

Turmeric And Pancreatic Cancer- A Review

James N Jacob*

Organomed Corporation, Grandview St., Coventry, RI, USA

Abstract

Pancreatic cancer belongs to the most malignant gastrointestinal cancers and the treatment options are limited. The two bioactive components of turmeric, curcumin and turmeric oil, are reported to have anticancer properties against pancreatic cancer as well as a number of other cancer cell lines. These turmeric products make use of a number of different signaling pathways in their mechanism of action. The low toxicity of these components and their ability to enhance the activity of other anti-cancer drugs make them good candidates for the development of new treatment options for pancreatic cancer. A brief review of the current state of these compounds in pancreatic cancer research is presented.

Keywords: turmeric, pancreatic cancer, curcumin, turmeric oil, paclitaxel, gemcitabine

*Corresponding author: James N. Jacob Organomed Corporation, 11 Grandview St., Unit 8, Coventry, RI 02816, USA Email: info@organomed.com

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Introduction

Pancreatic cancer (PC) is one of the most fatal of all cancers and is the fourth cancer-related death in the United States. It is estimated that 45,220 men and women (22,740 men and 22,480 women) will be diagnosed with cancer, and 38,460 men and women will die of cancer of the pancreas in the United States in 2013 [1]. In most cases the disease is diagnosed at a far advanced clinical stage. The vast majority of all pancreatic cancers are adenocarcinomas arising from cells of the pancreatic ducts [2]. Treatment options are limited and are often limited to palliative care and pain control. The causes of pancreatic cancer remain unknown [3] and 80 to 85% of patients present with advanced unresectable disease. Pancreatic cancer responds poorly to most chemotherapeutic agents [4].

Natural products have been used for treating various ailments from pre-historic times. In recent years this has been gaining popularity in alternative and complementary medicines. Current medical research is actively searching for natural drugs with minimum toxicity. The often quoted phrase by Hippocrates "Let food be your medicine" is meaningful in showing that our health depends on the food we eat. The ancient medical systems like Ayurveda give us much insight in to this truth. One major plant used for medicinal properties is turmeric (Figure 1a, 1b). Turmeric is known as the "golden spice" as well as "the spice of life" [5]. Its use dates back nearly 4000 years to the Vedic period and it has been used to treat abdominal pain, diarrhea, chest pains, colic and it is commonly administered internally as a stomachic, tonic and blood purifier and topically for prevention and treatment of skin diseases and for wound healing [5]. Many of the chronic and acute illnesses are associated with activation of genes involved in inflammation. The two active components in turmeric are the yellow solid, curcumin, and turmeric oil. The active compounds in turmeric have strong anti-inflammatory properties and they have been shown to have the potential for prevention and cure of cancer.

Curcumin

A number of articles and reviews are available on the anticancer properties of curcumin [6, 7]. Curcumin has a surprisingly wide range of beneficial properties, including anti-inflammatory, antioxidant, anti-proliferative and anti-angiogenic, chemopreventive

and chemotherapeutic activity [8]. Curcumin has been shown to be nontoxic and its anti-inflammatory activity is due to its ability to inhibit nuclear factor kappaB (NFkB), cyclooxygenase-2 (COX-2), lipoxygenase (LOX) and inducible nitric oxide synthase (iNOS) [7]. Pre-clinical studies in a variety of cancer cell lines including breast, cervical, colon, gastric, hepatic, leukemia, oral epithelial, ovarian, pancreatic, and prostate have shown that curcumin possesses anti-cancer activity in vitro and in pre-clinical animal models [9, 10]. Natural curcumin is a mixture of three compounds, curcumin, demethoxy curcumin and bisdemethoxycurcumin (Figure 2).

Various preclinical cell culture and animal studies suggest that curcumin has potential as an antiproliferative, anti-invasive, and antiangiogenic agent; as a mediator of chemoresistance and radioresistance; as a chemopreventive agent; and as a therapeutic agent in wound healing, diabetes, Alzheimer disease, Parkinson disease, cardiovascular disease, pulmonary disease, and arthritis [11].

