Nutrition

Curcumin and Pancreatic Cancer: A Research and Clinical Update
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Pancreatic cancer is currently one of the most deadly types of cancer. Poor patient prognosis is linked to the lack of effective early detection techniques and emerging resistance to current therapeutic strategies. Thus, current research efforts are focusing on overcoming drug resistance. One branch of this field of study is the use of natural compounds to combat pancreatic cancer and drug resistance. Curcumin, a turmeric derivative, is one such compound that has been shown to have potent anti-cancer properties in the context of pancreatic cancer. However, curcumin’s poor bioavailability limits its clinical utility. Multiple approaches have been taken to overcome this problem, including curcumin modifications, curcumin combination therapy with other natural and synthetic therapeutic agents and the use of nano-formulations. This review is intended to provide a compendium of the cutting-edge investigations related to preclinical and clinical uses of curcumin, including its analogues and nano-formulations, in the context of pancreatic cancer. Journal of Nature and Science, 1(6):e124, 2015

Curcumin | curcumin analogues | curcumin nano-formulations | pancreatic cancer

Introduction
Pancreatic cancer is one of the most devastating types of cancer. The American Cancer Society has estimated that 48,960 individuals will be diagnosed with pancreatic cancer in the United States this year. Furthermore, approximately 40,560 of these patients (83%) will perish from this disease this year and only 7% of patients will survive at least five years (1). Inadequate detection techniques, the aggressive nature of the disease, and the emerging resistance to the current treatment approaches have contributed to these unacceptably high mortality rates (2). Tumor removal in combination with post-surgical chemotherapy treatment is considered the most effective treatment approach to date. Unfortunately, the early detection of pancreatic cancer, which is a requirement for eligibility for surgery, is challenging due to the lack of accurate and reliable methods. However, patients that are ineligible for surgery still have the option to receive a battery of chemotherapeutic agents in combination with radiation therapy. Most combinational therapies consist of using anti-metabolites, DNA damage inducers, tyrosine kinase inhibitors and topoisomerase inhibitors, with the gold standard chemotherapeutic agent for pancreatic cancer being Gemcitabine, an anti-metabolite and inducer of DNA damage. However, despite clinical responses in some cases, overall patient survival and quality of life are not improved by these therapies (3-8). The chemo- or radiation-therapy resistance developed by most patients with pancreatic cancer has hindered the efficacy of combinational chemotherapeutic and radiation-based treatment strategies (9). Thus, a better understanding of the mechanisms of therapeutic resistance and the development of novel therapeutic approaches are of paramount importance to eradicate this disease.

A low incidence of cancer has been documented in countries that incorporate high consumption of turmeric root into their diets (10, 11). This association has been extensively investigated, particularly in the context of the biological roles of turmeric root derivatives. Curcumin is a derivative of the turmeric root that has been extensively investigated because its low toxicity in normal tissues and capacity to hinder multiple signaling pathways that are crucial for the initiation and progression of various cancers, including pancreatic cancer (12). Additionally, curcumin has been shown to synergistically enhance the anti-cancer effects of chemotherapeutic agents, including Gemcitabine, in pancreatic cancer (13). Due to curcumin’s poor bioavailability in clinical trials involving pancreatic cancer patients (14-17), novel approaches such as curcumin analogues and nano-particle formulations of curcumin have been developed (14, 18, 19) and are currently under investigation in various pancreatic cancer (18, 20-22). Currently, the literature concerning the pre-clinical and clinical anti-cancer properties of curcumin in various cancer types has been eloquently reviewed (12, 23, 24); however, a comprehensive review addressing the current state of curcumin research in the context of pancreatic cancer is lacking. Therefore, the purpose of this review is to provide a compilation of cutting-edge studies involving the pre-clinical and clinical utility of curcumin and its analogues/nano-formulations in pancreatic cancer.

