lines although at higher concentrations.

Handler *et al.* [49] have reported synthesis of curcumin analogs **28 and 29** wherein the former was found to be most potent compound inhibiting COX-1 and COX-2 enzymes. Jankun *et al.* [50] have used a homology model of the three-dimensional structure of human P-12-LOX by performing computational docking studies of synthetic curcumin derivatives to identify inhibitors superior than curcumin. Over 75% of the compounds of interest were successfully docked into the active site of P-12-LOX, many of them sharing similar binding modes. Curcuminoids that did not dock into the active site failed to inhibit P-12-LOX. From a set of curcuminoids that were successfully docked, two compounds [**E22C** (**16**) and **E26C** (**30**)] were found to inhibit human lipoxygenase better than curcumin. False-positive curcuminoids showed high LogP values, indicating poor water solubility, a possible reason for lack of inhibitory activity and/or non-realistic binding.

Kapoor *et al.* [51] have linked a deoxy-11-mer oligonucleotide (5′-GTTAGGGTTAG-3′), complementary to a repeat sequence of human telomerase RNA template through phosphate and C-2 linker to the bioactive tetraglycine conjugate of curcumin (**31**). This molecule was transfected into KB and HeLa cell lines and was found to affect cell growth in the former at a concentration of 25–50 μM. The compound probably acts as a pro-drug being targeted by anti-sense mechanism to telomerase.

Khan and co-workers [52] have synthesized aromatic and heterocyclic aromatic curcuminoids and have evaluated their anti-inflammatory activities (AIA) *in vivo* model of acute carrageenan-induced paw edema and chronic adjuvant arthritis. At dose of 100 mg/kg, the compounds **RK-97 (32), RK-103 (33), RK-104 (34) and RK-106 (35)** have exerted potent activity in the anti-arthritic assay with little gastric or systemic toxicity. Amongst the compounds evaluated, **RK-106** was the only compound to inhibit the production of TNF-α and IL-1β in a monocytic cell-line THP-1 at 100 μM concentration. Li *et al.* [53] have prepared a water-soluble polyethylene glycol (PEG)-conjugate of curcumin (**36**) in which curcumin was covalently linked to PEG (35kD). PEGylated curcumin showed enhanced solubility, targeted delivery and greater reduction of cell growth than free curcumin in pancreatic cancer cells. Cells treated with PEGylated curcumin had increased arrest at the mitotic phase with the formation of abnormal multi-nucleated cells, indicating that this compound affects cell cycle progression, which may contribute to cell growth inhibition. PEGylated curcumin increased protein stability of these proteins in pancreatic cancer cells and directly inhibited the activity of Jab1/CSN-associated kinases. Moreover, the inhibitory effect of PEGylated curcumin on cell proliferation was blunted in pancreatic cancer cells with Jab1 knock-down. The results suggested that PEGylated curcumin inhibits cell proliferation through suppression of Jab1/CSN activity.

Manju *et al.* [54] have synthesized polyvinyl pyrrolidone–curcumin conjugate (**37**) to enhance water solubility of curcumin. The drug conjugate self-assembled in aqueous solution to form nano-sized micellar aggregates, which were cationic and stable against hydrolytic degradation. The net zeta potential of these in the pH range 3−7.4 was +20 to +25 mV, reflecting the potential stability of the conjugate micelle at physiological pH. The cytotoxic potential of the conjugate was evaluated against L929 fibroblast cells indicating that the conjugate has higher cytotoxicity than free curcumin probably due to enhanced aqueous solubility and polymer-mediated drug internalization. Pandey *et al.* [28] have PEGylated curcumin (**38–41**) as water soluble drug candidate with enhanced aqueous

solubility and bioavailability. Based on the luciferase-based reporter gene assay most of the PEGylated curcumin analogs were found to strongly activate Nrf2 several folds higher than the free curcumin wherein the copolymer **38** was identified as the most potent Nrf2 activator, which induced Nrf2-driven NQO1 expression in a concentration dependent manner.

Mishra *et al.* [55] have examined pro-oxidant and antioxidant properties of dipiperoyl (**42**) and diglycinoyl (**43**) derivatives which showed higher apoptotic activity at lower concentrations than diacetylcurcumin. The apoptotic activity of these derivatives correlated with the generation of ROS by the tumor cells, whereas GSH levels remained unaffected. The studies also indicated down-regulation of Bcl-2 protein and activation of caspase-3 in the apoptotic death of tumor cells. Qui *et al.* [56] have synthesized a series of curcumin derivatives with modifications in the aryl ring and have evaluated their inhibitory activities on thioredoxin reductase (TrxR) by DTNB assay *in vitro*. Most of the analogs were found to inhibit TrxR in the low micromolar range. Structure-activity relationship analysis revealed that analogs with furan moiety (**44–47**) have excellent inhibitory effect on TrxR in an irreversible manner, indicating that the furan moiety may serve as a possible pharmacophore during the interaction of curcumin analogs with TrxR. The compound **46** showed growth inhibitory activity against different TrxR over-expressed A549/R and MCF-7/R cancer cell lines.

Safavy *et al.* [57] have prepared conjugates of curcumin with two polyethylene glycol (PEG) derivatives in order to improve its lower water solubility and improve its cytotoxicity against human cancer cell lines. The soluble conjugates **48** and **49** exhibited enhanced cytotoxicity against different pancreatic cancer line including LS-174T, MIAPaCa-2 and BxPC-3 cell lines. The half-Life ($t_{1/2}$) of curcumin drug release from the High- and Low-MW PEG conjugates was found to be 60 and 200 minute, respectively. It was suggested that water-soluble conjugates may provide useful starting point for the development of injectable curcumin conjugates. Another aryl-side chain modified analogue dimethoxycurcumin (**23**) was found to be more potent *in vitro* against human HCT116 colon cancer cells in terms of its ability to inhibit proliferation and induce apoptosis. Nearly 100% of curcumin compared to less than 30% of dimethoxycurcumin was degraded in cells treated for 48 h. Incubation with liver microsomes confirmed the limited metabolism of dimethoxycurcumin. Although both compounds were rapidly degraded *in vivo*, the demethoxycurcumin was more stable. It is likely that differential extent of apoptosis induced by these compounds was associated with their different metabolic profiles [58].

Wichitnithad *et al.* [59] have synthesized a novel series of succinyl-derivatives of three curcuminoids as potential prodrugs (**50–53**). Their anti-proliferative activity was evaluated using Caco-2 cells. The succinate pro-drugs were found to possess much lower IC_{50} values (1.8–9.6 M) compared to the parent compounds. Curcumin diethyl disuccinate exhibited the highest potency and was chosen for stability studies. Hydrolysis of this compound in phosphate buffer at pH 7.4 and in human plasma followed pseudo first-order kinetics indicating that the compound was much more stable than curcumin and was able to release curcumin in human plasma.

Youssef *et al.* [60] prepared a series of novel analogues of curcumin, and analyzed their cytotoxic activity against L1210 (murine leukemia) and human lymphoblast Molt4C/8 CEM cell lines where compounds **54–57** were found to be cytostatic. Vyas *et al.* [61] conjugated curcumin with a recombinant chimeric antibody cPiPP (**58**), exhibiting high affinity and specificity for human chorionic gona-dotropin- (hCG-)/hCG, which was tested for growth inhibitory properties against MOLT-4 and U-937 cells. Interestingly, the antibody did not impair the growth of MOLT-4 and U-937 cells while its conjugate was lethal to both cell

lines. The immuno-conjugate killed tumor cells bearing the CD33 marker of an AML patient expressing hCG- □ but not for the patient who was negative for hCG- □

Yodkeeree *et al.* [62] have reported that demethoxycurcumin (DMC, **59**) inhibits adhesion, migration and invasion of MDA-MB-231 human breast cancer cells. MDA-MB-231 cells treated with DMC had decreased levels of extracellular matrix (ECM) degradation-associated proteins including matrix metalloproteinase-9 (MMP-9), membrane type-1 matrix metalloproteinase (MT1-MMP), urokinase plasminogen activator (uPA) and uPA receptor (uPAR), while the level of uPA inhibitor (PAI-1) was up-regulated. Moreover, DMC also reduced the expression of intercellular adhesion molecule-1 (ICAM-1) and chemokine receptor 4 (CXCR-4), which is involved in the modulation of the tumor metastasis process. It was found that DMC treatment inhibited DNA binding activity of NF- □B, which is known to mediate the expression of MMPs, uPA, uPAR, ICAM-1, and CXCR-4 proteins. Ryu *et al.* [63] have shown that DMC and bis-demethoxycurcumin (BDMC, **60**) suppressed □catenin response transcription (CRT) that was activated by Wnt3a conditioned-medium (Wnt3a-CM) without altering the level of intracellular □catenin, and inhibited the growth of various colon cancer cells, with comparable potency to curcumin. Additionally, DMC and BDMC down-regulates p300, which is a positive regulator of the Wnt/ □catenin pathway.