Curcumin and Pancreatic Cancer

Curcumin exhibits great promise as a therapeutic agent, and is currently used in human clinical trials for a variety of conditions, including multiple myeloma, pancreatic cancer, myelodysplastic syndromes, colon cancer, psoriasis and Alzheimer's disease [8]. Treatment of pancreatic cancer cells with curcumin resulted in an induction of apoptosis. The results indicated that curcumin inhibits several key factors in cancer cellular pathways and may be of interest in pancreatic cancer [12]. The effect of curcumin on Survivin/baculoviral inhibitor of apoptosis repeat-containing 5 (BIRC5) and on the role of signal transducer and activator of transcription 3 (STAT3) activation in Survivin/BIRC5 was studied. The two pancreatic cancer cell lines were incubated with different amounts of curcumin. This resulted in a down regulation of proliferation in all cell lines tested. The expression of Survivin/BIRC5 on mRNA and protein level was significantly down regulated and the phosphorylation of STAT3 was blocked. The activities of curcumin derive from its complex chemistry as well as its ability to influence multiple signaling pathways, including survival pathways such as those regulated by NF-κB, Protein Kinase B (Akt), and growth factors; cytoprotective pathways dependent on nuclear factor erythroid 2-related factor 2 (Nrf2); and metastatic and angiogenic pathways. Curcumin is a free radical scavenger and hydrogen donor, and exhibits both pro- and antioxidant activity. It also binds metals, particularly iron and copper, and can function as an iron chelator [8]. Curcumin is remarkably non-toxic and exhibits limited bioavailability [8].

The multiple mechanisms of the antitumor effect of curcumin putatively include down-regulating the expression of gene products such as nuclear factor-kappaB, growth suppression, inducing apoptosis, and modulating various signal transduction pathways and the expression of



Figure 1: A) Turmeric root, B) Turmeric powder

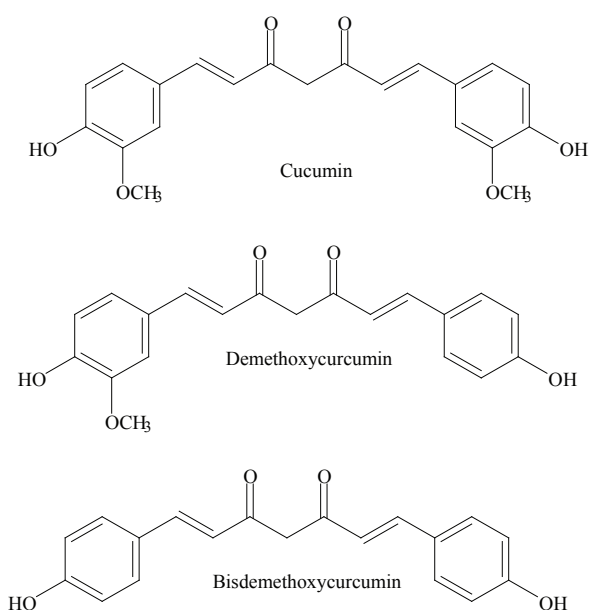


Figure 2: structures of curcumin, Demethoxycurcumin, Bisdemethoxycurcumin

many oncogenes. The mechanisms underlying the antitumor activity of curcumin have not, however, been completely delineated [13]. Curcumin alters miRNA expression in human pancreatic cells, up-regulating miRNA-22 and down-regulating miRNA-199a, suggesting that modulation of miRNA expression may be an important mechanism underlying the biological effects of curcumin [13]. It is reported that curcumin directly interacts with adipocytes, pancreatic cells, hepatic stellate cells, macrophages, and muscle cells and it suppresses the proinflammatory transcription factors [14]. These curcumin-induced alterations reverse insulin resistance, hyperglycemia, hyperlipidemia, and other symptoms linked to obesity [15]. Curcumin up-regulates caspase family proteins and down-regulates anti-apoptotic genes (Bcl-2 and Bcl-X(L)). In addition, cDNA microarrays analysis adds a new dimension for molecular responses of cancer cells to curcumin at the genomic level [15].

