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Lesson Learned from Nature for the Development of Novel Anti-Cancer Agents: Implication of Isoflavone, Curcumin, and their Synthetic Analogs

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Abstract

In recent years, naturally occurring dietary compounds have received greater attention in the field of cancer prevention and treatment research. Among them, isoflavone genistein and curcumin are very promising anti-cancer agents because of their non-toxic and potent anti-cancer properties. However, it is important to note that the low water solubility, poor *in vivo* bioavailability and unacceptable pharmacokinetic profile of these natural compounds limit their efficacy as anti-cancer agents for solid tumors. Therefore, the development of synthetic analogs of isoflavone and curcumin based on the structure-activity assay, and the encapsulation of isoflavone and curcumin with liposome or nanoparticle for enhancing the anti-tumor activity of these natural agents, is an exciting area of research. Emerging *in vitro* and *in vivo* studies clearly suggest that these analogs and formulations of natural compounds could be much more potent for the prevention and/or treatment of various cancers. In this review article, we will summarize the current knowledge regarding the anti-cancer effect of natural compounds and their analogs, the regulation of cell signaling by these agents, and the structure-activity relationship for better design of novel anti-cancer agents, which could open newer avenues for the prevention of tumor progression and/or treatment of human malignancies.

Keywords

Isoflavone; curcumin; chemoprevention; cancer therapy

INTRODUCTION

It is well known that most human cancers are induced by environmental factors including chemical, radioactive and biological factors that exist in our environment. There are significant differences in the cancer incidence, mortality, and survival among ethnic groups, who have different lifestyles and have been exposed to different environmental factors [1,2]. Studies have also shown that 30 to 40 percent of cancers are directly linked to dietary choices [3] and these cases of cancer are preventable by appropriate diets. This means that appropriate diets may prevent 3 to 4 million cases of cancer every year globally. The consumption of fruits, soybean and vegetables has been associated with reduced risk of several types of cancers [4,5]. Diets containing substantial and varied amounts of vegetables

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and fruits may prevent 20% or more of all cases of cancer [3]. The *in vitro* and *in vivo* experimental studies have demonstrated that some dietary components including isoflavones, curcumin, indole-3-carbinol (I3C), 3,3'-diindolyl-methane (DIM), (−)-epigallocatechin-3-gallate (EGCG), etc, have inhibitory effects on human cancers [6–9], suggesting that they may serve as potent non-toxic agents for the prevention of tumor progression and/or could serve as therapeutic agents alone or in combination with conventional therapeutics.

In recent years, the dietary compounds and their synthetic analogs have received greater attention in the field of cancer research. Among them, isoflavone genistein, curcumin, and their analogs are promising anti-cancer agents because of their non-toxic and potent anti-cancer properties, which is the focus of this article although many other dietary agents are equally important. Soy isoflavones are mainly derived from soybean showing inhibitory effects on various cancers including breast and prostate cancers. Interestingly, the lower risks of breast and prostate cancers in Asians, who consume 20–50 times more soy than Americans, suggest that the components in the soybean may act as natural chemopreventive agents [10–13]. Soy isoflavones including genistein have been demonstrated to be responsible for reducing the incidence of hormone-related cancers. In laboratory *in vitro* various cancer cells [14,15]. Moreover, the evidences from *in vivo* studies have demonstrated that isoflavone genistein exerts its inhibitory effects on the development and progression of cancers [16]. Furthermore, we have shown that isoflavone genistein inhibits cancer cell invasion, metastasis, and angiogenesis through the regulation of genes critically involved in the control of cell proliferation, apoptotic cell death, migration, invasion, angiogenesis and metastasis [17,18], suggesting that isoflavone genistein could a promising agent for cancer prevention and/or treatment of human malignancies.

Curcumin is a polyphenolic compound derived from dietary spice turmeric and possesses diverse pharmacological effects including antioxidant, anti-inflammatory, anti-proliferative, and anti-angiogenic activities. Curcumin has been used for centuries in Asia, both in traditional medicine and in cooking where curcumin gives natural yellow color to the food. The first article regarding the use of curcumin to treat human biliary diseases was published in The Lancet in 1937 [19]. After several decades of research since then, it has been well known that curcumin possesses potent antiinflammatory activity because of its inhibitory effects on cyclooxygenases 1, 2 (COX-1, COX-2), lipoxygenase (LOX), TNF-α, interferon γ (IFN-γ), inducible nitric oxide synthase (iNOS), and NF-κB [20,21]. Importantly, experimental evidences suggest that curcumin could exert its inhibitory effects on cancer development and progression. The mechanisms implicated in the inhibition of tumorigenesis by curcumin are unclear but could involve a combination of anti-oxidant, anti-proliferation, pro-apoptotic, and anti-angiogenic properties through the regulation of genes and molecules that are involved in multiple signaling pathways. Moreover, preclinical animal experiments and phase I clinical trials have demonstrated minimal toxicity of curcumin even at relatively high doses (12 g/day) [22]. However, curcumin exhibits poor bioavailability because of poor absorption and rapid metabolism [22]. To improve the bioavailability of curcumin, liposomal curcumin, nanoparticle curcumin, and structural analogs of curcumin have been synthesized and investigated to determine the absorption and anti-cancer activity [23,24]. The results are promising, which further suggest that curcumin or its novel structural analogs could serve as potent agents for the prevention and/or treatment of human malignancies, and thus requires more phase II and III clinical trials.

ISOFLAVONE GENISTEIN AND ITS ANALOG

Molecular Structure and Biological Properties of Isoflavone Genistein

Isoflavones are a subclass of a family of ubiquitous flavonoids, and have been found in relatively high concentration in soybeans and most soy-protein products. The basic structure of isoflavone is the flavone nucleus, which is composed of 2 benzene rings linked through a heterocyclic pyrane ring (Fig. (**1**)). In contrast to flavonoids, isoflavones possess a 3-phenylchroman skeleton that is biogenetically derived from the 2-phenylchroman skeleton of the flavonoids. The structure of isoflavone genistein is very similar to that of estrogen (Fig. (**1**)), thus isoflavones have also been known as phytoestrogens. Because of the structural similarity to estrogen, isoflavone genistein have been shown to bind to estrogen receptors (ER). By interaction with ER, genistein blocks the binding of more potent estrogens, thereby exerting a potential role in the prevention of hormone related cancer. However, it is important to note that genistein could either induce cell proliferation by estrogenic agonistic properties (at concentrations ≤1 μM) or prevent hormone-dependent growth of cancer cells by potential estrogen-antagonistic activity (at concentrations ≥5 μM) dependent on its concentrations [25]. Moreover, we and others have found that genistein could also inhibit cell growth and induce apoptosis in ER negative breast cancer cells [14,26], suggesting that genistein may exert its effects through ER dependent or independent mechanisms.