Thus, it may be concluded that some of the modifications made to the aryl side chain result in improving the potency of Curcumin but not their specificity towards type of cancer cells. Similarly data on their *in vivo* activities in most cases is lacking.

3.2.2. Modifications of Diketo Functionality—Das and coworkers [64] have investigated the role of carbonyl and hydroxyl groups of Curcumin in PKC binding by synthesizing pyrazole (**61–62**) and isoxazole (**63–65**) derivatives and studying their interaction with protein kinase-C □(PKC- □), especially with the activator-binding second cysteine-rich C1B sub-domain. All synthesized derivatives showed higher binding with the PKC- □C1B compared with PKC- □C1B and PKC- □C1B. Compound **63** exhibited most potent PKC binding activity. Molecular docking revealed that isoxazole (**63**) and pyrazole (**61**) derivatives bind to the activator binding site of PKCs and both carbonyl and hydroxyl groups of curcumin play role in such binding process, depending on the nature of Curcumin derivative and the PKC isotype. Compared with Curcumin, its isoxazole (**63**) and pyrazole (**61**) derivatives exhibited increased cell growth inhibitory and pro-apoptotic effects in liver cancer HA22T/VGH cells as well as in other tumor cell types. The anti-tumor effects of isoxazole (**63**) and pyrazole (**61**) were not influenced by concomitant administration of N-acetylcysteine, as a source of –SH groups, or buthionine sulfoximine as an inhibitor of glutathione synthesis. Additionally treatment with Curcumin, but not with isoxazole (**63**) and pyrazole (**61**), significantly decreased the content of reduced glutathione in the HA22T/VGH cells. Isoxazole (**63**) and pyrazole (**61**) lacked the ability of the parent compound to sensitize the HA22T/VGH cells to cisplatin (CIS), an effect which is known to occur through an interaction of curcumin and cisplatin at the level of the thiolic groups. Thus, the ability of interacting with cell thiols might not be required for these curcumin derivatives and they may be devoid of chemo-sensitization capabilities [65].

Poma *et al.* [66] have also examined the effects of curcumin and compound **63** in the MCF-7 breast cancer cell line, and in its multi-drug resistant variant MCF-7R, which lacks estrogen receptor alpha (ER- □) and exhibits over-expression of P-glycoprotein (P-gp), IAP (inhibitory of apoptosis proteins) and COX-2 proteins. It was observed that the anti-tumor activity of curcumin and compound **63** is equivalent in the MDR cell line. It seems that the overall anti-tumor activities of curcumin or **63** are not hampered by P-gp expression or lack of ER- □in breast cancer cells. Remarkably, the agents appeared to modify their molecular effects according to the diverse gene expression patterns existing in the MDR and parental

MCF-7 cells. Sahoo and co-workers [67] have examined the interaction of **63** with human serum albumin (HSA) using various biophysical methods. The observed fluorescence quenching of HSA by 63 is due to complex formation with quenching constant of the order of 10^5 M^{-1}.

The semicarbazone derivative of curcumin (CRSC, **66**), has been described by our group which was evaluated for antioxidant, anti-proliferative, and radical scavenging activities [68]. CRSC was found to inhibit radiation induced lipid peroxidation in the rat liver microsomes at 10 ☐M concentration. Its interaction with 2, 2 ☐diphenyl-1-picrylhydrazide (DPPH) was studied using a stopped-flow spectrophotometer. The rate constant for curcumin was found to be 1640 ± 38 M^{-1} s^{-1} and the reaction was completed within 10–20s, while the reaction with CRSC was much slower under similar conditions and took more than 200 s. The rate constant for the reaction was determined to be 274 ± 7 M^{-1} s^{-1}. The difference in their rate constants was attributed to the steric hindrance provided by the bulky semicarbazide side chain and its higher reduction potential. CRSC exhibited potent cytotoxic activity (74% growth inhibition) against breast cancer MCF-7 cell line at 1 ☐g/mL concentration as compared to curcumin (36% growth inhibition). Lal *et al.* [69] have synthesized 3,4-dihydropyrimidinones of curcumin by multi-component one-pot condensation of curcumin, substituted aromatic aldehydes and urea/thiourea under solvent free conditions using $SnCl_2.2H_2O$ catalyst and have evaluated cytotoxic profile of the compound. Among all derivatives, compound **67–69** showed better cytotoxic activity than curcumin against human Hep-G2, HCT-116 and QG-56 cancer cell lines, respectively.

Shim *et al.* [70] have described hydrazinocurcumin (HC, **61**) and benzoylhydrazino-curcumin (HBC, **70**) derivatives which were found to be inhibitory against proliferation of bovine aortic endothelial cells (BAECs) at nanomolar concentration (IC_{50}=520 nM) without cytotoxicity. *In vivo* and *in vitro* angiogenesis experiments showed HC as a new potent candidate for developing anti-angiogenic agents. These researchers have further identified Ca^{2+}/calmodulin (Ca^{2+}/CaM) as a direct target protein of HBC using phage display biopanning [71]. Ca^{2+}/CaM-expressing phages specifically bound to the immobilized benzoylhydrazino-curcumin (HBC) and the binding was found to be Ca^{2+} dependent. In order to isolate the direct binding protein of HBC, the biotinyl-HBC (**71**) was synthesized as a molecular probe for target identification and was found to be two fold less potent than HBC against colon cancer cells. Flexible docking demonstrated that HBC was compatible with the binding cavity for a known inhibitor, viz.W7 (N-(6-amino-hexyl)-5-chloro-1-naphthalensulfonamide), in the C-terminal hydrophobic pocket of Ca^{2+}/CaM. It was suggested that HBC-induced prolonged phosphorylation of ERK1/2 and activation of $p21^{WAF1}$ (p21) expression, resulting in the induction of G0/G-cell cycle arrest in HCT15 colon cancer cells.

Simoni *et al.* [72] have studied enaminones, oximes, and isoxazole derivatives of curcumin. These were evaluated against hepatocellular HA22T/VGH cancer cells, MCF-7 breast cancer cells and its multi-drug resistant variant MCF-7R, respectively. The compounds **63, 72 and 73** showed growth inhibitory activity against all cancer cell lines. Enhanced anti-tumor activity on all cell lines was found with isoxazole (**63**) and benzyloxime (**73**) derivatives. Swarts *et al.* [73] have investigated semicarbazone and pyrazole derivatives of curcumin as potential mitigation agents to treat acute radiation syndrome (ARS). Pyridyl (**74–75**), furyl (**76**), and phenyl (**77**) derivatives of curcumin semicarbazone were found to provide the highest dose modifying factors (DMF) with respect to survival in sub-TBI (bone marrow sparing) exposures in mouse models. In order to investigate the basis for the mitigating effects of these agents on ARS, their oxidation potentials and radical scavenging properties were compared with other semicarbazone and pyrazole derivatives of curcumin. Such comparison did not show sufficient differences in their reducing or hydrogen atom

donating properties to be the basis of dose-modifying activities of these compounds. Therefore, their DMFs probably reflect the structure-activity relationship, wherein the interaction with key receptors/enzyme expression results in modifications of cellular or tissue responses to radiation, rather than on the ability of these derivatives to modify radiation-induced flux of free radicals.

Recently, Arif *et al.* [74] have shown inhibition of the histone acetyltransferase (HAT) activity of p300 by a water-soluble hydrazinocurcumin (**78,** CTK7A), which substantially reduced the oral tumor growth in a xenograft mouse model. The compound was found to inhibit HAT p300/CBP and PCAF which suggest that this water-soluble derivative inhibits histone acetylation in the cellular system, at least, partially through the inhibition of p300 auto-acetylation. The compound was found to be non-toxic to the mice after intra-peritoneal (i.p.) administration. There was no observed weight loss at doses up to 100 mg/kg body weight twice a day during a month long treatment. KB cells-derived tumors were about 50% smaller in mice treated with this compound than in control mice.