Curcumin: Molecular mechanisms in pancreatic cancer
Curcumin’s effects in pancreatic cancer have been widely studied. It has been shown to influence a range of cellular functions including proliferation, survival, angiogenesis, and invasion and metastasis. For instance, curcumin causes G2/M cell cycle arrest in pancreatic cancer cells following DNA damage and ATM-Chk1-dependent inhibition of CDK-1 and Cyclin B1 activity (25). Interestingly, this study also demonstrated that curcumin showed lower cytotoxic effects and no DNA damage or cell cycle arrest in normal human pancreatic ductal epithelial cells (25) compared to pancreatic cancer cells. Curcumin has also potent effects on cell survival, most notably through regulation of the inhibitor of apoptosis (IAP) family, which includes Survivin, cellular IAPs 1 and 2 (cIAP1 and cIAP2) and X-chromosome linked IAP (XIAP). One of the key roles of the IAP proteins in normal cells is to modulate the balance between cell survival and cell death. The unbalanced regulation of IAP proteins can drive cells to a more pro-survival phenotype. Indeed, pancreatic cancer cells overexpress IAP proteins and the overexpression of these proteins is associated with poor patient outcomes in pancreatic cancer (26-29). In addition, studies have demonstrated that resistance to radiation and chemotherapy is also related to the overexpression of the IAP proteins (30-37). Studies from our laboratory have demonstrated that although other standard chemotherapeutic agents are ineffective at reducing these IAP family members (38), curcumin abolishes Survivin, cIAPs 1 and 2, and XIAP protein and mRNA expression in pancreatic cancer cells (39). This is consistent with previous reports that Survivin expression is reduced following curcumin treatment in pancreatic cancer cells as a result of inhibition of upstream STAT3 signaling (40) or reduction in NF-κB activity (41). The importance of STAT3 and NF-κB signaling in pancreatic cancer has been well established (42, 43). Interestingly, Jutooru et al. also demonstrated that curcumin reduces Sp1 and NF-κB activity, resulting in down-regulation of downstream genes including Survivin, MMP-9, VEGF and Cyclin D1. Furthermore, these studies demonstrated that reduction in NF-κB activity was dependent on Sp1 reduction following curcumin treatment, suggesting that curcumin’s effects on Sp1 represent an upstream event in pancreatic cancer cells (44).

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Studies by Sun et al. complement these findings by demonstrating that curcumin modulates microRNA (miRNA) expression profiles in pancreatic cancer cells (45). MiRNAs are small non-coding RNAs (46-48) that have recently gained increased attention in the literature due to their involvement in important biological processes via post-transcriptional modulation of gene expression (47-50). Altered post-transcriptional gene regulation conferred by miRNAs has been linked to pancreatic cancer (51). One miRNA that is altered after curcumin treatment is miRNA-22, whose increased expression after treatment results in downregulation of target transcripts for Sp1 and estrogen receptor 1 (ESR1) (45). Another miRNA whose expression is altered after curcumin treatment is miRNA-221, which is known to promote tumor growth and invasion via upregulation of miRNA-7 and subsequent inhibition of the ATP-dependent multidrug resistance protein-5 (MRP5), an efflux pump notorious for promoting the export of chemotherapeutic drugs (60). Interestingly, curcumin has been shown to suppress the activity of MRP5 and enhance the effects of 5-fluorourasil (5-FU) in vitro (61). In summary, curcumin’s effects in pancreatic cancer are truly multi-dimensional, regulating miRNA expression, transcription factor activity and gene expression resulting in increased cell death and reduced pro-angiogenic, metastatic, and chemoresistance signaling. It is important to note that although several STAT3 inhibitors (NCT00955812, NCT02058017, NCT01423903, NCT01867073, NCT01563302, NCT01839604) and IAP antisense compounds (NCT000882869, NCT00557596, NCT00558545, NCT01018069, NCT00372736, NCT0186328, NCT00620321) have been studied in various phase I/II clinical trials, the majority of curcumin’s targets have yet to be addressed in clinical trials. Furthermore, no compound has been demonstrated to possess the vast arsenal of anti-cancer mechanisms displayed by curcumin.