It has been well known that isoflavone genistein has many important biological effects that are beneficial for human health, especially the anti-cancer effect of isoflavone genistein. In addition to its function as an estrogen agonist or antagonist, genistein is a known inhibitor of protein-tyrosine kinase [27]. The inhibitory activity of genistein on protein-tyrosine kinase could contribute to anti-proliferative or pro-apoptotic effects of genistein. Moreover, it has been reported that soy isoflavones have antioxidant effect against TNF-α induced NF-κB activation in humans both *in vitro* and *in vivo* [15,28,29], which could be responsible for the inhibition of cancer cell growth. In animal studies, soy isoflavones have been found to suppress spontaneously developed and chemical induced prostate and breast cancers [30,31], suggesting their inhibitory effects on tumorigenesis. Growing body of evidences have shown that isoflavone genistein can inhibit cancer cell growth and induce apoptotic cell death in various cancer cells through regulation of cell signaling transduction pathways [32,33]. Moreover, genistein could potentiate anti-cancer activity of chemotherapeutic agents, and also inhibit angiogenesis and cancer metastasis [17,18,34], suggesting that isoflavone genistein could be a potent agent for the treatment of cancers in combination with conventional chemotherapeutics, which of course must be tested through innovative clinical trials in order to fully appreciate the value of isoflavones in human health and diseases.

The Effects of Isoflavone Genistein on Cellular Signaling

It has been known that isoflavone genistein exerts its effects on multiple signaling pathways (Fig. (**2**)). We have found that genistein significantly inhibited the NF-κB DNA-binding activity *in vitro* in prostate, breast, lung, and pancreatic cancer cells [35–37]. Other investigators have reported similar results showing that isoflavone genistein inhibited the activation of NF-κB in human lung epithelial cells and myeloid cells [38,39]. Moreover, we have investigated the *in vivo* effects of isoflavone genistein on NF-κB signaling. We found that when human volunteers received 50 mg of soy isoflavone supplements Novasoy™ (containing genistein, daidzein, and glycitein at a 1.3:1:0.3 ratio) twice daily for three weeks, TNF-α treatment *ex-vivo* failed to activate NF-κB activity in lymphocytes harvested from these volunteers, while lymphocytes from these volunteers collected prior to soy isoflavone intervention showed activation of NF-κB DNA binding activity upon TNF-α treatment *ex-vivo* [40]. These results demonstrate that soy isoflavone supplementation has a

protective effect against TNF-α induced NF-κB activation in humans, suggesting that soy isoflavone could exert its cancer chemopreventive activity through the regulation of NF-κB signaling. More importantly, we also found that isoflavone genistein could enhance the anti-tumor activity of chemotherapeutic agents *via* the down-regulation of NF-κB signaling [36], suggesting the therapeutic value of isoflavone in cancer treatment.

In addition to the role of NF-κB as a target of genistein, the activation of NF-κB is also known to be mediated by the activation of Akt. Akt signaling is another target of isoflavone genistein (Fig. (**2**)). We found that isoflavone genistein treatment significantly decreased the phosphorylation of Akt protein at Ser473 and inhibited the Akt kinase activity [15], which could be responsible for the inhibition of NF-κB. Genistein pre-treatment also abrogated the activation of Akt by EGF. To further explore the inhibitory mechanism(s) of genistein on Akt and NF-κB pathways, Akt expression construct was transiently co-transfected with NF-κB-Luc reporter construct into PC-3 prostate cancer cells. Luciferase assay showed an increased luciferase activity in PC-3 cells co-transfected with the constructs. However, genistein treatment decreased the luciferase activity in the co-transfected PC-3 cells. These results were further confirmed by examining the NF-κB DNA-binding activity in co-transfected cells using EMSA, and the results suggests that isoflavone genistein inhibits NF-κB signaling through Akt pathway. We also observed similar results in MDA-MB-231 breast cancer cells [37]. Therefore, the down-regulation of NF-κB and Akt signaling pathways by isoflavone genistein could contribute to the inhibition of cancer cell growth and the induction of apoptosis.

It has been known that Wnt signaling interacts with Akt signaling, promoting cancer cell proliferation. We have found that isoflavone up-regulated the expression of GSK-3β, enhanced GSK-3β binding to β-catenin, and increased the phosphorylation of β-catenin, suggesting that isoflavone could inactivate Wnt signaling, leading to the inhibition of prostate cancer cell growth [41]. The results from other laboratories also showed that isoflavone genistein decreased basal and Wnt-1-induced cell proliferation and attenuated the expression of Wnt-1 target c-Myc and Cyclin D1 [42] and that isoflavone also inhibited the expression of Wnt-5a [43]. All these results suggest that isoflavone genistein has the promising inhibitory effects on Wnt signaling, which could be useful for targeted treatment of certain human malignancies.

We have also investigated the effects of isoflavone genistein on Notch signaling. We found that isoflavone genistein inhibited Notch signaling, leading to the down-regulation of NF-κB activity, resulting in the inhibition of cell proliferation, and the induction of apoptosis in pancreatic cancer cells [44,45]. Other investigators also reported that genistein could inhibit the expression of Notch-2 [43], which is consistent with our findings. Therefore, isoflavone genistein could inhibit cancer cell growth and induce apoptosis through the inhibition of Notch signaling as well (Fig. (**2**)), implicating that isoflavone is a multi-targeted agents.

Isoflavone genistein could also target AR signaling (Fig. (**2**)). We have previously found that genistein transcriptionally down-regulated AR, decreased nuclear AR binding to androgen responsive element (ARE) and, thereby, inhibited the transcription and protein expression of PSA in androgen-sensitive LNCaP cells [46,47]. In an *in vivo* animal study, dietary genistein has also been found to down-regulate the expression of AR [48]. Furthermore, we have found that isoflavone-induced inhibition of cell proliferation and induction of apoptosis are partly mediated through the regulation of the Akt/FOXO3a/GSK-3β/AR signaling network [49]. These results suggest that the down-regulation of AR expression could be an important strategy for the prevention and/or treatment of prostate cancer, especially hormone refractory prostate cancer for which there is no curative treatment.