3.2.3. Modifications of Double Bond—Chun *et al.* [75] have evaluated the anti-tumor promoting potential of Yakuchinone-A (**79**) and -B (**80**), major pungent ingredients of *Alpinia oxyphylla* Miquel, which can be considered as curcumin analogs where the double bond between the aryl rings are reduced. The topical application of Yakuchinone A or B significantly suppressed TPA-induced epidermal ornithine decarboxylase activity while higher concentration reduced TPA-stimulated production of tumor necrosis factor- (TNF-) in cultured human pro-myelocytic leukemia (HL-60) cells. Both compounds blunted the TPA-induced superoxide generation in differentiated HL-60 cells in a concentration-dependent manner as well as inhibited lipid peroxidation in rat brain homogenates. Furthermore, both compounds nullified activation of the activator protein-1 (AP-1) in immortalized mouse fibro-blast cells in culture. Overall Yakuchinone-B showed better activity than Yakuchinone-A, but less than curcumin.

Wu *et al.* [76] have found that treatment with tetrahydrocurcumin (THC, **9**), which is the double-bond reduced derivative of curcumin, results in autophagic cell death in human HL-60 pro-myelocytic leukemia cells by increasing the formation of auto-phagic cell death marker, acidic vascular organelle (AVO). THC significantly down-regulated phosphatidylinositol 3-kinase/protein kinase B and mitogen-activated protein kinase signaling, decrease in the phosphorylation of mammalian target of rapamycin, viz. glycogen synthase kinase 3 and p70 ribosomal protein S6 kinase respectively. Yodkeeree *et al.* [77] have shown that treatment with THC reduced HT1080 cell invasion and migration in a dose-dependent manner. The inhibition of cancer cell invasion was associated with down-regulation of ECM degrading enzymes as well as inhibition of cell adhesion to ECM proteins. Curcumin and THC were also found to attenuate pathological features of angiogenesis including micro-vascular dilatation, and hyper-permeability. Treatment with curcumin and THC resulted in a significant decrease in the capillary vascularity (CV). However, the beneficial effects of THC treatment on CV were observed from day 21 onwards [78]. Chen *et al.* [79] have studied the cytotoxicity of hexahydrocurcumin (**10**) and its effect on cell cycle in human colorectal SW480 cancer cells. Treatment of these cells with compound **10** resulted in a massive accumulation of the cells in the G1/G0 phase of the cell cycle.

3.2.4. Modifications at Active Methylenic Group—Ohtsu *et al.* [80] have prepared curcumin analogs by modifying the active methylenic group and have evaluated their potential as androgen receptor (AR) antagonists against two human prostate cancer cell lines, PC-3 and DU-145 transfected with AR and androgen receptor co-activator, ARA70 constructs. Compounds **23** and **81–83** showed potent anti-androgenic activities superior to

hydroxyflutamide, which is the standard anti-androgenic compound currently available for the treatment of prostate cancer. The compound **23** has shown reduction of dihydrotestosterone (DHT)-induced AR activity in PC-3 cells, while in DU-145 cells transfected with wild-type AR and ARA70 compounds **81** and **82** were almost equipotent and were slightly more active than **23**. Structure-activity relationship (SAR) studies indicated that the bis-(3, 4-dimethoxyphenyl) conjugated β-diketone moiety and the intra-molecular symmetry of molecules seem to be important factors related to the anti-androgenic activity of these curcumin analogs. The data further suggested that co-planarity of the β-diketone moiety and presence of strong hydrogen bond donor groups was crucial for the anti-androgenic activity, which was consistent with previous SAR results for Hydroxyflutamide analogs. When the pharmacophoric elements of DHT and compound **23** are superimposed, the resulting construct implies that the curcumin analogs may function as a 17β-substituted DHT.

Lin *et al*. [81] have designed 4-fluoro-4-ethoxycarbonylethyl curcumin (**83**) and 4-ethoxycarbonylethylenyl curcumin (**84**) to overcome the problems inherent in the tautomerism of 4-Ethoxycarbonylethyl curcumin (ECECur) (**82**). These compounds and their synthetic intermediates (including compound **85**) were evaluated for their inhibitory activity against LNCaP and PC-3 prostate cancer cell lines at a concentration of 3 μM. While the keto-enol analogs showed varying anti-androgen potencies, the diketo compounds showed no activity. Tetrahydropyranylation of the phenoxy groups had a positive impact on the anti-androgenic activity of 4-ethoxycarbonylethylenyl curcumin. Di-tetrapyranylated-4-ethoxycarbonylethylenyl curcumin (**85**), which exists only in the keto-enol form, has potent anti-androgenic activity, which may be a good lead compound for further structural modifications. Based on the SAR information, five new compounds were designed and subsequently synthesized. Among them, compound **86** was found to be the most potent anti-androgenic agent and is considered to be a promising drug candidate for the treatment of prostate cancer. Lin *et al*. [82] have synthesized further curcumin analogs containing monophenyl and substituted phenyl/heterocyclic moieties at the methylenic position of curcumin with various linkers. These new compounds were tested for cytotoxicity against two human prostate cancer cell lines, viz. androgen-dependent LNCaP and androgen-independent PC-3 cells. Anti-androgenic activity was also evaluated on LNCaP cells and PC-3 cells transfected with wild-type AR. The compounds **87–92** showed most potent activity against PC-3 and LNCaP cells. The anti-androgenic activity of compounds **90** and **92** were studied and found to exert transactivation of LNCaP and PC-3 cells transfected with wild-type AR. Amolins and coworkers [83] have synthesized another group of curcumin derivatives substituted at methylenic group with pyrazole and isoxazole pharmacophores and have studied their anticancer activity against MCF-7 and SKBR3 cancer cell lines. Compounds **93–95** were the most potent cytotoxic compounds against MCF-7 and SKBR3 cancer cell lines, while their pyrazole (**96–98**) and isoxazole (**99–100**) counterpart were found to be less active.

Arezki *et al*. [84] have synthesized ferrocenyl conjugates of curcumin which were evaluated for their cytotoxicity on B16 melanoma cells and normal NIH 3T3 cells as well as for inhibition of tubulin polymerization and effect on the morphology of endothelial cells. The compounds **101–105** were found to induce cytotoxicity against B16 melanoma cells, while compound **102** was found to inhibit tubulin polymerization. Lin *et al*. [85] have developed signal transducer and activator of transcription-3 (STAT3) inhibitors, known as **FLLL31 (106)** and **FLLL32 (107)**, which are derived by functionalization of the methylenic position in curcumin. These compounds are designed to bind selectively to Janus kinase-2 and the STAT3 Src homology-2 domain, which serve crucial role in STAT3 dimerization and signal transduction. It was found that these compounds are effective inhibitors of STAT3 phosphorylation, DNA-binding activity, and transactivation leading to the impediment of

multiple oncogenic processes and induction of apoptosis in pancreatic and breast cancer cell lines. It was observed that administration of **FLLL32** can inhibit tumor growth and vascularity in chicken embryo xenografts as well as substantial reduction in tumor volumes in mouse xenografts. The findings indicated the potential of these new compounds in targeting pancreatic and breast cancers that exhibit constitutive STAT3 signaling. These workers have further shown that the phosphorylated or activated form of STAT3 was expressed in colon cancer stem-like cells, which was attenuated by STAT3-selective inhibitor **FLLL32** [86]. The compound also inhibited the expression of STAT3 downstream target genes including survivin, Bcl-xL, as well as Notch-1, -3, and -4 in colon cancer stem-like cells, which may be involved in stem cell function. It exerted anti-proliferative activity against SW480, HCT116 and DLD-11 colon cancer cell lines with lower IC_{50} values compared to curcumin, respectively. **FLLL32** specifically reduced STAT3 phosphorylation at Tyr705 (pSTAT3) and induced apoptosis at micro-molar concentration in human melanoma cell lines. The compound displayed specificity for STAT3 over other homologous STAT proteins [87].

Chakraborti *et al.* [88] have studied a series of curcumin analogs for their tubulin binding affinities and tubulin self-assembly inhibition. It was found that curcumin acts as a bifunctional ligand and analogs with substitution at the diketone functionality or acetylation of the terminal phenolic groups are less effective. The benzylidiene derivative **108** was more effective than curcumin in inhibiting tubulin self-assembly. It was shown that curcumin binds tubulin away from the colchicine-binding site. Docking studies suggested that the curcumin-binding site was closer to the vinblastine-binding site. Structure-activity studies suggested that the tridentate nature of compound **108** was responsible for its higher affinity for tubulin compared to curcumin.