### Curcumin: Analogues and nano-formulations in pancreatic cancer

Curcumin in pancreatic cancer

The metabolism of curcumin involves hepatic enzymes such as glucuronidases and sulfotransferases, which are responsible for conjugating glucuronic acid or sulfate, respectively, to the hydroxyl groups on the ketone or enol forms of curcumin (62, 63). These reactions enhance the hydrophilic potential of curcumin, facilitating its elimination (62, 63). Unfortunately, these systemic clearance mechanisms are responsible for hindering curcumin’s delivery to tumors (62). Thus, the development of analogues of curcumin has focused on modifying the hydroxyl and other functional groups on the ketone or enol forms of curcumin to ensure greater stability and extend its half-life in circulation (Table 1).

Early studies by Aggarwal et al., investigated the anti-cancer activity of a [Dlys]-LHRH-curcumin conjugate. This compound was developed with the rationale that luteinizing hormone releasing hormone (LHRH) and its corresponding receptor, LHRHR, are important regulators of cellular proliferation in human tumors in an autocrine and paracrine fashion (64). Pancreatic cancer cells express higher levels of LHRH receptors than normal cells and the importance of these receptors is highlighted by the finding that the proliferation of cancerous cells may be interrupted in vitro using antagonists of LHRH receptors (64-67). The [Dlys]-LHRH-curcumin conjugate was found to suppress pancreatic cancer

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**Table 1. Enhancement of curcumin bioavailability and stability: curcumin analogues**

<table>
<thead>
<tr>
<th>Name</th>
<th>Preclinical Data</th>
<th>Ref.</th>
</tr>
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<tbody>
<tr>
<td>[Dlys]-LHRH-curcumin</td>
<td>Decreases tumor growth <em>in vivo</em></td>
<td>(66)</td>
</tr>
<tr>
<td>GO-Y030</td>
<td>Inhibits STAT3 activation and induces apoptosis <em>in vitro</em></td>
<td>(72)</td>
</tr>
<tr>
<td>FLLL11 and FLLL12</td>
<td>Inhibit STAT3 and AKT phosphorylation and activation and induce apoptosis <em>in vitro</em></td>
<td>(18)</td>
</tr>
<tr>
<td>FLLL31 and FLLL32</td>
<td>Anti-proliferative and anti-angiogenic effects</td>
<td>(71)</td>
</tr>
<tr>
<td>PEGylated-curcumin</td>
<td>Suppresses cancer growth via inactivation of Jab1 and enhances Gemcitabine <em>in vitro</em></td>
<td>(68)</td>
</tr>
<tr>
<td>EF31 and UBS109</td>
<td>Anti-angiogenic</td>
<td>(20, 73)</td>
</tr>
<tr>
<td>CDF</td>
<td>Enhance oxiplatin and SFU efficacy</td>
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<tr>
<td></td>
<td>Modulate DNMT-1 expression</td>
<td></td>
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<td></td>
<td>Decreases the expression of miR-21 leading to PTEN activation <em>in vitro</em> and <em>in vivo</em></td>
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<tr>
<td></td>
<td>Stop tumor progression <em>in vivo</em> via modulation of COX-2, PTEN, miR-21, miR-200 and NF-kB</td>
<td></td>
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<tr>
<td></td>
<td>Enhances Gemcitabine efficacy <em>in vitro</em></td>
<td></td>
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<tr>
<td></td>
<td>Increases miR-146a leading to a decrease of EGFR expression <em>in vitro</em></td>
<td>(74, 75, 77, 80, 82, 106)</td>
</tr>
<tr>
<td></td>
<td>Decreases miR-221 and increases expression of PTEN, p22, p57 and PUMA leading to a decrease in cell proliferation and migration <em>in vitro</em></td>
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<td></td>
<td>Increases the expression of miR-26a, miR-143 and miR-101 and decreases let-7 levels <em>in vitro</em></td>
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<td></td>
<td>Down-regulates Ras and reduces tumor growth</td>
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**Notes:**

1. *in vitro* indicates the effect was observed in laboratory cultures.
2. *in vivo* indicates the effect was observed in animals or patients.