The above mentioned findings along with those that we were unable to cite in this brief review article clearly suggest that isoflavone genistein exerts pleiotropic effects on cell signal transduction pathways in cancer cells; however, pure genistein by itself may not be an attractive agent for the treatment of human cancers as documented earlier by our laboratory [32,33,50]. In order to further enhance the activity of isoflavone, synthetic analogs of isoflavone with robust biological activity could be very attractive for the treatment of human cancers, and thus it is further discussed below.

Novel Synthetic Analogs of Isoflavone as Anti-Cancer Agents

It is well accepted that the molecular structure of an agent is tightly related with its biological activity. The extensive changes in biological activity have been observed after the modifications of molecular structure. The structure and function analysis showed that the anti-tumor properties of isoflavonoids are in part due to some structural motifs that include a benzopyran motif with a double bond between C2-C3 positions and a side chain containing a phenyl ring having metal chelating ability [51]. These structures can be easily built into a compound 3-formylchromone by condensing it with various amines in alcoholic medium yielding corresponding Schiff bases. Moreover, these compounds could form metal conjugates with therapeutically important metal ions such as copper to become more effective.

We have designed and synthesized copper conjugated isoflavone derivatives [50] (Fig. (**1**)). We tested the effects of synthetic derivatives of isoflavone on the growth of BT-20 breast, PC-3 prostate, Colo357 and BxPC-3 pancreatic cancer cells. We found that the synthetic derivatives of isoflavone inhibited cell proliferation in all cancer cell lines tested at much lower IC_{50} value (10 μM) compared to genistein, suggesting that these derivatives of isoflavone are more potent in inhibiting the growth of cancer cells. Moreover, we observed that synthetic derivatives of isoflavone at lower doses could induce more apoptosis compared to parent genistein. Furthermore, we found that synthetic derivatives of isoflavone significantly inhibited the activation of Akt and NF-κB. These results are similar to those observed by genistein treatment, suggesting that the growth inhibitory and apoptosis inducing effects of the synthetic derivatives of isoflavone are partly mediated by the inactivation of Akt and NF-κB signaling pathways [50].

Studies from other laboratory have shown that Phenoxodiol, a synthetic analog of the plant isoflavone genistein resulted in improved broad-spectrum anticancer efficacy. The most important property of phenoxodiol is its ability to sensitize resistant tumor cells to chemotherapy. Therefore, it has been used for early- and late-stage prostate cancer including hormone-refractory prostate cancer, early stage cervical and vaginal cancer, chemo-resistant ovarian cancer, and renal cancer [52–54]. It has also been reported that phenoxodiol inhibited DMBA-induced mammary carcinogenesis in Sprague-Dawley rats [55]. Importantly, phenoxodiol could sensitize cancer cells to the anti-tumor effects of standard chemotherapeutics [53,56,57]. Moreover, it has been found that phenoxodiol suppresses the function of *tNOX*, leading to the induction of apoptosis through the inhibition of anti-apoptotic proteins XIAP and FLICE [53]. In animal studies, phenoxodiol has been found to stimulate both NK and tumor-specific cell lytic activity, causing significantly reduced tumor growth rates and prolonged survival [58]. In clinical trials, phenoxodiol has shown some beneficial effects on disease stabilization without severe toxicity [59]; however further in-depth research in this area is certainly needed.

Phytoestrogen biochanin A is another isoflavone with anti-carcinogenic properties and has been found to inhibit N-nitroso-N-methylurea-induced rat mammary carcinogenesis [60]. However, recent report showed that genistein was found to be more effective than biochanin A in providing protection against oxidative stress [61]. In order to further investigate the

relationship between structure and anti-cancer activities, Vasselin *et al*. have reported a series of synthetic fluoro- and amino-substituted isoflavones as potential anti-tumor agents based on structural similarities to known isoflavones [62]. These isoflavone analogs have shown significant inhibitory effects on cancer cell proliferation at very low IC_{50} (<1μM) in breast cancer cells, suggesting their potent anti-tumor activity. Certain oxime- and methyloxime-containing isoflavone analogs were also synthesized and evaluated for their antiproliferative activity against cervical, hepatocellular, and oral epithelial cell carcinoma. These analogs of isoflavone arrested cancer cells at G2/M phase and showed strong anti-proliferative activities at GI_{50} values of less than 1 μM [63]. Whatmore, *et al*. also reported that several synthesized isoflavone analogs, SU1433, SU 5416 and SU6668, were potent inhibitors of VEGF-induced angiogenesis compared to naturally occurring isoflavones, suggesting the potent anti-tumor and anti-angiogenic effects of these compounds [64]. In order to enhance the intrinsic activity of genistein, its glycosidic derivatives were also synthesized and found to be more potent in their cytostatic and cytotoxic effect than genistein [65]. These reports all suggest that synthetic isoflavone analogs could have more potent activity than naturally occurring isoflavone and could be useful for combination therapy with conventional chemotherapeutics in order to achieve better treatment outcome, and thus such studies must be done in human patients not only for assessing its value as therapeutics but also for assessing pharmacokinetic, pharmacodynamic, and toxicity profile.

Clinical Trials Using Isoflavone for Cancer Treatment

Because isoflavone genistein transcriptionally down-regulates AR and its target PSA, an important biomarker for the diagnosis of prostate cancer and the prediction of prostate cancer progression, we have conducted a phase II clinical trial to investigate the modulation in serum PSA levels in patients diagnosed with prostate cancer by soy isoflavone supplementation [66]. This pilot clinical data demonstrated that soy isoflavone supplementation could decrease the rate of rise in serum PSA levels without any toxicity in prostate cancer patients [66]. Another phase II clinical trial has been conducted to evaluate the efficacy of isoflavone in patients with PSA recurrent prostate cancer after prior therapy [67]. It was found that dietary intervention with isoflavone supplementation decreased the slope of rising PSA, providing beneficial evidence in support of the use of isoflavone supplements against prostate cancer [67]. In another clinical trial focusing on determining the biological effects of soy protein isolate (SPI) consumption on circulating hormone profiles and AR expression patterns in men at high risk for developing advanced prostate cancer, the authors have found that consumption of SPI significantly suppressed AR expression but did not alter ER-β expression or circulating hormones, suggesting that isoflavone could be beneficial in preventing prostate cancer by inhibition of AR and PSA expression [68]. Several other clinical trials have also shown similar results documenting reduced PSA after receiving isoflavone supplements [69,70]. Based on the molecular evidence showing that isoflavone targets multiple cellular signaling pathways, more and more clinical trials are being conducted to investigate the value of isoflavone in human cancer (www.ClinicalTrials.gov). These clinical trials are focused on investigating the effects of isoflavone on the prevention of various cancer developments, and the combination treatment of various cancers with chemotherapeutic agents or other “natural products” are emerging. We believe that the conventional cancer therapeutics combined with supplement of isoflavone and its analog could be an important novel strategy for the treatment of human cancers and/or the prevention of cancer progression. Further rationally-designed clinical trials are needed in order to fully appreciate the health benefit of isoflavone and its analogs in humans.