Chen *et al.* [89] have studied the effects of **C086** (compound **109**) on growth inhibition and NF-□B regulation in colon cancer cells and xenograft tumors. The compound exhibited potent anti-proliferative activity against HT29, SW480, KM12, SW1116, WiDr and Colon26 cancer cell lines. In a xenograft model of SW480 in nude mice, the oral administration of **C086** showed significant growth suppression of SW480 tumors and decreased NF-□B expression in tumor tissues. Using TNF-□ to induce NF-□B activation in SW480 cells, it was revealed that **C086** inhibited I□B-□ phosphorylation and its subsequent degradation thereby suppressing the nuclear translocation and DNA binding activity of NF-□B. It was also observed that NF-□B-regulated gene products C-myc, cyclin D1 and Bcl-2, involved in cellular proliferation and anti-apoptosis, were down-regulated in **C086** treated group.

Fadda *et al.* [90] have synthesized curcumin analogues **110–116** and have evaluated them for *in vitro* and *in vivo* cytotoxicities against ehrlich ascites carcinoma (EAC). *In vitro* results revealed that compounds **115 and 116** were the most potent analogs. Ferrari *et al.* [91] have synthesized curcumin analogs (ester and acid series) which showed IC_{50} values lower than curcumin when evaluated their against human ovarian carcinoma cells (A2780, C13*, and A2780/CP), and human colon carcinoma cells (HCT116 and LoVo). The compounds exhibited selectivity against colon carcinoma cells which could be ascribed to their high lipophilicity that favors a greater and faster cellular uptake and thereby overcoming their apparently higher instability under physiological condition. Qiu *et al.* [92] have synthesized a series of new 4-arylidene curcumin analogs which inhibited growth of a panel of lung cancer cells at sub-micromolar concentrations. Compounds **117–126** were found to exert superior growth inhibitory activities against A549 Cells through NF-□B inhibition which can be explained, at least, in part by inhibition of I□B phosphorylation and degradation via IKK blockage.

Sertel *et al.* [93] have analyzed the cytotoxic activity of curcumin and its four derivatives (**127–130**), among which the ethoxy-curcumin-tri-thiadiazol-amino-methyl-carbonate (**128**) compound was found to be the most potent one. The compounds were not cross-resistant to standard anticancer drugs and were not involved in ATP-binding cassette transporter-mediated multi-drug resistance. Zhou *et al.* [94] have prepared βionone-curcumin conjugates which led to the identification of a novel anti-androgen compound **131** having two bulky side chains, which was a pure antagonist of the wild-type and T877A, W741C, and H874Y mutated AR cells, showing no cross-reactivity with progesterone receptor. Compounds **131** and **132** have been found to exert cytotoxicity towards LNCaP, PCa-2b, 22Rv1, C4-2B and PC-3 prostate cancer cells. Molecular modeling indicated that compound **131** adopts "Y"-shape conformation and forms multiple hydrogen bonds with androgen receptor (AR) backbone.

In our group, we have synthesized some novel curcumin analogs using Knoevenagel condensation (**133–135**) to convert enolic diketones of curcumin into non-enolizable moieties. Their Schiff bases (**136–138**) were prepared using a bioactive thiosemicarbazone pharmacophore. The compounds were evaluated for their potential in inhibiting TNF-induced NF-κB activation and proliferation in human leukemic KBM-5 cells [95]. Later on, we extended our studies to include fluoro-substituted Knoevenagel condensates of Curcumin (**139–143**) and evaluated their growth inhibitory activities against colon and pancreatic cancer cell lines [96]. Out of these efforts emerged a compound known as difluorinated-curcumin commonly referred to as **CDF** (**139**) with superior anticancer activity in colon, prostate and pancreatic cancer cell lines. The compound was found to have inhibitory effect on purified rabbit 26S proteasome. Molecular docking studies into COX-2 protein cavity revealed that CDF did not introduce any major steric changes in the parent Curcumin molecule and facilitated more H-bonding interactions, resulting in higher binding energy of -7.91 Kcal/mol compared to curcumin (-5.71 Kcal/mol). We showed that Curcumin and CDF both down-regulated the expression of NF-κB in MIAPaCa-2 cells but the latter did it at minimal concentration of 2 μM or less. Both CDF and Curcumin decreased the PGE_2 levels in MIAPaCa-2 cells. However, in BxPC-3 cells, only CDF- treated cells had a decrease in PGE_2 level. These results clearly suggested that COX-2 is a better target of CDF compared to Curcumin [96].

We further studied the pharmacokinetics of Curcumin and CDF compound by administering 250 mg/kg orally to female ICR-SCID mice. Compared to Curcumin, CDF achieved a similar C_{max} (0.21 Ig/mL) with a relatively slow oral absorption with T_{max} of 8 h. However, CDF had 2.7-fold higher systemic drug level than Curcumin (AUC_{last}, 1.22 vs. 0.44 Ig/mL*h). Serendipitously CDF was found to accumulate preferentially in pancreas (10.6-fold higher then Curcumin), suggesting that it had improved bioavailability and preferential affinity towards pancreatic tissue. These findings make CDF an ideal candidate for cancer prevention and treatment of pancreatic cancers in conjunction with other cytotoxic agents.

We have studied the combination of CDF (1 μM/L) with Gemcitabine (10nM/L) in BxPC-3 cell lines [97]. The results indicated that the combination therapy exhibited far more efficacy than CDF alone. The combination significantly induced apoptosis in pancreatic BxPC-3, MIAPaCa-E and MIAPaCa-M cancer cell lines. Combination of CDF with Gemcitabine brought about a significant reduction of cell viability and almost eliminated pancreatosphere formation after four weeks of treatment suggesting that CDF could be a useful therapeutic agent for elimination of Cancer Stem-like Cells (CSCs). CDF also attenuated CD44 and EpCAM expressions in pancreatospheres. The *in vivo* subcutaneous xenograft tumor model induced by MIAPaCa-2 cells in CB17-SCID mice was helpful in showing that the combination of CDF with Gemcitabine significantly inhibited tumor growth in MIAPaCa-2 tumors much more than either of the individual agents. There was no significant weight loss

in mice during the treatment period (30 days), which suggested that these treatments had no major adverse effects on animals. CDF treatment with or without Gemcitabine showed increased expression of tumor suppressive micro-RNAs (miRNAs), viz. miR-200b and miR-200c, respectively [98].

In another investigation carried out with an orthotropic xenograft model of human pancreatic cancer cells, CDF inhibited tumor growth through reduced expression of histone methyltransferase EZH2, Notch-1, CD44, EpCAM, and Nanog signaling pathways, which was consistent with increased expression of let-7, miR-26a, and miR-101 respectively [98]. The effects of CDF in combination with 5-fluorouracil and oxaliplatin (5-FU + Ox) against colon cancer were evaluated against chemo-resistant HCT-116 and HT-29 cells [99] which showed a significant inhibition of cellular growth when the cells were incubated for 48 h. These results clearly suggest that combination of CDF with conventional chemotherapeutics agents might have a potential in preventing the emergence of chemo-resistant colon cancer cells. Recent study in our laboratory has shown, for the first time, that Ras expression and its activity are significantly higher in MIAPaCa-2 cells as compared to COLO-357 and BxPC-3 cell lines [100]. It was found that CDF treatment either *in vitro* studies or MIAPaCa-2 induced tumors *in vivo* results in the re-expression of let-7 and miR-143 along with down-regulation of miR-21 expression, which is consistent with decrease of Ras expression and inhibition of tumor growth. It was concluded that the loss of let-7 and miR-143 expression and increased expression of miR-21 leads to increased expression of Ras and its GTPase activity, which could be attenuated by CDF treatment in pancreatic cancer cell lines.

We have also assessed the effects of CDF on the regulation of AR/TMPRSS2-ERG/Wnt signaling [101]. It was observed that activation of AR resulted in the induction of ERG expression through TMPRSS2-ERG fusion. It was found that ERG over-expression and nuclear translocation activated the activity of Wnt signaling. Interestingly, we observed that CDF inhibited the signal transduction in AR/TMPRSS2-ERG/Wnt signaling network, leading to inactivation of the Wnt signaling consistent with inhibition of prostate cancer cell invasion.