Curcumin In Combination With Other Supplements

Wang et al examined whether isoflavone together with curcumin could elicit a greater inhibition of growth of PC cells than either agent alone, and also sought to determine the molecular mechanism of action [16]. They found that the inhibition of cell growth and induction of apoptosis was significantly greater in the combination group than that could be achieved by either agent alone. It is found that diet containing multiple natural products should be preferable over single agents for the prevention and/or treatment of PC. According to the authors the superior effects of the combinatorial treatment could partly be attributed to the inhibition of constitutive activation of Notch-1 and NF-kappaB signaling pathways [16]. The transcription factor, WT1 is involved in cellular proliferation and is frequently expressed in pancreatic cancer. The expression of WT1 on messenger RNA and protein level was significantly down-regulated in a concentration dependent manner after treatment with curcumin on pancreatic cell line PANC-1. Combined treatment of curcumin and small inhibitory RNA (siRNA) resulted in significant inhibition of cell proliferation [17]. A synergistic effect was reported when mice were treated with curcumin and an omega-3 fatty acid, decosa-hexaenoic acid (DHA) [18]. In tumor xerograph fed curcumin combined with fish oil diet expression and activity of iNOS, COX-2, and 5-Lox are down-regulated, and p21 is upregulated [18].

Curcumin in Combination With Other Anti-Cancer Drugs

Gemcitabine is a first line cancer drug widely used for the treatment of pancreatic cancer. However, its therapeutic efficiency is significantly limited by resistance of pancreatic cancer cells to this and other chemotherapeutic drugs [19]. Ramachandran et. al. investigated the cytotoxic effect of a supercritical and hydroethanolic extract of turmeric, alone and in combination with gemcitabine in two pancreatic carcinoma cell lines (BxPC3 and Panc-1) [19]. The extract is highly cytotoxic to BxPC3 and Panc-1 cell lines with IC_{50} values of 1.0 and 1.22 microg/ml, respectively. Even though gemcitabine IC_{50} value for both of these cell line is 0.03 microg/ml; 30 to 48% of the pancreatic cancer cells are resistant to gemcitabine even at concentrations >100 microg/ml. In comparison, turmeric extract induced cell death in 96% of the cells at 50 microg/ml. The authors claim that combination of gemcitabine and turmeric extract was synergistic with IC_{90} levels achieved in both pancreatic cancer cell lines at lower concentrations [19]. It was reported that Bisdemethoxycurcumin (BDMC) from *C. longa*, acts as an inhibitor to inactivate human pancreatic α -amylase, a therapeutic target for oral hypoglycemic agents in type-2 diabetes [20]. Bioactivity guided isolation of rhizome isopropanol extract of BDMC as a lead small molecule inhibitor of isopropine and human pancreatic α -amylase with an IC_{50} value of 0.026 and 0.025 mM, respectively [20]. Epithelial-mesenchymal transition (EMT) induced by transforming growth factor- β 1 (TGF- β 1) is involved in the promotion of tumor invasion and metastasis, and is closely related to the drug resistance of tumor cells. In order to investigate whether curcumin can reverse the TGF- β 1-stimulated EMT of pancreatic cancer PANC-1 cells, and its possible mechanism, the pancreatic cancer cell line PANC-1 was stimulated with TGF- β 1 (5 ng/ml) for 7 days to induce formation of EMT, and the TGF- β 1-stimulated PANC-1 cells were treated with different concentrations of curcumin for 48 h [21]. Curcumin significantly inhibited the invasion and migration of TGF- β 1-stimulated PANC-1 cells and it inhibits the proliferation of TGF- β 1-stimulated PANC-1 cells [21]. The antiproliferative activity of curcumin and its modulatory effect on gene expression of pancreatic cancer cell lines were investigated and the results showed that curcumin induces growth arrest and apoptosis in

pancreatic cancer cell lines. Its effect was more obvious on the highly COX-2 expressing cell line and up-regulation of the extrinsic apoptotic pathway was among signaling pathways modulating the growth inhibitory effects of curcumin on pancreatic cancer cells [22].