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**References:**

(45) EF31 and UBS109. Enhance oxiplatin and SFU efficacy. Modulate DNMT-1 expression. Decreases the expression of miR-21 leading to PTEN activation *in vitro* and *in vivo*. Stop tumor progression *in vivo* via modulation of COX-2, PTEN, miR-21, miR-200 and NF-kB. Enhances Gemcitabine efficacy *in vitro*. Increases miR-146a leading to a decrease of EGFR expression *in vitro*. Decreases miR-221 and increases expression of PTEN, p22, p57 and PUMA leading to a decrease in cell proliferation and migration *in vitro*. Increases the expression of miR-26a, miR-143 and miR-101 and decreases let-7 levels *in vitro*. Down-regulates Ras and reduces tumor growth.

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growth in xenograft mice with higher efficacy compared to unmodified curcumin (66).

Curcumin has also been conjugated to a water-soluble polyethylene glycol compound (PEGylated curcumin), which was found to enhance curcumin’s ability to suppress pancreatic cancer growth via the inhibition of JAB1 (68), a protease that has been shown to promote pancreatic cancer cell proliferation and survival (69, 70). In addition, PEGylated curcumin was able to sensitize pancreatic cancer cells to Gemcitabine, inducing apoptosis (68).

Curcumin has been modified through the addition of methyl or cyclohexyl functional groups, yielding analogues FLL3L1 and FLL3L2. These compounds have also been tested in pancreatic cancer and have been shown to influence DNA methylation patterns through modulation of DNA methyltransferase (DNMT)-1 expression (73). Furthermore, these analogues have increased anti-angiogenic effects in vitro (71). Analogues FLL3L1 and FLL3L2, characterized by ketone elimination and ether curcumin analogues, have also been investigated in the context of STAT3 and pancreatic cancer; these compounds are more effective than curcumin in inducing apoptosis via inhibition of STAT3 and AKT phosphorylation (18). A similar analogue, GO-Y030, also inhibits phosphorylation and activation of STAT3 in pancreatic cancer cells, inducing apoptosis (72).

The addition of pyridine and piperidine moieties has yielded novel curcumin analogues UBS109 and EF31. These compounds have also been tested in pancreatic cancer and have been shown to influence DNA methylation patterns through modulation of DNA methyltransferase (DNMT)-1 expression (73). Furthermore, these analogues have increased anti-angiogenic effects in vitro and in vivo models of pancreatic cancer through inhibition of NF-κB activity and reduction of HIF-1α and VEGF expression (20).

Difluorinated curcumin (CDF) has been shown to sensitize pancreatic cancer cell lines to Gemcitabine through inhibition of NF-κB and COX-2 (74). CDF is also a suppressor of tumor growth via the reduction of histone methyltransferase EZH2, Notch-1, CD44, EpCAM and Nanog in an orthotopic xenograft pancreatic cancer model (75). Furthermore, CDF has been demonstrated to influence miRNA expression profiles in pancreatic cancer. In particular, CDF upregulates miRNA-146a and downregulates miRNAs -21 and -221 in pancreatic cancer. MiRNA-146a has gained attention in pancreatic cancer because its downregulation is associated with high levels of EGFR and induction of NF-κB (76). Recently, CDF has been shown to increase the expression of miR-146a resulting in a reduction in EGFR protein levels in a pancreatic cancer xenograft mouse model (77). It has been previously demonstrated that miRNA-21 upregulation in pancreatic cancer cells is linked to inactivation of the tumor suppressor gene PTEN following the induction of the PI3/Akt/mTOR pathway (78, 79). Interestingly, CDF has been reported to decrease miRNA-21 expression, resulting in restoration of PTEN activity in vitro and in vivo (74, 75). Moreover, this study concluded that the CDF curcumin analogue is able to inhibit tumor progression in a pancreatic cancer xenograft mouse model via modulation of COX-2, PTEN, miRNA-21, miRNA-200 and NF-κB (75, 80). MiRNA-221 is present in high levels in pancreatic cancer cell lines and tumor tissues in contrast to normal pancreatic duct epithelial cells and normal pancreas tissues (81, 82). CDF decreases the expression of miR-221 and activates PTEN, p27kip1, p53 and PUMA protein leading to suppression of pancreatic cancer cell proliferation and migration (82).