3.2.5. Metal Complexation—It has been well established that metal complexation can improve and enhance the biological activity of the parent drug molecule [102, 103]. Since the enolic tautomers as well as the diketo functionality of the modified Curcumin are capable of complexing with biologically relevant metals, it can be considered as one of the methods for improving its bioactivity. Recently, curcumin has been found to alter iron metabolism by chelating iron and suppressing the protein hepcidin, causing iron deficiency in susceptible patients [104]. Curcumin interaction with copper and iron has also been suggested as one possible mechanism of action in animal models of Alzheimer's disease. With this in mind, we summarize here recent reports on metal complexation of curcumin and its analogs which may have some bearing on its anticancer activity.

Alcalde *et al.* [105] have investigated a new curcuminoid ligand, viz. **9Accm (Compound 144)** and its corresponding copper-complex, [Cu(phen)Cl(9Accm)] for their interactions with calf thymus DNA which indicate a weak electrostatic interaction with the double helix. Annaraj and co-workers [106] have examined the binding mode of ternary copper (II) complexes of Curcumin Schiff bases (**145–146**) involving phenanthroline/bipyridyl as ancillary ligands with herring sperm DNA by spectral and electrochemical techniques. These studies revealed that interaction with DNA slightly improves reversibility of the quasi-reversible Cu $^{+2/+1}$ redox couple with considerable reduction in current intensity. The results indicate that these ternary copper complexes (**146**) can intercalate more effectively into the DNA base pairs than usual bipyridyl (**145**) counterparts.

Barik *et al.* [107] have studied the mononuclear copper complex of Curcumin (**147**) for its superoxide dismutase (SOD) activity. It was found that the copper atom was coordinated through the oxygen donor atoms of Curcumin along with an acetate anion and one water molecule. The compound could scavenge superoxide radicals and was found to regenerate completely, indicating catalytic activity in neutralizing superoxide radicals. The complex also inhibited radiation-induced lipid peroxidation.

Caruso *et al.* [108] have evaluated the anti-proliferative activity of novel Ruthenium-Curcumin complex (**148**) on five cancer cell lines which showed compound's preference for the colorectal HCT-116 cancer cells followed by breast MCF-7 and ovarian A2780 cell lines. The human glioblastoma U-87 and lung carcinoma A549 cells were found to be less sensitive. John and coworkers [109] have synthesized copper complexes of four new Curcumin analogs (**149–152**) wherein the metal complexes were found to be remarkably active.

Valentini *et al.* [110] have evaluated a novel water soluble ternary Pd (II) complex, **153**, containing Curcumin and bipyridyl ligands against human prostate LNCaP, PC-3, and DU-145 cancer cells. ROS production induced by the treatment with this complex activated apoptosis through mitochondrial membrane de-polarization in all prostate cancer cells, accompanied by up-regulation of Bax and down-regulation of Bcl-2 proteins. While Curcumin produced cell growth delay due to the G2 phase arrest in these prostate cancer cells, an apoptosis was observed in cells treated with the metal complex mediated through JNK activation and mitochondrial membrane depolarization.

3.2.6. Appended Curcumin mimics—Appended Curcumin mimics refers to those compounds that have partial structural resemblance to Curcumin motif but are appended with different pharmacophores for targeting proteins that are crucial for survival of tumor cells in question. In the following discussion, we summarize some of these analogs which offer some advantages in terms of tumor specificity, pharmacokinetics or non-toxicity towards normal cells.

Ruan and co-workers [111] have recently reported on the synthesis and anti-proliferative activity of a series of resveratrol analogs bearing curcumin motif (**154**) against a panel of cancer cell lines including murine melanoma B16-F10, human hepatoma HepG2 and human lung carcinoma A549 cells. Amongst the several compounds that were evaluated for their anticancer activity, the compound possessing methoxy substitution at the aromatic C-ring (**154**) exhibited highest activity against murine B16-F10 cells. SAR studies indicated that the anti-proliferative activity was influenced by the substitutions on C-ring. These results demonstrated that hydrophobic and electron-donating methyl/methoxy groups can increase the anti-proliferative activity considerably. Mechanistic investigation showed that these compounds inhibited tubulin polymerization efficiently. Cell cycle analysis of the most potent methoxy analog showed the induction of G2/M-phase cell cycle arrest in B16-F10 cancer cells. The molecular modeling studies of the potent compound in the tubulin-colchicine binding site of tubulin revealed that hydrophobic pockets of the tubulin-colchicine binding site are occupied by the methoxy group on C-ring and the monocarboxyl group of the Curcumin moiety. It indicates that these substituents have relevance in the anti-tubulin activity.

Recently Cao and co-workers [112] have reported pyridinyl analogs of dibenzylideneacetone (**155–156**) by the condensation of substituted nicotinaldehyde and acetone. These curcumin analogs were evaluated for their anti-inflammatory activity by NF-B inhibition assay and also for their cytotoxicity against colorectal carcinoma HCT-116 cells. Almost all synthesized, analogs exhibited better cytotoxicity than curcumin, but one

analog **155** showed highest efficacy in inhibiting NF-□B, and more potency in suppressing growth of colon cancer cells.

Somers-Edgar and co-workers [113] have synthesized a series of novel cyclohexanone curcumin analogs containing heterocyclic substitutions at the terminal benzene rings. These analogs exhibited anti-cancer activity towards ER-negative MDA-MB-231 human breast cancer cells. Amongst the analogs screened, **157** and **158** were remarkably potent against MDA-MB-231 cells. Mechanistically these compounds induced G2/M-phase cell cycle arrest and caused apoptosis. They also modulated the expression of key cell signaling proteins including Her-2, Akt and NF-□B in a time-dependent manner. In case of MDA-MB-231 cells, EGFR protein levels were decreased, while □catenin protein level and the activity of P38 MAPK, Akt and JNK1/2 were increased. Thus, replacement of the phenyl group with heterocyclic rings turned out to be beneficial in evolving anti-cancer agents with some advantages against ER-negative breast cancer cells.

In another study, Kudo *et al.* [114] have evaluated large number of structural curcumin analogs, including acyclic 1, 5-diaryl-3-oxo-1, 4-pentadiene analogs, 1, 7-diaryl-1, 6-heptadiene-3, 5-dione, and acyclic 1, 5-diaryl-3-oxo-1, 4-pentadiene curcumin analogs (**159–163**) which have been examined for their anti-proliferative activity. The growth-inhibition potential of these compounds was studied on a panel of cancer cell lines. All compounds had at least 10 times higher growth-inhibitory potential than curcumin. Cell cycle analysis revealed growth inhibition of HCT-116 cells correlated with increase of the sub-G1 fraction.

Kalai and co-workers [115] have reported a series of 3, 5-bis-(arylidene)-4-piperidone (DAP) curcumin analogs. The anticancer efficacy of these analogs was evaluated against A2780, MCF-7 cancer cell lines and H9c2 cardiomyoblast cells. Compounds without nitroxide moiety demonstrated a substantial cytotoxic effect against A2780 and MCF-7 cells. The electron-withdrawing fluoro- and trifluoro-methane substituents (**164, 165**) exhibited greater cytotoxicity than trimethoxy derivative. Molecular modeling studies demonstrated that these analogs have high binding affinity for STAT3 at the deoxyribonucleic acid (DNA) binding domain of the molecule.

Curcumin analogs possessing indan-2-one and dibenzylidene-piperidin-4-one motif (**166 and 167**) have been recently described by Karthikeyan *et al.* [116] which have been evaluated against a panel of cancer cell lines including HCT-116, Panc-1, H460, Calu-1 and ACHN cells respectively. The monocarbonyl analog with the ethoxy substituent (**166**) on the phenyl ring exhibited highest efficacy overall. Dayton's group [117] studied the cellular uptake, retention and bio-absorption potential of monocarbonyl fluorocurcumin, viz. HO-3867 (**168**), against a series of cancer cells including cisplatin-resistant A2780R cells. The cellular uptake of HO-3867 was 10-fold greater than Curcumin at 60 min of incubation at concentrations of 10–100 □M. The cellular absorption was highest in MCF-7 cells. *In vivo* studies indicated that the compound was absorbed significantly in the liver compared to serum and kidney.