Limitations In The Use Of Curcumin

Curcumin in multiple preclinical models, as well as in preliminary clinical trials, have indicated minimal toxicity even at relatively high doses [23]. However, the clinical advancement of this promising molecule has been hindered by its poor water solubility, short biological half-life, and low bioavailability after oral administration [23]. A variety of approaches are being pursued to overcome these limitations, which include synthesis of curcumin analogues, the use of adjuvants (e.g. piperine), and the development of improved delivery platforms for the parental compound, including liposomal, nanoparticulated and phospholipid complex formulations of curcumin [24]. Mach et al reported a study was designed to determine the minimum effective dose (MED) as well as the optimal dosing schedule of liposomal curcumin in a xenograft mouse model of human pancreatic cancer [24]. The MED determination and optimal schedule was evaluated in female ethylic nude mice injected subcutaneously with MiaPaCa-2 cells. The 20 mg/kg dose had the greatest decrease in tumor growth at 52% decrease in tumor growth when compared to no treatment control mice [24]. MED was determined to be 20 mg/kg and was used for the optimal dosing schedule determination and no toxicity was observed at any dose. The MED for liposomal curcumin is 20 mg/kg for optimal tumor growth inhibition and this dose was recommended for additional preclinical studies to define safety and tolerability of liposomal curcumin in rat and dog models [24].

Nanocurcumin And Synthetic Analogs Of Curcumin

Nanoparticle-based drug delivery approaches have the potential for rendering hydrophobic agents like curcumin dispersible in aqueous media, thus circumventing the pitfalls of poor solubility. Polymeric nanoparticle encapsulated formulation of curcumin (nanocurcumin) was synthesized utilizing the micellar aggregates of cross-linked and random copolymers of N-isopropylacrylamide (NIPAAm), with N-vinyl-2-pyrrolidone (VP) and poly(ethyleneglycol)- monoacrylate (PEG-A) [25]. Nanocurcumin's mechanisms of action on pancreatic cancer cells is similar to that of free curcumin, including induction of cellular apoptosis, blockade of NF κ B activation, and downregulation of steady state levels of multiple pro-inflammatory cytokines (IL-6, IL-8, and TNF α) [25]. In xenograft models of human pancreatic cancer established in athymic mice, administration of parenteral nanocurcumin significantly inhibited primary tumor growth in both subcutaneous and orthotopic settings. It was reported that the combination of parenteral nanocurcumin with gemcitabine resulted in enhanced tumor growth inhibition versus either single agent, suggesting an additive therapeutic influence in vivo. This combination completely abrogates systemic metastases in orthotopic pancreatic cancer xenograft models and tumor growth inhibition is accompanied by significant reduction in activation of NF κ B [26]. Curcumin-loaded magnetic nanoparticle (MNP-CUR) formulation was evaluated for the in vitro and in vivo therapeutic efficacy in pancreatic cancer and human pancreatic cancer cells (HPAF-II and Panc-1) exhibited efficient internalization of the MNP-CUR formulation in a dose-dependent manner [27].