CURCUMIN AND ITS ANALOGS

Molecular Structure and Biological Properties of Curcumin

Curcumin is a naturally occurring compound present in turmeric. It is the main curcuminoid from turmeric which is a member of the ginger family. The curcuminoid is responsible for the yellow color of turmeric. Curcumin exists in at least two tautomeric forms, keto and enol. The enol form is more energetically stable in the solid phase and in solution. The structure of curcumin was first identified in 1910. Curcumin is a homodimer of feruloylmethane and consists of several functional groups (Fig. (**3**)). It contains a methoxy group and a hydroxyl group, a heptadiene with two Michael acceptors, and an α,β-diketone.

Curcumin has been known to possess anti-inflammatory, antioxidant, and anti-cancer activities. Therefore, it has been used for the treatment of inflammatory diseases, diabetes, depression, arthritis, neurological diseases, Crohn's disease, and the other disorders of the cardiovascular, pulmonary, and neurological systems [22,71–74]. Accumulating experimental evidence suggests that curcumin interferes with a variety of molecules which are involved in cancer development and progression, leading to the inhibition of cancer cell growth [20]. Importantly, curcumin could be useful as a chemo-sensitizer in cancer chemotherapy [75], which may result in better treatment outcome in patients although such clinical trials have not be done yet which indeed could be due to poor systemic and target tissue bioavailability of curcumin.

The Effects of Curcumin on Cellular Signaling

Curcumin has been used for centuries as a therapeutic agent for the treatment of inflammatory diseases in Asian medicine. Since NF-κB is significantly activated in the processes of inflammation, it has been well known that curcumin is a strong inhibitor of NF-κB (Fig. (**4**)). Curcumin could inhibit IKK, suppress both constitutive and inducible NF-κB activation, regulate Bax-mediated apoptosis, and potentiate TNF-induced apoptosis [76,77]. Curcumin also sensitizes human colorectal cancer xenografts in nude mice to γ-radiation by targeting NF-κB-regulated gene products [78]. It has also been reported that treatment with a liposomal formulation of curcumin resulted in a dose-dependent growth suppression of cancer cells and a decreased activation of NF-κB [79]. Moreover, expression of NF-κB target genes including cyclin D1, cyclooxygenase-2 (COX-2), matrix metalloproteinase-9 (MMP-9), Bcl-2, Bcl-xL, Mcl-1L, and Mcl-1S were reduced [78], indicating the effect of curcumin on NF-κB signaling pathway. Furthermore, clinical trial showed that curcumin down-regulated NF-κB and COX-2 in peripheral blood mononuclear cells from patients with pancreatic cancer [80] although the anti-cancer activity of curcumin in this trial was found to be minimal. However, it is clear that curcumin could inhibit NF-κB signaling *in vitro* and *in vivo* but the clinical benefit of curcumin has not yet been proven.

In addition to NF-κB signaling, Akt signaling could also be inhibited by curcumin (Fig. (**4**)). It has been shown that curcumin inhibited the phosphorylation of Akt, mTOR, and their downstream targets in prostate cancer cells [81]. Curcumin has also been found to inhibit the proliferation of cisplatin-resistant ovarian cancer cells through the inhibition of Akt activation [82]. The analog of curcumin, 4-hydroxy-3-methoxybenzoic acid methyl ester (HM-BME), also inhibited the proliferation of cancer cells and induced apoptosis through the down-regulation of phosphorylated Akt, the inhibition of Akt kinase activity, and the reduction of NF-κB DNA-binding activity [83]. These findings together with other reports [84,85] all suggest that curcumin could inhibit Akt signaling and facilitate inhibition of proliferation and induction of apoptosis in various cancers.

It has been also shown that curcumin could exert its inhibitory effects on Wnt signaling (Fig. (**4**)). Experimental studies have shown that curcumin suppressed β-catenin mediated

transcription activated by Wnt3a, and inhibited the growth of colon cancer cells [86]. Curcumin also induced caspase-3-mediated degradation of β-catenin [87], resulting in the decreased binding of β-catenin to TCF, and thereby causing inactivation of Wnt signaling. In addition, curcumin has shown to down-regulate p300 which is a positive regulator of the Wnt/β-catenin pathway [87], further suggesting its inhibitory effects on Wnt signaling. Moreover, gene expression profile analysis showed that the expression of Frizzled-1 (Wnt receptor) was most strongly attenuated by curcumin [88]; therefore it is quiet clear that curcumin could inhibit proliferation of cancer cells through the inhibition of Wnt signaling.

Curcumin also showed its inhibitory effects in both androgen-dependent and independent prostate cancers. Curcumin has been found to down-regulate the transactivation and expression of AR and AR-related molecules (AP-1 and NF-κB), and inhibited colony formation in prostate cancer cells [89]. Moreover, some curcumin analogs have been shown to possess potent anti-androgenic activities [90], and were found to be superior than hydroxyflutamide which is the currently available anti-androgenic agent for the treatment of prostate cancer; however, clinical studies using curcumin analogs has not been done yet. Structure-activity relationship studies demonstrated that some moieties seem to be important factors related to the anti-androgenic activity [90]. Therefore, these analogs could serve as newer anti-androgenic agents for controlling the growth of AR-mediated prostate cancers.

Curcumin has been used for the prevention and treatment of a number of inflammatory diseases because of its anti-inflammatory activity. The role of LOX and COX isoforms, particularly COX-2, in the inflammation has been well established. Therefore, the effects of curcumin on COX and LOX were investigated. Experimental evidence has shown that curcumin could regulate LOX and COX-2 predominately at the transcriptional level, and to a certain extent, at the posttranslational level [91]. Thus, the dual COX/LOX inhibitory potential of curcumin provides distinctive advantages over synthetic COX-2-specific inhibitors. Because the up-regulation of COX-2 is commonly observed in various cancers, the inhibition of COX-2 expression by curcumin could contribute in suppressing the growth of cancer cells; however clinical trials have not been completed to-date.

