

Review

Curcumin AntiCancer Studies in Pancreatic Cancer

Sabrina Bimonte ^{1,*}, Antonio Barbieri ^{2,*}, Maddalena Leongito ¹, Mauro Piccirillo ¹, Aldo Giudice ³, Claudia Pivonello ⁴, Cristina de Angelis ⁵, Vincenza Granata ⁶, Raffaele Palaia ¹ and Francesco Izzo ¹

¹ Division of Abdominal Surgical Oncology, Hepatobiliary Unit, Istituto Nazionale per lo studio e la cura dei Tumori “Fondazione G. Pascale”—IRCCS—Via Mariano Semmola, Naples 80131, Italy; maddalena.leongito@virgilio.it (M.L.); mauropiccirillo73@libero.it (M.P.); r.palaia@istitutotumori.na.it (R.P.); f.izzo@istitutotumori.na.it (F.I.)

² S.S.D Sperimentazione Animale, Istituto Nazionale per lo studio e la cura dei Tumori “Fondazione G. Pascale”—IRCCS, Naples 80131, Italy

³ Epidemiology Unit, Istituto Nazionale per lo studio e la cura dei Tumori “Fondazione G. Pascale”—IRCCS—Via Mariano Semmola, Naples 80131, Italy; aldo.giudice@libero.it

⁴ Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, Università di Napoli Federico II, Naples 80131, Italy; cpivonello@gmail.com

⁵ I.O.S. & Coleman Srl, Naples 80011, Italy; cristinadeangelis83@hotmail.it

⁶ Division of Radiology, Istituto Nazionale per lo studio e la cura dei Tumori “Fondazione G. Pascale”—IRCCS—Via Mariano Semmola, Naples 80131, Italy; cinzia.granata80@libero.it

* Correspondence: s.bimonte@istitutotumori.na.it (S.B.); a.barbieri@istitutotumori.na.it (A.B.); Tel.: +39-081-5903-221 (S.B.)

† These authors contributed equally to this work.

Received: 23 May 2016; Accepted: 13 July 2016; Published: 16 July 2016

Abstract: Pancreatic cancer (PC) is one of the deadliest cancers worldwide. Surgical resection remains the only curative therapeutic treatment for this disease, although only the minority of patients can be resected due to late diagnosis. Systemic gemcitabine-based chemotherapy plus nab-paclitaxel are used as the gold-standard therapy for patients with advanced PC; although this treatment is associated with a better overall survival compared to the old treatment, many side effects and poor results are still present. Therefore, new alternative therapies have been considered for treatment of advanced PC. Several preclinical studies have demonstrated that curcumin, a naturally occurring polyphenolic compound, has anticancer effects against different types of cancer, including PC, by modulating many molecular targets. Regarding PC, *in vitro* studies have shown potent cytotoxic effects of curcumin on different PC cell lines including MiaPaCa-2, Panc-1, AsPC-1, and BxPC-3. In addition, *in vivo* studies on PC models have shown that the anti-proliferative effects of curcumin are caused by the inhibition of oxidative stress and angiogenesis and are due to the induction of apoptosis. On the basis of these results, several researchers tested the anticancer effects of curcumin in clinical trials, trying to overcome the poor bioavailability of this agent by developing new bioavailable forms of curcumin. In this article, we review the results of pre-clinical and clinical studies on the effects of curcumin in the treatment of PC.

Keywords: curcumin; natural compound; pancreatic cancer; therapy

1. Introduction

Pancreatic cancer is one of the deadliest cancer worldwide [1]. Surgical resection remains the only curative therapeutic treatment for this disease, although only the minority of patients can be resected due to late diagnosis [2]. Systemic gemcitabine-based chemotherapy has been used as the standard therapy for patients with advanced PC, although this treatment is associated with many side effects and poor overall survival [3,4]. In order to improve the overall survival of patients with PC,

many studies combined the use of gemcitabine with different agents, although the results were not encouraging [5–11]. For these reasons, new alternative therapies involving natural compounds with minimal toxicity, such as curcumin, have been considered for treatment of PC. Curcumin, a naturally occurring polyphenolic compound, derives from turmeric (*Curcuma longa*). It has been commonly used as a food additive or dietary pigment and in traditional medicine [12–16]. Preclinical in vitro and in vivo studies have demonstrated that curcumin has several pharmacologic effects, including antioxidant, anti-inflammatory, and anticancer activities, in different types of cancer, including PC, by modulating multiple signaling pathways [15,17–44]. Taken together, these results suggest that curcumin can be considered a new therapeutic drug in PC treatment [45]. In addition it has many advantages for patients, such as safety and minimal toxicity. Several researchers tested the anticancer effects of curcumin in clinical trials, trying to overcome the poor bioavailability of this agent by developing new bioavailable forms of curcumin [15,46–57]. In this article, we review the results of pre-clinical and clinical studies on the effects of curcumin in the treatment of pancreatic cancer.