A lipophilic derivative of curcumin, diacetyl curcumin (DAC) and a hydrophilic derivative, diglutaryl curcumin (DGC) were synthesized and their in vivo analgesic and anti-inflammatory activities were

compared with those of curcumin and aspirin. The in vitro anti-cancer activities of curcumin and the two derivatives against three cell cancer lines, breast, pancreas and prostate, were compared with those against a non-cancerous cell line. The inhibitory effects were comparable to each other and nearing that of curcumin while they showed low inhibitory effect towards the non-cancerous cell line. The mouse tail flick assay showed that curcumin, DAC and DGC increased latency time and DGC was most effective as an analgesic, even more so than aspirin. The maximum percentage effect (MPE) was highest with DGC at 3 hours. The carrageenan induced paw edema model indicated anti-inflammatory activity of all three curcumin formulations. The percentage inhibition of paw edema was maximum for DAC, followed by aspirin and curcumin [28]. Two structural analogues of curcumin were tested in human pancreatic cancer cell lines. The authors compared the impact of curcumin with the analogs on cell viability in five different pancreatic cancer cell lines [29]. Although all three compounds were capable of lowering viability in all cell lines tested, the analogs (IC₅₀ values between 0.28-3.2 and 0.91-3.43 micromol/l, respectively) were substantially more potent than curcumin (IC₅₀ values between 8.67 and 20.35 micromol/l) [29]. In addition, the analogs inhibited phosphorylation of signal transducer and activator of transcription 3 and AKT, two cell signaling pathways frequently found persistently active in many forms of cancer. The analogs were found to be more effective than curcumin in inducing apoptosis as evidenced by increased cleavage of poly adenosine diphosphate ribose polymerase (PARP) and caspase-3 in pancreatic cancer cell lines. These results indicated that these curcumin analogues, are more effective than curcumin in inhibiting cell viability and inducing apoptosis, and may have translational potential as chemopreventive or therapeutic agents for pancreatic cancer [30].

Curcumin acetates and amino acid conjugates of curcumin were studied in terms of their proteasome inhibitory and antiproliferative effects against several human cancer cell lines. It was found that the water soluble amino acid conjugates of curcumin showed a potent antiproliferative effect and are potent proteasome inhibitors [31]. Docking studies of the curcumin amino acid conjugates for proteasome inhibition were carried out to explain their biological activities. It is suggested that they may serve as the water soluble analogs of curcumin [31]. The histone methyltransferase EZH2 expression is increased in various human cancers, including highly aggressive pancreatic cancers, but the mechanisms underlying for its biologic effects are not yet well understood. EZH2 function in pancreatic cancer using difluorinated-curcumin (CDF), a novel analogue of curcumin that has antioxidant properties was studied [32]. CDF decreased pancreatic cancer cell survival, clonogenicity, formation of pancreatospheres, invasive cell migration, and cancer stem cells (CSC) function in human pancreatic cancer cells. It was concluded that CDF inhibited pancreatic cancer tumor growth and aggressiveness by targeting an EZH2-miRNA regulatory circuit for epigenetically controlled gene expression [32]. CDF- β -cyclodextrin inclusion complex (1:2) (CDFCD) was synthesized and its activity was tested against multiple cancer cell lines, and in vivo bioavailability was checked [33]. CDF- β -cyclodextrin was found to lower IC₅₀ value by half when tested against multiple cancer cell lines. It preferentially accumulated in the pancreas, where levels of CDF- β -cyclodextrin in mice were 10 times higher than in serum, following intravenous administration of an aqueous CDF- β -cyclodextrin preparation leading to its potent anticancer activity against pancreatic cancer cells [33].

Turmeric Oil

The oil from turmeric (*Curcuma longa*) contains several

sesquiterpenes with medicinal properties. The oil fractions were purified by repeated high vacuum distillations to constant boiling points and by column chromatography. The major components in the oil fractions were identified as α , β and ar-turmerones. The purified turmeric oil (TO) fractions had growth inhibitory activity against breast (SKBR-3), pancreatic (PANC-1), and prostate (PC-3) cancers and reduced activity against a non-cancerous cell line, WI-38 (19). A combination of the distillation fraction of turmeric oil and paclitaxel showed substantial increase in growth inhibitory activity against the three cancer cells compared to paclitaxel alone while reduced activity against the non-cancerous cell line. Percent inhibition may be related to the structural parameters of the turmerones. The results suggest that components in turmeric oil fractions have anti-cancer activity against breast, pancreatic and prostate cancer and strong positive effect on the activity of paclitaxel [10].