Recent Advances in Novel Synthetic Analogs of Curcumin and their Biological Activity

Despite the biological activity of curcumin *in vitro* and in selected models *in vivo*, curcumin has shown poor systemic and tissue bioavailability [22,92]. Preclinical and clinical studies have shown that the concentrations of curcumin achieved in plasma and target tissues are very low. The plasma and colorectal tissue concentrations of curcumin in patients receiving 3,600 mg curcumin orally were 11.1 nM [93] and 12.7 nM [94], respectively. Moreover, the level of curcumin concentration in the liver was found to be below the limit of detection [94]. These data suggests that novel synthetic analog of curcumin must be developed or the bioavailability of curcumin must be improved by novel methods such nano-formulation or other methods so that the value of curcumin or its synthetic analog could be appreciated toward launching novel clinical trials.

Recently, we have designed and synthesized new difluoro Knoevenagel condensates of curcumin and Schiff bases along with their copper (II) complexes (Fig. (**3**)), and evaluated their biological activities with respect to the suppression of 26S proteasome, the inhibition of proliferation, and the induction of apoptosis in colon and pancreatic cancer cells [95]. We found that all copper complexes possessed distorted square planar geometries with 1:1 metal to ligand stoichiometry with reversible copper redox couple. The difluoro compound CDF inhibited the activities of rabbit 20S proteasome and cellular 26S proteasome, leading to the inhibition of cell proliferation and the induction of apoptosis, which was consistent with our previous findings [96]. These results suggest that our newly synthesized classes of curcumin analogs especially CDF could be useful as chemopreventive and/or therapeutic agents

against cancers. These preliminary results were encouraging, and thus further studies were conducted and are also being done to test whether curcumin analog could show superior bioavailability compared to curcumin and, in turn, could show better anti-tumor activity. Indeed, animal experiments and pharmacokinetic analysis revealed that CDF had better retention and bioavailability, and that the concentration of CDF in the pancreas tissue of mice was 10-fold higher compared to curcumin [97], suggesting better tissue bioavailability of CDF. We have also tested the effects of CDF on NF-κB and PGE_2, an enzymatic product of COX-2, and we found that CDF significantly down-regulated the NF-κB DNA binding activity and decreased PGE_2 expression level [97]. The molecular docking studies have shown that the fluorocurcumin analogs did not introduce any major steric changes compared to the parent curcumin molecule, which was consistent with the down-regulation of NF-κB and the reduced level of PGE2 in cells treated with CDF. These results demonstrate that CDF could inhibit cancer cell growth and induce apoptotic cell death through the inactivation of proteasome, NF-κB and COX-2 signaling. More importantly, our results have shown that the bioavailability of CDF is much superior compared to curcumin, suggesting that CDF could be clinically useful as an anti-cancer agent, which awaits further investigations.

Another synthetic curcumin analog GO-Y030 has been tested for its inhibitory effects on human breast and pancreatic cancer cells [98]. It has been found that both curcumin and GO-Y030 reduced cell viability and induced apoptosis, but GO-Y030 was substantially more potent compared to curcumin. Further investigation revealed that GO-Y030 inhibited STAT3 phosphorylation and transcriptional activity whereas comparable dosages of curcumin had little or no effect on STAT3. These results suggest that GO-Y030 inhibits cell growth through the down-regulation of STAT3 activation and that GO-Y030 could be potentially useful as a therapeutic agent for the treatment of cancers expressing high levels of activated STAT3 [98]. Other curcumin analogs, FLLL11 and FLLL12, also inhibited phosphorylation of STAT3 in breast and prostate cancer cells [99]. In addition, FLLL11 and FLLL12 exhibited more potent activities than curcumin on the down-regulation of STAT3, Akt, and HER-2/neu, as well as the inhibition of cancer cell growth and migration [99]. GO-Y030, FLLL11, and FLLL12 also induced apoptosis through the increased cleavage of PARP and caspase-3 in pancreatic and colorectal cancer cells, suggesting their potential use as chemopreventive or therapeutic agents for various cancers [100,101]. However, further preclinical animal experiments, pharmacokinetics, and clinical studies are needed in order to appreciate whether these analogs could have any value for the treatment of human malignancies.

Although curcumin has long been used for the treatment of many diseases, it remains unknown whether the activity of curcumin is based on its scaffold or whether it results from the Michael acceptor properties of the α,β-unsaturated diketone moiety central to its structure. By modifying diketone system of curcumin, two curcumin analogs (benzyloxime and isoxazole) were synthesized and tested. Results showed that the analogs remarkably increased anti-tumor potency in MCF-7 and MDR transfected MCF-7 breast cancer cells. Furthermore, these curcumin analogs potently reduced the expression levels of Bcl-2, Bcl-X_L, and COX-2 in MCF-7 and MDR transfected MCF-7 breast cancer cells. These results suggest that these analogs could be effective anticancer agents for the treatment of hormone-independent MDR breast cancer [102]. In another report, electron-rich pyrazole and isoxazole analogs were synthesized and evaluated against two breast cancer cell lines [103]. All these analogs showed much lower IC_{50} values in sub-micromolar range, and showed ten to fifty times more potent than curcumin, suggesting that they could serve as potential antitumor agents toward cancer therapy [103,104] although *in vivo* studies and pharmacokinetics are yet to be done using these analogs.

In addition to the above mentioned studies, several new curcumin analogs were also studied regarding their structure-activity relationships and the mechanism of action. It has been reported that analogs with furan moiety have excellent inhibitory effect on thioredoxin reductase (TrxR) in an irreversible manner, suggesting that the furan moiety could serve as a possible pharmacophore during the interaction of curcumin analogs with TrxR [105]. A synthetic monoketone compound, EF24, was developed from curcumin and showed potent anticancer activity through the down-regulation of NF-κB signaling [106]. EF24 induced apoptotic cell death of lung, breast, ovarian, and cervical cancer cells with ten times higher potency than that of curcumin has been reported. EF24 inhibited the phosphorylation and degradation of IκB and blocked the nuclear translocation of NF-κB, leading to the inhibition of NF-κB activation [106]. EF24 also induced cell cycle arrest and apoptosis by means of a redox-dependent mechanism in MDA-MB-231 human breast cancer cells and DU-145 human prostate cancer cells [107]; however, it is really surprising why these analogs has not been tested for their systemic and tissue bioavailability yet. Enone analogs of curcumin with a 3-carbon, 5-carbon, or 7-carbon spacer were compared with curcumin for their abilities to inhibit the TNF-α-induced activation of NF-κB and it was found that enone analogs with the 5-carbon spacer were especially active for the inhibition of NF-κB [108]. Four novel dienone cyclopropoxy curcumin analogs were further synthesized and tested in mice bearing Ehrlich ascites tumor (EAT) *in vivo* [109]. It has been found that the analogs increased the life span of mice bearing EAT with significant reduction in the microvessel density in the peritoneum walls of mice with concomitant reduction in the ascites volume in this animal model [109].