Taken together, these studies demonstrate that curcumin analogues have significant anti-tumor effects in pancreatic cancer, suggesting that they are promising candidates for evaluation in clinical trials. To date, however, there have been no clinical trials involving these compounds, though most curcumin analogues have shown clear benefits in preclinical modes of pancreatic cancer. Thus, these analogues represent a promising “next step” in the incorporation of curcumin into the clinical treatment regimen for pancreatic cancer patients.

Curcumin nano-formulations in pancreatic cancer (Table 2)

Early studies by Li et al. demonstrated that liposomal preparations of curcumin involving lipids 1,2-Dimyristoyl-sn-glycero-3-phosphocholine (DMPC) and 1,2-dimyristoyl-sn-glycero-3-[phospho-rac-(1-glycerol)] sodium salt (DMPG) reduced cell viability in six pancreatic cancer cell lines as well as tumor volume in a pancreatic cancer xenograft model. Like curcumin, liposomal curcumin abolishes NF-κB binding in pancreatic cell lines, resulting in reduced expression of downstream target genes such as COX-2, IL-8 and VEGF in vitro and in vivo (83). Mach et al. built on this work by establishing a putative dosing regimen for preclinical and clinical trials based on the minimum effective dose of liposomal curcumin in a MIA PaCa-2-derived xenograft model (22). Another study involving lipid-based curcumin found that combination with nano-encapsulated aspirin and free sulforaphane was more efficient than curcumin alone in inducing apoptosis in human pancreatic cancer cell lines (84). Curcumin nano-formulations can be also prepared using sugar molecules instead of lipids arranged in a cyclic fashion (85). A recent example is ruboside-solubilized curcumin, thought to form nanomicelles in water, that has improved water solubility and equivalent cytotoxicity in various cancer cell lines, including the pancreatic cancer cell line Panc-1, compared to free curcumin (86). A separate study showed that the curcumin analogue CDF may be packaged within these sugar structures, termed cyclodextrins, and retain its anti-cancer properties upon delivery to pancreatic cancer cells (85). Furthermore, this study reported that the serum levels of nano-CDF were 10 times higher than CDF alone (85).

In 2007, Bish et al. developed a micelle-based polymeric nanoparticle encapsulation of curcumin called nanocurcumin, or NanoCurc. In early studies, the in vivo cytotoxicity of nanocurcumin was tested against eight pancreatic cancer cell lines, demonstrating comparable efficacy to free curcumin in most cell lines. Like free curcumin, nanocurcumin blocks NF-κB activity and reduces the expression of NF-κB-regulated genes including IL-6, IL-8, and TNF-α, which are known pro-inflammatory cytokines (87). These studies were later expanded to include combination therapy involving NanoCurc and Gemcitabine in a preclinical xenograft pancreatic cancer model, resulting in suppression of tumor growth via reduction of NF-κB activity as well as MMP-9 and Cylcin D1 expression (88).

Recently, magnetic nanoparticles have been used to encapsulate curcumin to prolong curcumin’s delivery to tumor tissues in a pancreatic cancer xenograft model. These curcumin-loaded magnetic particles were found to suppress pancreatic tumor growth, improving survival by downregulating pro-survival proteins such as BCL-XXL, MCL-1 and PCNA. Importantly, increased β-catenin and reduced collagen 1 expression were detected following treatment with magnetic nanoparticle-based curcumin, suggesting possible effects on metastatic activity in this model (89).

Another recent nano-formulation was developed by Wei et al., involving the ester-mediated conjugation of curcumin to cholesterol-hyaluronic acid (CHA) nanogel that targets curcumin to CD44 (a cell surface receptor for hyaluronic acid)-expressing cells. This formulation was tested in a MIA PaCa-2-based xenograft model, demonstrating significant reduction in tumor growth compared to free curcumin. In addition, CHA-nanogel curcumin also reduced mRNA expression of NF-κB and target genes TNF-α and COX-2 compared to control (90).