Lin and co-workers [118] have studied the efficacy of synthetic monocarbonyl curcumin analogues, **FLLL11 (169)** and **FLLL12 (170)**, in eight different breast and prostate cancer cell lines. The compounds were substantially more effective than curcumin in inhibiting AKT phosphorylation and down-regulating the expression of HER2/neu. In addition, they also inhibited phosphorylation of signal transducer and transactivator STAT3, an oncogene frequently found activated in many cancer types. These results suggest that **FLLL11** and **FLLL12** may have translational potential as chemopreventive or therapeutic agents for breast and prostate cancers. Yamakoshi and co-workers [119] reported novel curcumin

analogs of the type, 1,5-bis(4-hydroxy-3-methoxyphenyl)-penta-(1E,4E)-1,4-dien-3-one, and evaluated their cytotoxicities against human colon cancer HCT-116 cell line. Amongst the three series of compounds reported by his group, compounds belonging to the symmetric 3, 5-substituted series, **(GO-YO30 (171) and GO-YO31 (172)** were found to be the most potent analogs. Similar monoketo-curcumin analogs having cyclopentanone (**173**), acetone (**174–176**) and cyclohexanone (**177**) central motifs have also been synthesized [120]. Their cytotoxicity was evaluated against panel of cancer cell lines which revealed that analogs from series B and C were more potent than series A. The dimethoxy **174** analog exhibited potent inhibitory activity against PC-3 and LNCaP cells. Structure-activity relationship studies indicated that the presence of strong electron withdrawing substituents at 2 position may be important for the enhancement of cytotoxicity.

Ohori *et al.* [121] have reported symmetrical 1, 5-diaryl-pentadienone curcumin analogs whose aromatic rings possess an alkoxy substitution at each of the 3 and 5 positions. The most active compound was **(GO-035**, **178**) which strongly suppressed the growth of DLD-1colon cancer cell line. Ravindran *et al.* [122] have reported anti-proliferative potential of hispolon group of compounds (**179–185**) which are the monoaryl curcumin analogs. Amongst these, hispolon (**180**) was the most cytotoxic against human leukemia KBM-5 cell line. It also exhibited highest cytotoxicity against HCT-116 and MCF-7 cells whereas dehydroxy-hispolon (**182**) showed maximum cytotoxicity against prostate PC-3 cells. Youssef and co-workers [123] have reported synthesis of monocarbonyl cyclic and non-cyclic curcumin analogs (**186–188)** amongst which **188** elicited highest activity toward non-small lung cancer cell line.

4. CONCLUSION

Curcumin is one of the most potent and multi-targeting phytochemicals against a variety of cancers. In the past few decades, hundreds of research papers have been devoted to elucidating its role in inhibiting proliferation, angiogenesis and metastasis of different cancers. These studies clearly indicated that the use of curcumin as a therapeutic agent was limited due to its low bioavailability and rapid metabolism. Various formulations including nano-particulates although enhanced the bioavailability of curcumin to varying extent were not successful in slowing down the rapid metabolism of the compound. Our review of existing literature clearly indicates that researches are now devoting their efforts to this aspect by structurally modifying the curcumin motif systematically. These efforts have led to some serendipitous discoveries of some new compounds which not only display slowing down of the metabolism but selective accumulation in pancreatic as well as prostate tissues. Some of the structural derivatives described in the present review indicate exciting possibilities of developing curcumin analogs selective towards some specific cancers giving hope of finding use of Curcumin or its analogs in the clinics for the prevention and/or treatment of these cancers.