1. ar-curcumen, 2. 7-epizingiberene, 3. β -sesquiphellandrene, 4. Curlone, 5. α -turmerone 6. β -turmerone, 7. ar-turmerone

Fractional distillation and chromatographic separation of turmeric oil (TO) gave column fractions (CF) having biological activity against the PANC-1 pancreatic cancer cell line with EC_{50} in the range of 23 to 33 μ g/mL. These fractions were analyzed by NMR and GCMS and found to contain the sesquiterpenes, ar-curcumen, 7-epi-zingiberene, β -sesqui-phellandrene, curlone, α -turmerone, β -turmerone and ar-turmerone (Figure 3). The ability of TO components to induce cell death was independent of caspase activity. Potency was higher at lower cell density and was reduced by increasing serum concentration, the latter indicating serum binding of active components [34].

Clinical studies

In a review Gwill et. al. gave the clinical evidence for curcumin as a chemopreventive and therapeutic agent and the in vitro background results [35]. Anti-cancer effects have been seen in a few clinical trials, mainly as a native chemoprevention agent in colon and pancreatic cancer, cervical neoplasia and Barrets metaplasia. Some clinical studies with healthy volunteers revealed a low bioavailability of curcumin, casting doubt on the use of curcumin only as food additive [35]. The clinical experience with curcumin, along with the anti-metabolite gemcitabine in the treatment of patients with advanced pancreatic carcinoma, produced an objective response in less than 10% of patients, with a minor effect on survival [35]. Curcumin's potent anti-proliferative activity interacting with several intracellular signal transduction pathways may potentiate the anti-tumor effect of gemcitabine. The preclinical data lead to various, but still few, clinical studies that demonstrated the possible efficacy of this treatment as a chemopreventive or chemotherapeutic agent [35]. According to a study repetitive systemic exposure to high concentrations of curcumin achieved by a micro particle product obtained mixing curcumin with emulsifiers did not increase the incidence of adverse events in cancer patients receiving gemcitabine-based chemotherapy [36]. A study was undertaken to evaluate the activity and feasibility of gemcitabine in combination with curcumin in patients with advanced pancreatic cancer. One of 11 evaluable patients (9%) had partial response, 4 (36%) had stable disease, and 6 (55%) had tumor progression, time to tumor progression was 1-12 months (median 2½), and overall survival was 1-24 months (median 5) [37]. A combination therapy using 8 g oral curcumin daily with gemcitabine-based chemotherapy was found to be safe and feasible in patients with pancreatic cancer [38]. It was reported that a combination of gemcitabine and curcumin with oral doses less than 8 g/day for patients with advanced pancreatic cancer is feasible [39].

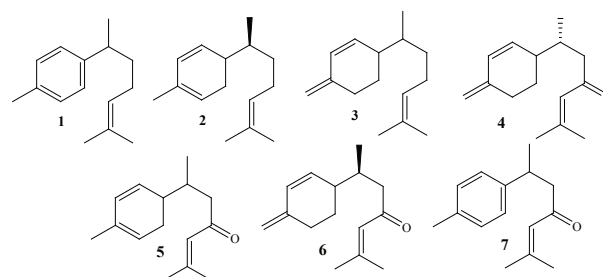


Figure 3: 1. ar-curcumen, 2. 7-epizingiberene, 3. β -sesquiphellandrene, 4. Curlone, 5. α -turmerone, 6. β -turmerone, 7. ar-turmerone

Conclusion

The remarkable anti-cancer properties of turmeric and its components are extremely promising because of the lack of toxicity and the multiple mechanisms and several cell signaling pathways. The low bioavailability of curcumin reduces its effectiveness but the research on new curcumin analogs and turmeric oil look promising. Additional research and clinical trials are needed to develop it as a drug, and as combination therapy with existing anti-cancer drugs for pancreatic cancer treatment.

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