Moreover, curcumin analogs, symmetrical 1,5-diarylpenta-dienone whose aromatic rings possess an alkoxy substitution at each of the positions 3 and 5, were designed and synthesized. It has been found that these analogs down-regulated β-catenin, Ki-ras, cyclin D1, c-Myc, and ErbB-2 at as low as one eighth the concentration at which curcumin normally showed its effects [110]. Furthermore, in a study regarding structure and activity, new curcumin analogs were classified into four series: monophenyl analogs, heterocycle-containing analogs, analogs bearing various substituent on the phenyl rings, and analogs with various linkers. These new analogs were tested for cytotoxicity against androgen-dependent LNCaP and androgen-independent PC-3 cells. It was found that ten analogs possessed potent cytotoxicity against both LNCaP and PC-3 cells, seven only against LNCaP, and one solely against PC-3, demonstrating their structure-activity relationship [111]. A number of curcumin analogs were further synthesized and evaluated as potential AR antagonists against PC-3 and DU-145 prostate cancer cells in the presence of AR and AR co-activator, ARA70. Structure-activity relationship studies indicated that the bis(3,4-dimethoxyphenyl) moieties, the conjugated β-diketone moiety, and the intramolecular symmetry of the molecules was important factors related to anti-androgenic activity. Further analysis demonstrated that the coplanarity of the β-diketone moiety and the presence of a strong hydrogen bond donor group were also crucial for the anti-androgenic activity [90]. In addition, it has been found that ASC-J9 and its analogs have inhibitory effects on prostate cancer cell proliferation through a novel mechanism of enhancing AR degradation [112]. These together with other information will likely guide further design of new curcumin analogs with better anti-prostate cancer activity in the near future.

Other synthetic curcumin analogs or copper complexes also showed their effects on COX signaling, angiogenesis, cell proliferation, and apoptotic cell death.

In order to find more selective COX-1 inhibitors, a series of novel curcumin analogs were synthesized and evaluated for their ability to inhibit COX-1 by measuring COX-1, COX-2, and PGE2. It was found that the most potent curcumin analogs were (1E,6E)-1,7-di-(2,3,4-trimethoxyphenyl)-1,6-heptadien-3,5-dione and (1E,6E)-methyl 4-[7-(4-

methoxycarbonyl)phenyl]-3,5-dioxo-1,6-heptadienyl]benzoate [113]. Another synthetic curcumin analog, dimethoxycurcumin was compared with curcumin for the ability to inhibit cell proliferation and induction of apoptosis in human HCT116 colon cancer cells, and the results showed much more potent activity than curcumin in inhibiting cell proliferation and inducing apoptosis [114]. Curcumin analogs also showed their anti-angiogenic activity *in vivo*. Intraperitoneal administration of the analogs tetrahydrocurcumin (THC), salicyl curcumin (SC) and curcuminIII (C-III) reduced the number of tumor directed capillaries induced by injecting B16F-10 melanoma cells on the ventral side of C57BL/6 mice [115]. Curcumin analogs also down-regulated the expression of angiogenesis-associated genes, VEGF and MMP-9 [116]. Four synthetic curcuminoids, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione (curcumin1), 1,7-bis(piperonyl)-1,6-heptadiene-3, 5-dione (piperonyl curcumin), 1, 7-bis(2-hydroxy naphthyl)-1, 6-heptadiene-2, 5-dione (2-hydroxy naphthyl curcumin), 1,1-bis(phenyl)-1, 3, 8, 10- undecatetraene-5, 7-dione (cinnamyl curcumin) and their copper(II) complexes were investigated for their *in vivo* anti-tumor activities. Copper chelates of synthetic curcuminoids showed enhanced anti-tumor activity with a significant reduction of solid tumor volume in mice [117]. Copper complexes of curcuminoids with a hydroxy group on the ring such as 2-hydroxy naphthyl curcumin were found to be most active [117], suggesting the importance of structure-activity relationship.

In order to further increasing the curcumin absorption by oral administration, several studies have focused on the preparation of liposome-encapsulated curcumin, and tested the biochemical properties of liposome-encapsulated curcumin. In an animal experiment using Sprague-Dawley (SD) rats, pharmacokinetic parameters showed that liposome-encapsulated curcumin possessed high bioavailability of curcumin, demonstrating a faster rate and better absorption of curcumin after administration of liposome-encapsulated curcumin [118]. Oral liposome-encapsulated curcumin gave higher C_{max} and shorter T_{max} values, indicating the enhanced gastrointestinal absorption by liposome encapsulation. Moreover, the plasma antioxidant activity after oral ministration of liposome-encapsulated curcumin was significantly higher than that of controls and the plasma curcumin concentration was significantly correlated with plasma antioxidant activities [118]. The minimum effective dose and the optimal dosing schedule of liposomal curcumin in a xenograft mouse model of human pancreatic cancer were investigated [119]. It was found that 20 mg/kg dose three times per week had the greatest decrease (52%) in tumor growth [119]. The effects of liposome-encapsulated curcumin were also examined in different cancer system. The liposomal curcumin has been found to dose-dependently inhibit growth of head and neck squamous cell carcinoma through the down-regulation of NF-κB and its targets, cyclin D1, COX-2, MMP-9, Bcl-2, Bcl-xL, Mcl-1L [24]. *In vivo*, liposomal curcumin also suppressed pancreatic cancer growth in murine xenograft models and inhibited tumor angiogenesis with down-regulation of NF-κB signaling [120]. Moreover, combination of liposomal forms of curcumin and resveratrol significantly inhibited the growth of prostate cancer *in vivo* [121]. *In vitro* studies showed that curcumin plus resveratrol significantly inhibited cell proliferation and induced apoptosis with down-regulation of p-Akt, cyclin D1, mTOR, and AR [121]. All these results demonstrate that liposomal curcumin could be more potent for the treatment of cancer because of its improved bioavailability although such studies have not been done for assessing the target tissue bioavailability or toxicity, which must be done prior to any clinical investigation.