Acknowledgments

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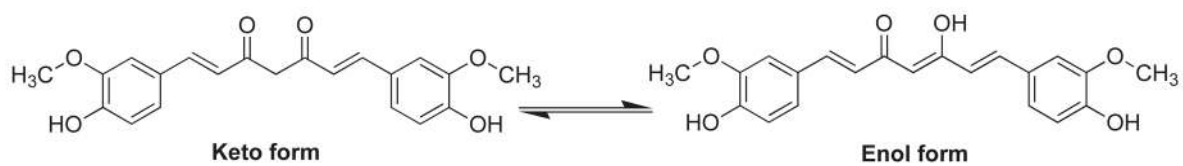
Fig. 1.
Keto-Enalo tautomerism in curcumin (**1**).
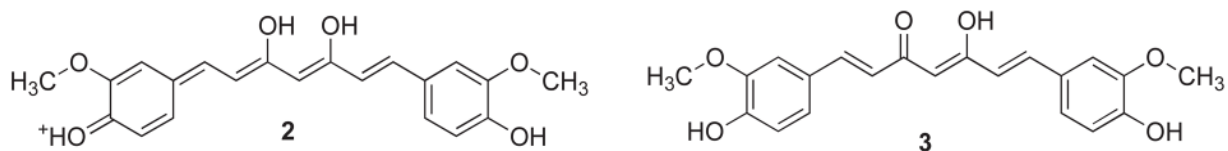
Fig. 2.
The form of curcumin present at pH < 1 (**2**) and pH 1–7 (**3**).
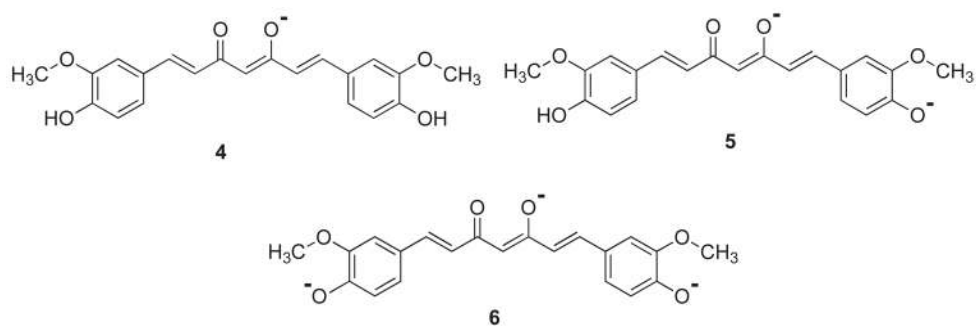
Fig. 3.
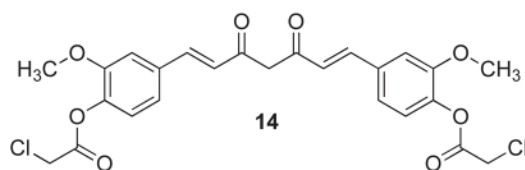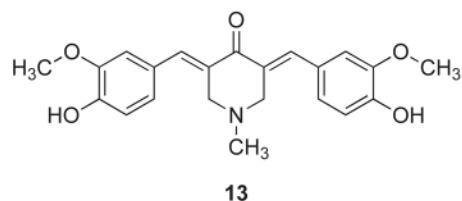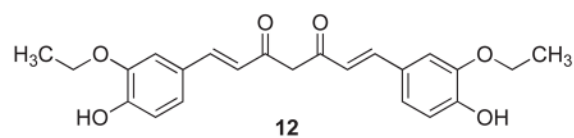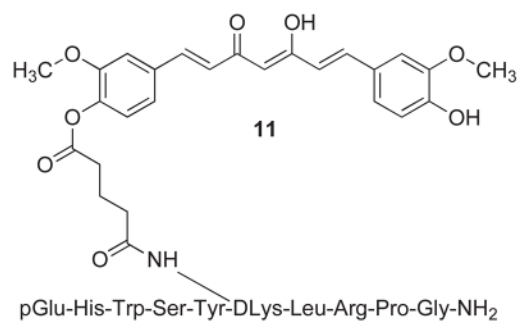Different forms of curcumin after dissociation with pKa value of 7.8 (**4**), 8.5 (**5**) and 9.0 (**6**).
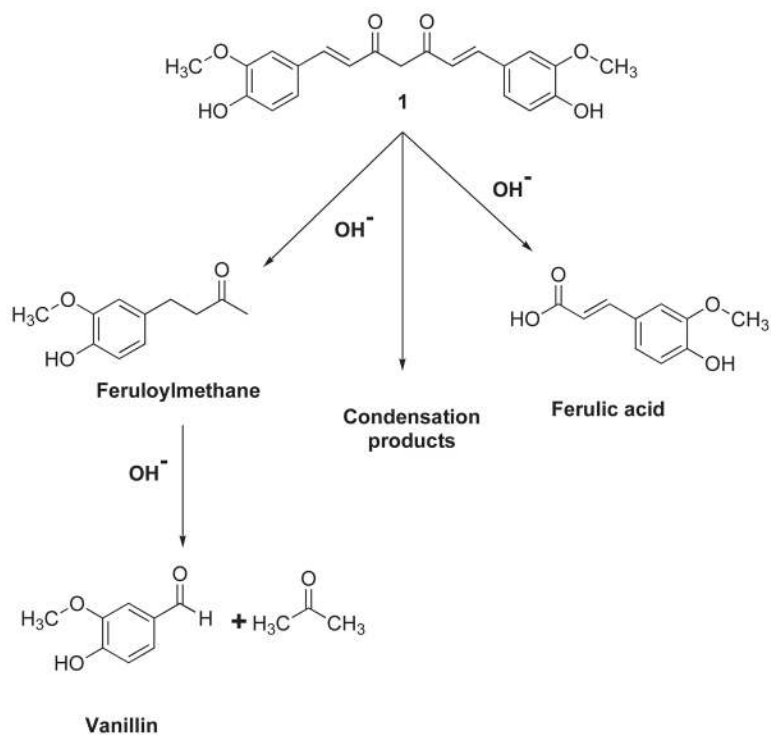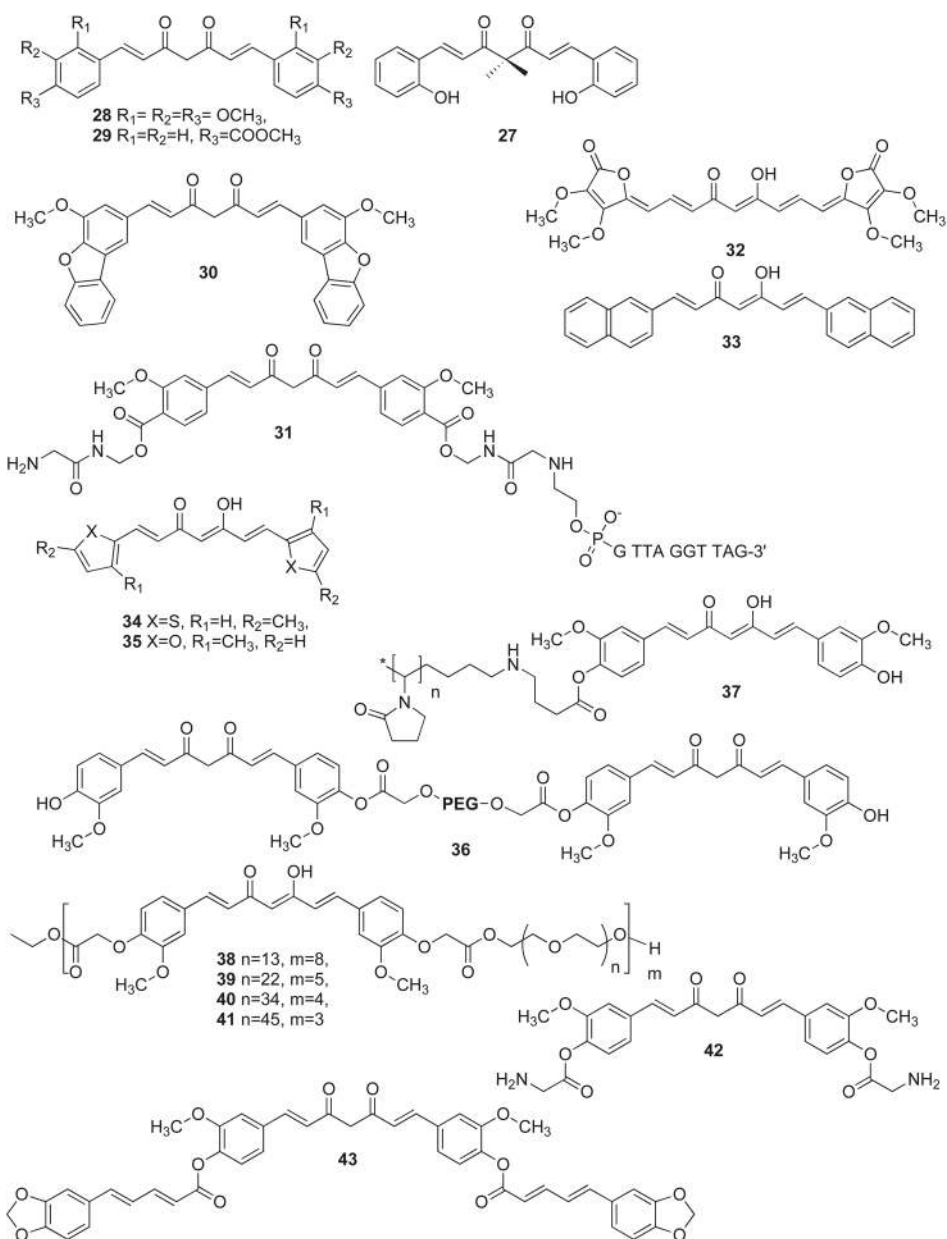
Fig. 4.
Decomposition products of curcumin.
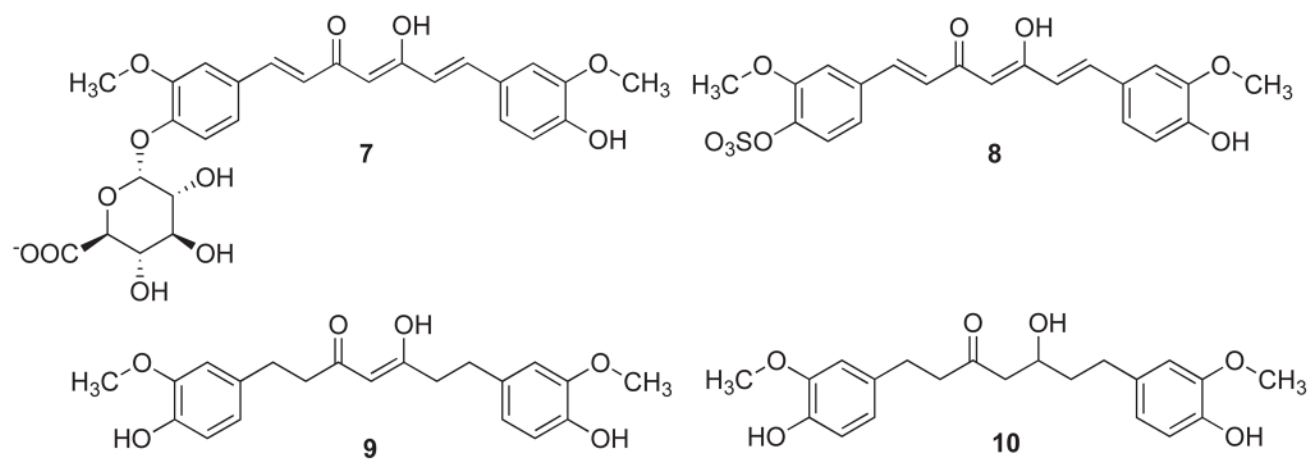
Fig. 5.
In vivo metabolites of curcumin **(7–10)**.
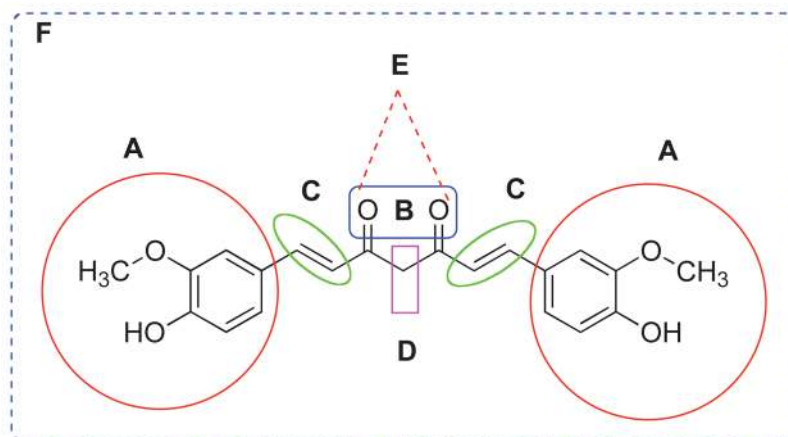
Fig. 6.
Structural possibilities for modification of curcumin - Aryl side chain modification **(A)**,
Modification of diketo functionality **(B)**, Modification of double bond **(C)**, Modification of
active methylene functionality **(D),** Metal complexes of curcumin **(E)** and Appended
curcumin mimics/structural analogs of curcumin **(F).**