Although these nano-formulations of curcumin have shown strong promise for integration into therapeutic approaches to pancreatic cancer, they have yet to be tested in clinical trials. Of the nano-formulations developed to date, Theracurmin, a colloidal nano-formulation using α-linolenic acid derived from flaxseed trees, has shown the most progress and translatability. First described in 2011 by Sasaki et al., Theracurmin was found to significantly increase curcumin’s bioavailability in healthy human volunteers (91). In 2014, Kanai reported the results of a phase I clinical trial of Theracurmin in patients with pancreatic cancer in combination with Gemcitabine. This reported that curcumin did not cause any unexpected adverse effects aside from abdominal pain in a subset of patients with peritonitis carcinomatosa. Furthermore, quality of
Life scores were significantly improved following Theracurmin incorporation as part of the therapeutic strategy (92). Most recently, nano-scale extracellular vesicles have been shown to target intercellular transporters of bioactive molecules that can modulate cancer growth (93-98). In addition, studies have shown that exosomal transport between cancer cells can be used as a therapeutic advantage. Specifically, Aspe et al. have shown that exosomes isolated from melanoma cell lines overexpressing the pro-apoptotic Survivin-T34A mutant carry the mutant Survivin into the pancreatic adenocarcinoma cell line MIA PaCa-2, inducing apoptotic cell death (99). Furthermore, the exosomal uptake of Survivin-T34A mutant by pancreatic cancer cells enhanced their sensitivity to Gemcitabine (99). In the context of curcumin, our studies have shown that exosomes extend the anti-cancer properties of curcumin from treated to naïve pancreatic adenocarcinoma cells (100). Specifically, exosomes isolated from PANC-1 cells treated with curcumin were found to contain curcumin. Furthermore, these curcumin-containing exosomes reduced the viability of naïve PANC-1 cells (100). The exosomal ability to carry functional curcumin between cells represents an exciting new direction in curcumin research: the extension of curcumin’s effects to other cellular components of tumors via exosomal delivery. In summary, nano- and microvesicular formulations of curcumin may represent a gateway to translating the known anti-cancer properties of curcumin to patient care by overcoming key obstacles such as bio-distribution and compound stability.

Curcumin: Clinical utility against pancreatic cancer

Currently, there are several studies with the impetus to apply curcumin’s anti-cancer properties in pancreatic cancer patients. Phase I studies with curcumin and cancer patients have demonstrated low toxicity and high consumption tolerance, up to 12 grams per day, with minimal secondary effects (diarrhea and nausea) (14, 15, 17, 101, 102). Phase II clinical trials involving curcumin treatment in patients with advanced pancreatic cancer consisted of 25 patients, of which 21 could be evaluated. One patient presented 18 months of disease without progression, two other patients showed partial response and another patient exhibited one-year survival while improving curcumin bioavailability. Interestingly, curcumin’s anti-cancer effects have recently been demonstrated to extend beyond direct intracellular effects to other cancer cells through exosomes, suggesting that these nano-scale vesicular transporters may play a key role in curcumin’s effects in the tumor microenvironment. In clinical trials, curcumin alone and in combination with Gemcitabine have exhibited general tolerability with low toxicity in pancreatic cancer patients. However, the efficacy of curcumin in patients with pancreatic cancer requires further investigation due to curcumin’s poor bioavailability. Several attempts using Theracurmin have been performed to overcome this treatment obstacle, demonstrating promising results in pancreatic cancer patients. Nevertheless, the anti-cancer effects of Theracurmin with Gemcitabine or other chemotherapeutic agents still require attention. With significant advances in curcumin modulation at the cellular and preclinical levels, it is the hope of the authors that these findings will soon be translated to clinical practice.