Other than liposomal formulation, nanoparticulate formulation of curcumin is another approach for improving the bioavailability of curcumin for enhancing treatment efficacy. A polymer-based nanoparticle approach to improve bioavailability of curcumin has been designed and tested where the authors have found that nanoparticle curcumin exhibited very rapid and more efficient cellular uptake than curcumin [23]. Nanoparticle curcumin was

more potent than curcumin in inducing apoptosis and suppressing proliferation of various cancer cells which was concomitant with down-regulation of NF-κB, cyclin D1, MMP-9, and VEGF [23]. Another recent report also showed that nanoparticle encapsulation improved oral bioavailability of curcumin by at least 9 fold when compared to curcumin [122]. Several other forms of nanoparticle curcumin including lipid-based and polymer-based nanoparticle-encapsulated curcumin also showed enhanced bioavailability and improved anticancer activities [123–125], suggesting that nanoparticle curcumin could serve as potent agents for the treatment of cancer; however their toxicity profile must be investigated prior to assess their anticancer efficacy against human malignancies.

Clinical Trials Using Curcumin for Cancer Therapy

Several clinical trials have been conducted to evaluate the value of curcumin in cancer treatment. In a phase I clinical trial using combination treatment with curcumin and quercetin to regress adenomas in patients with familial adenomatous polyposis (FAP), all 5 patients had a decreased polyp number and size from baseline after 6 months of curcumin and quercetin treatment without appreciable toxicity [126], suggesting that curcumin could inhibit adenoma growth *in vivo*. Moreover, another phase I trial has been conducted to evaluate the dose and the biomarkers in fifteen patients with advanced colorectal cancer refractory to standard chemotherapies. It was found that a daily dose of 3.6 g curcumin caused 62% decreases in inducible PGE2 production in blood samples, indicating the biological activity in humans [127]. In addition, the effects of curcumin has been tested in a phase I clinical trial in patients with resected urinary bladder cancer, arsenic Bowen's disease of the skin, uterine cervical intraepithelial neoplasm, oral leucoplakia, and intestinal metaplasia of the stomach [128]. The results showed that histologic improvement of precancerous lesions was seen in 1 out of 2 patients with resected bladder cancer, 2 out of 7 patients of oral leucoplakia, 1 out of 6 patients of intestinal metaplasia of the stomach, 1 out of 4 patients with cervical intraepithelial neoplasm and 2 out of 6 patients with Bowen's disease after curcumin treatment. This study also demonstrated that curcumin was non-toxic to humans. Recently, a phase II trial of curcumin in patients with advanced pancreatic cancer has been reported [129]. In this study, out of 21 cases, two patients showed clinical evidence for biological activity after curcumin treatment. Among them, one had ongoing stable disease for more than 18 months and another patient had a significant tumor regression (73%) [129]. Theses results suggest that oral curcumin is well tolerated and has biological activity in some patients with cancers. More new clinical trials are being conducted to investigate the value of curcumin in cancer patients (www.ClinicalTrials.gov). These clinical trials have investigated the efficacy of curcumin in the prevention setting for the development of various cancers, and the combination treatment of cancer with conventional chemotherapeutic agents or other dietary agents. We also believe that cancer chemotherapy combined with curcumin or its analog supplement could be an important novel strategy for the treatment of cancers and/or for the prevention of cancer progression of most human malignancies.

CONCLUSIONS AND PERSPECTIVES

The data from *in vitro* experiments and *in vivo* animal and limited human studies clearly suggest that naturally occurring compounds including isoflavones and curcumin could exert their inhibitory effects on carcinogenesis, cancer cell growth and tumor progression, which could be mediated through the regulation of multiple signaling pathways. Both isoflavone and curcumin inhibit NF-κB and Akt pathways by targeting similar molecules in these two pathways. However, isoflavone has stronger inhibitory effect on AR and Notch signaling while curcumin show its potent effects on the inhibition of COX-2 and Wnt3/β-catenin, suggesting their differential effects on cellular signaling. It is important to note that the

water solubility and bioavailability of these natural agents could significantly influence the efficacy of these natural compounds, suggesting that the synthetic analogs of isoflavone and curcumin based on the structure-activity assays, and the encapsulation of isoflavone, curcumin and perhaps their analogs with liposome or nanoparticle could significantly enhance anti-tumor activity of these natural agents. The *in vitro* and *in vivo* preclinical studies also suggest that these analogs and formulations of natural compound could serve as potent agents for the prevention of tumor progression and/or treatment of human malignancies either alone or in combination with conventional chemotherapeutics, which will likely open newer avenues for the successful treatment of cancer. However, further in-depth experimental investigations along with animal studies, and finally clinical trials are needed in order to fully evaluate the value of these naturally occurring compounds and their synthetic analogs together with novel formulations for the prevention of tumor progression and/or treatment of human malignancies guided by superior systemic as well as target tissue bioavailability and pharmacokinetic profiles.

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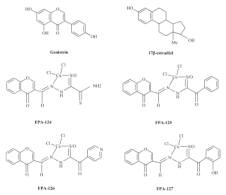

Fig. 1.
Molecular structures of isoflavone, estrogen, and representative isoflavone analogs.

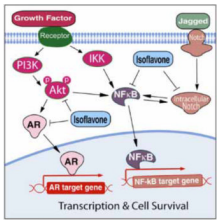

Fig. 2.
Cellular signaling altered by isoflavone.