11

pGlu-His-Trp-Ser-Tyr-DLys-Leu-Arg-Pro-Gly-NH₂

12

13

14

15

15 R₂=R₃=

16

17

18 R= -CO-CH (CH (CH₃)₂)NH₂,
19 R= -COCH₂NH₂

20

21

22 R= -OSO₂NH₂, 23 R= OCH₃

44 R_1=CH3, R_2=H, R_3=OH, R_4=OCH3,
45 R_1=CH2OH, R_2=R_3=R_4=OCH3,
46 R_1=CH2OH, R_3=OCH3, R_2=R_4=H

50 R_1=OCH3, R_2=H, R_3=CH3
51 R_1=R_2=OCH3, R_3= CH3,
52 R_1=R_2=OCH3, R_3= CH2CH3,
53 R_1=R_2=H, R_3=CH3

54 R=3,4-(OCH3)2, n=0,
55 R=3-OCH3, 4-OH, n=0,
56 R=4-OH, n=1,
57 R=3-OCH3, 4-OH, n=1

7A

61 R= H, 62 R=C4H9

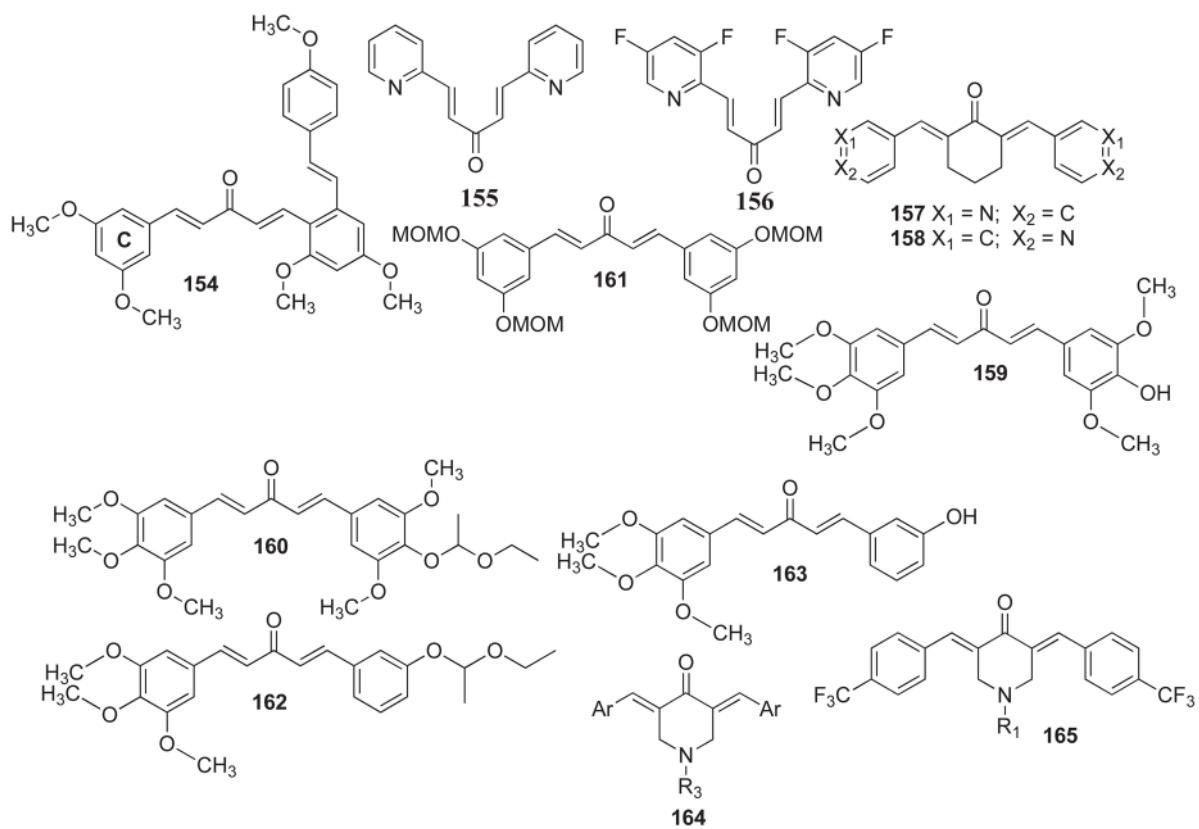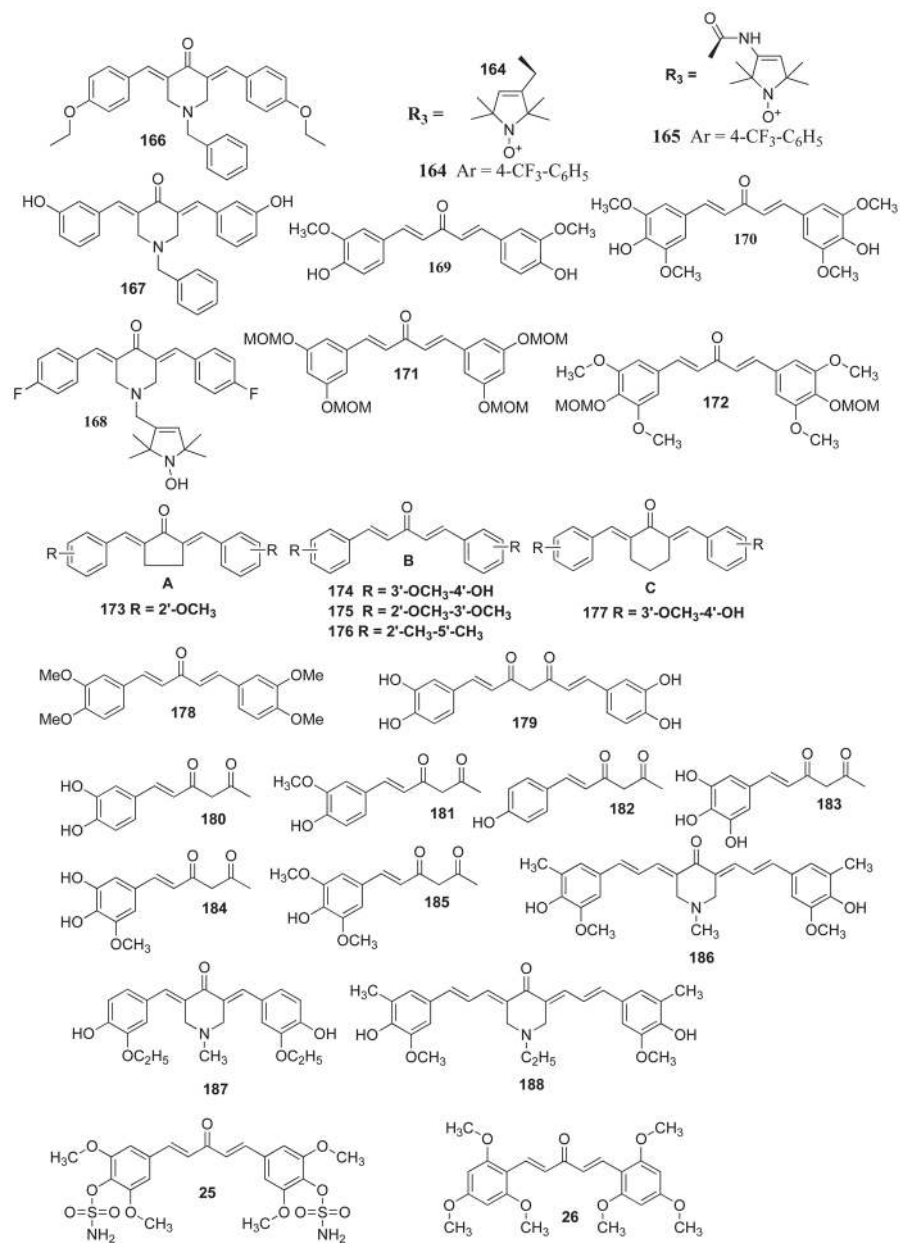63 R=H, 64 R=C4H9, 65 R=C8H17

67 R=H, 68 R=4-OH-3-OCH3,
69 R= 4-OH

Fig. 7.
(A) Aryl side chain modifications **(11–23, 27–60); (B)** Modification of diketo functionality **(24, 61–78); (C)** Modification of double bond **(9–10, 79–80); (D)** Modification of active methylene functionality **(81–143)** and **(E)** Metal complexes of curcumin **(144–153)**.

Fig. 8.
Structural analogs of curcumin **(154–188, 25–26)**.