<table>
<thead>
<tr>
<th>Table 2. Enhancement of curcumin delivery using nano-formulations of curcumin</th>
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<td><strong>Curcumin Nano-Formulations</strong></td>
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<tr>
<td>Nanoformulation</td>
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<tr>
<td>Rabdosioside-based</td>
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<td>Magnetic-based</td>
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<td>Cha-Nanogel</td>
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<td>Theracurmin</td>
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In this clinical trial the efficacy of curcumin and Gemcitabine treatment could be only analyzed in 11 patients because the individual and combinational treatment was toxic to five patients and another unfortunately succumbed to their disease (104). At the end of the study one patient exhibited partial response, four patients had no disease progression and six patients had disease progression (104). Based on the data, the study concluded that the time of disease progression was 1-12 months and the overall survival was 1-24 months (104). The authors discussed that in their study 8 g/day of curcumin is not well tolerated in combination with Gemcitabine; however, further studies are needed to validate this conclusion (104). In clinical trials, curcumin has been shown to have relatively low toxicity. However, its use is still challenged by poor bio-distribution in spite of administration at high doses (14-17). As described above, a recent study that evaluated the bioavailability of Theracurmin, a colloidal nano-formulation of curcumin (91), in human subjects concluded that curcumin plasma levels were higher in patients treated with Theracurmin compared with the patients treated with free curcumin (14). For this reason Theracurmin has been considered a promising treatment agent for cancer clinical trials. A phase I study involving treatment of fourteen pancreatic cancer patients with Theracurmin containing 200 and 400 mg of curcumin in combination with Gemcitabine demonstrated that the curcumin peak plasma levels ranged between 324 and 440 ng/mL, respectively (105). It is noteworthy to mention that the plasma curcumin levels using Theracurmin are higher than the curcumin peak plasma levels, approximately 85 ng/mL, reported after 8 grams consumption of free curcumin (16). This study showed that the efficacy of curcumin after Theracurmin delivery in pancreatic cancer patients induced no response in general, a median survival time of 4.4 months for 14 patients and more than 12 months survival in three patients (105).

Conclusion

This review summarizes a wide range of preclinical studies that have demonstrated that curcumin is a potent anti-cancer agent alone and in combination with standard chemotherapeutic agents. In addition, curcumin analogues and nano-formulations have shown promising effects against pancreatic cancer growth and survival while improving curcumin bioavailability. Interestingly, curcumin’s anti-cancer effects have recently been demonstrated to extend beyond direct intracellular effects to other cancer cells through exosomes, suggesting that these nano-scale vesicular transporters may play a key role in curcumin’s effects in the tumor microenvironment. In clinical trials, curcumin alone and in combination with Gemcitabine has exhibited general tolerability with low toxicity in pancreatic cancer patients. However, the efficacy of curcumin in patients with pancreatic cancer requires further investigation due to curcumin’s poor bioavailability.


20. Kanai M, Imaizumi A, Otsuka Y, Sasaki H, Hashiguchi M, Tsujiko K, et al. p53 upregulated modulator of apoptosis; DNMT, DNA methyltransferase; HIF-1α, hypoxia-inducible factor 1, alpha subunit; CDF, diuronifururrolin; EZH2, enhancer of zeste homolog 2; CD44, cluster of differentiation 44; EpCAM, epithelial cell adhesion molecule; EpGR, epidermal growth factor receptor; PTER, phosphatase and tensin homolog; PDK3, phosphoinositide-dependent kinase 3-isoform-2; mTOR, mammalian target of rapamycin; p27kip1, cyclin-dependent kinase inhibitor 1B; p53, cyclin-dependent kinase inhibitor 1C; PUMA, p53 upregulated modulator of apoptosis; DMPC, 1,2-dimyristoyl-sn-glycero-3-phosphocholine; DMPG, 1,2-dimyristoyl-sn-glycero-3-[phospho-(1-glycerol) sodium salt], IL-8, interleukin-8; IL-6, interleukin-6; TNF-α, tumor necrosis factor; BCL-XL, B-cell lymphoma-extra-large; MCL-1, myeloid leukemia cell differentiation protein 1; PCNA, proliferating cell nuclear antigen; CHA, cholesteroly-hyaluronic acid.


44. Jutooru I, Chadalapaka G, Lei P, Safe S. Inhibition of NFκB and STAT3 phosphorylation by curcumin or its analogue CDF. Cancer research. 2010;70(9):3606-17.