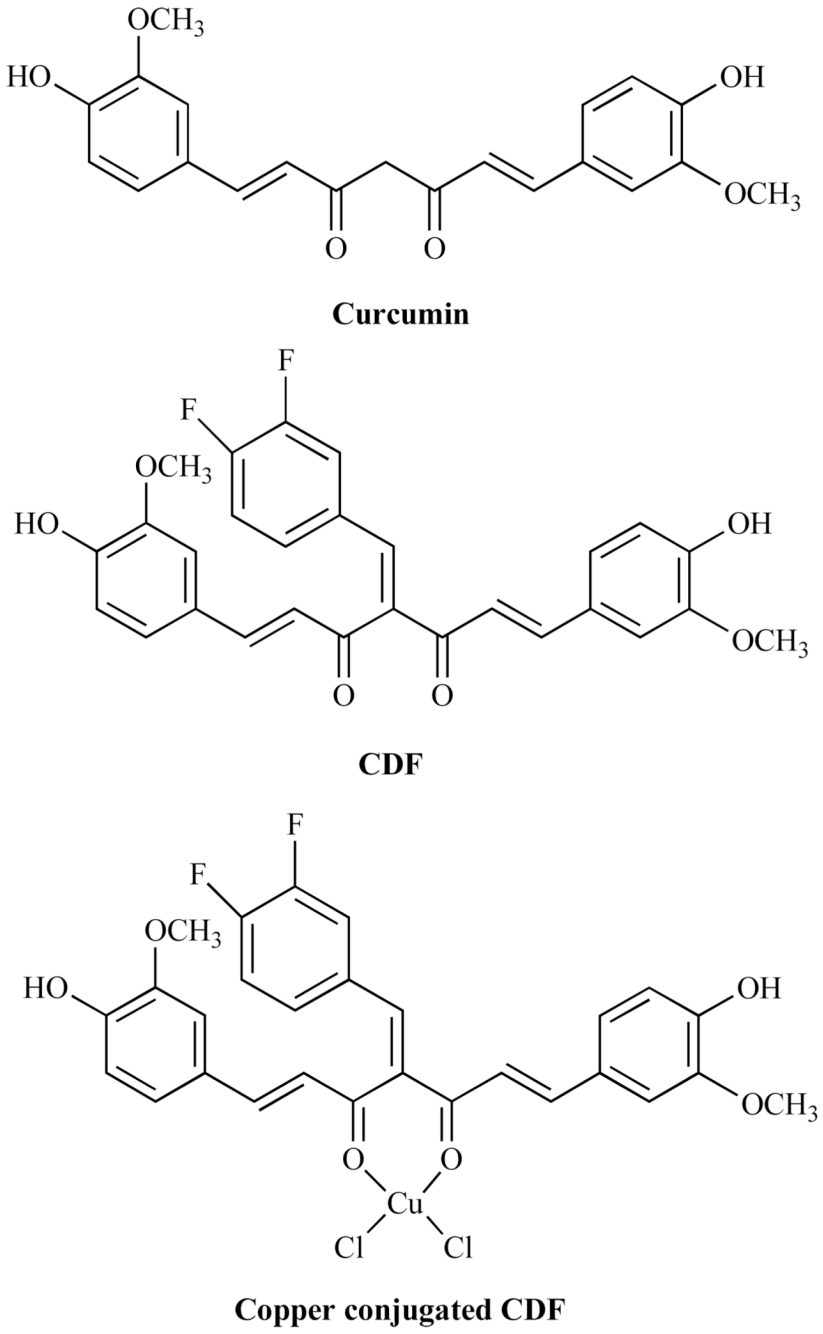

Fig. 3.
Molecular structures of curcumin and its representative analogs.

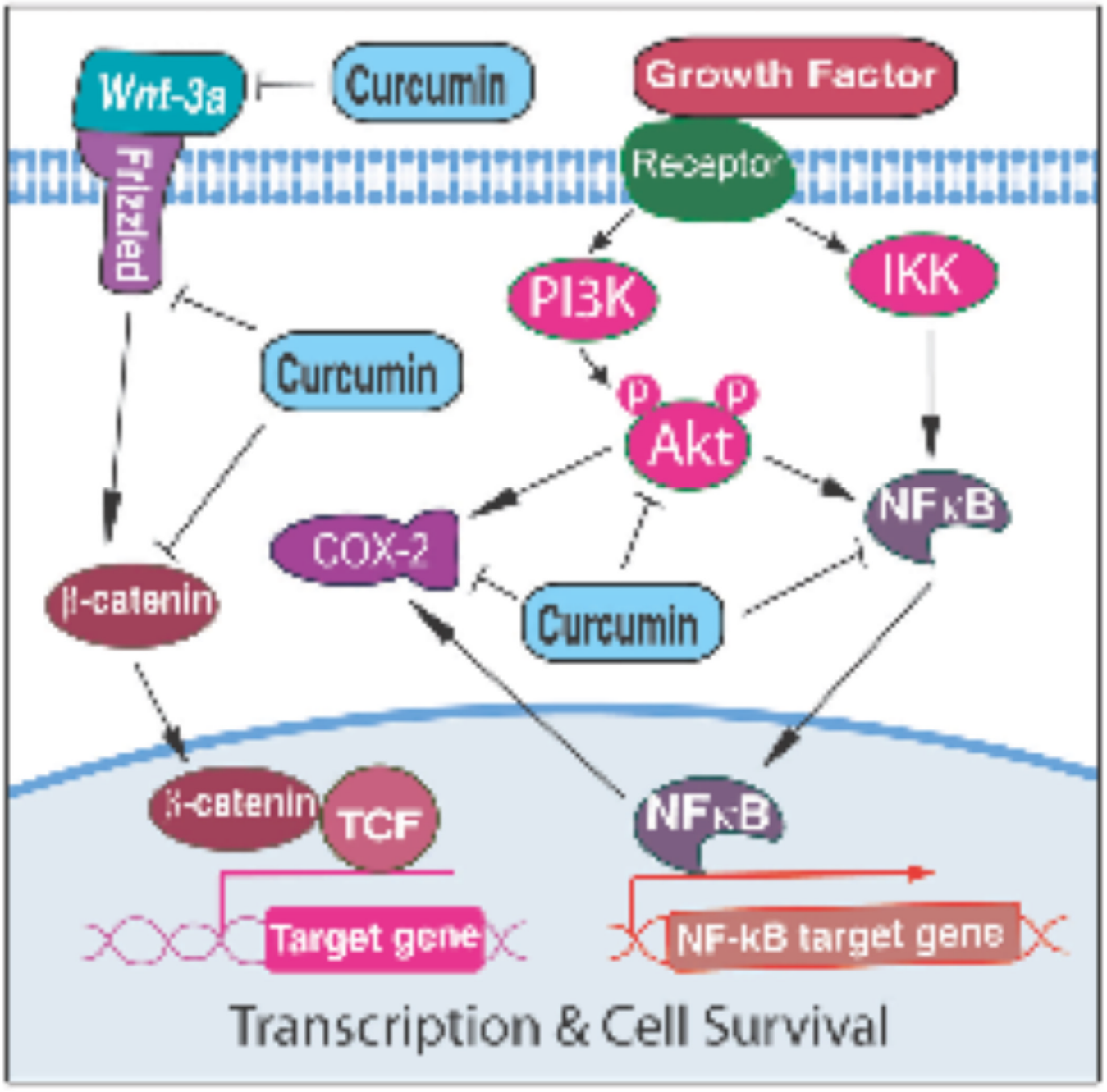

Fig. 4.
Cellular signaling altered by curcumin.