2. Effects of Curcumin in Treatment of PC

(a) *In Vitro Studies: Dissecting the Molecular Mechanism Underlying the Antitumor Effects of Curcumin in PC Cell Growth*

Several preclinical studies showed that curcumin has antitumor effects by modulating multiple cell-signaling pathways in different types of cancers, including colorectal [28,33,58], pancreatic [17,18,22,27–31,34,35,42,43,59–67], breast [26], lung [32], hepatic [20], ovarian [25], head and neck [68], and prostate [24].

Regarding PC, in vitro studies on the effects of curcumin have been performed on different PC cells lines including MiaPaCa-2, MPanc-96, BxPC-3, Panc-1, AsPC-1, and L3.6pL. Results from these studies showed that the anti-proliferative effects of curcumin are mainly due to the inhibition of oxidative stress and angiogenesis and the induction of apoptosis [17,18,22,29,34,42,43,59,60,65,69–73]. The first report on the antitumor effect of curcumin in PC was described by Li et al. [17]. The authors demonstrated that curcumin down-regulated Nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and growth control molecules induced by NF- κ B in human pancreatic cells in a time- and dose-dependent manner. These effects were accompanied by marked growth inhibition and apoptosis. Similar results were obtained by Wang et al. [22]. Then authors demonstrated that the Notch-1 signaling pathway was associated with NF- κ B activity during curcumin-induced cell growth inhibition and apoptosis of pancreatic cells, suggesting that the down-regulation of Notch signaling by curcumin could represent a novel strategy for the treatment of patients with PC. In another study, it was demonstrated that curcumin treatment inhibited the proliferation of BxPC-3 human pancreatic cancer cells by DNA damage-mediated G2/M cell cycle arrest, by inhibition of cyclin B1/Cyclin-dependent kinase 1 (Cdk1) expression and by the activation of ataxia tel-angiectasia mutated (ATM)/Checkpoint kinase 1(Chk1)/Cell Division Cycle 25C (Cdc25C) [29]. Jutooru et al. showed that curcumin inhibited NF- κ B expression and Panc-1 and L3.6pL cancer cell growth by down-regulation of the specificity protein Sp1 [59]. We also demonstrated that curcumin inhibited the proliferation and enhanced the apoptosis of MIA PaCa-2 cells, through the suppression of NF- κ B-activation [18]. Recent findings showed that curcumin induced apoptosis in PC cells through the induction of forkhead box O1 (FOXO1) and the inhibition of the phosphatidylinositol 3-kinase/phosphatidylinositol 3-kinase (PI3K/Akt) pathway [43]. The antitumor role of curcumin in PC was also demonstrated by Diaz et al. in Panc-1 cells. The authors showed that curcumin induced pancreatic adenocarcinoma cell death via the reduction of the inhibitors of apoptosis (IAP) [42]. Finally, very recently, it was demonstrated that a small-molecule tolfenamic acid and dietary spice curcumin treatment enhanced the anti-proliferative effect in PC cells L3.6pL and MIA PaCa-2 through Sp1 suppression, NF- κ B disruption of translocation to the nucleus and cell cycle phase distribution [34].

These results suggest that curcumin exerts its antitumor effect on PC by acting on different molecular mechanisms. Specifically, other studies showed that treatment of PC cells with curcumin

has been associated with reduced migration and invasiveness of tumor cells, inhibition of cancer stem cell function, reversal of the epithelial-mesenchymal transition (EMT), and suppression of miR-221, Cyclooxygenase 2 (COX-2) and their effectors and pro-inflammatory cytokines [69,70]. In addition, it has been demonstrated that curcumin can also block signal transducer and activator of transcription 1 (STAT1) and signal transducer and activator of transcription 3 (STAT3) phosphorylation, and epidermal growth factor receptor (EGFR) and (neurogenic locus notch homolog protein-1) Notch-1 signaling pathways, which play important roles in pancreatic tumor growth [74]. It has been also demonstrated that siRNA/shRNA, small-molecule kinase inhibitors, and curcumin targeting these tumor stem cell markers and tumor suppressor miRNAs could be the perfect therapeutic agents for the treatment of PC [31,67,69,75–77] (Figure 1).

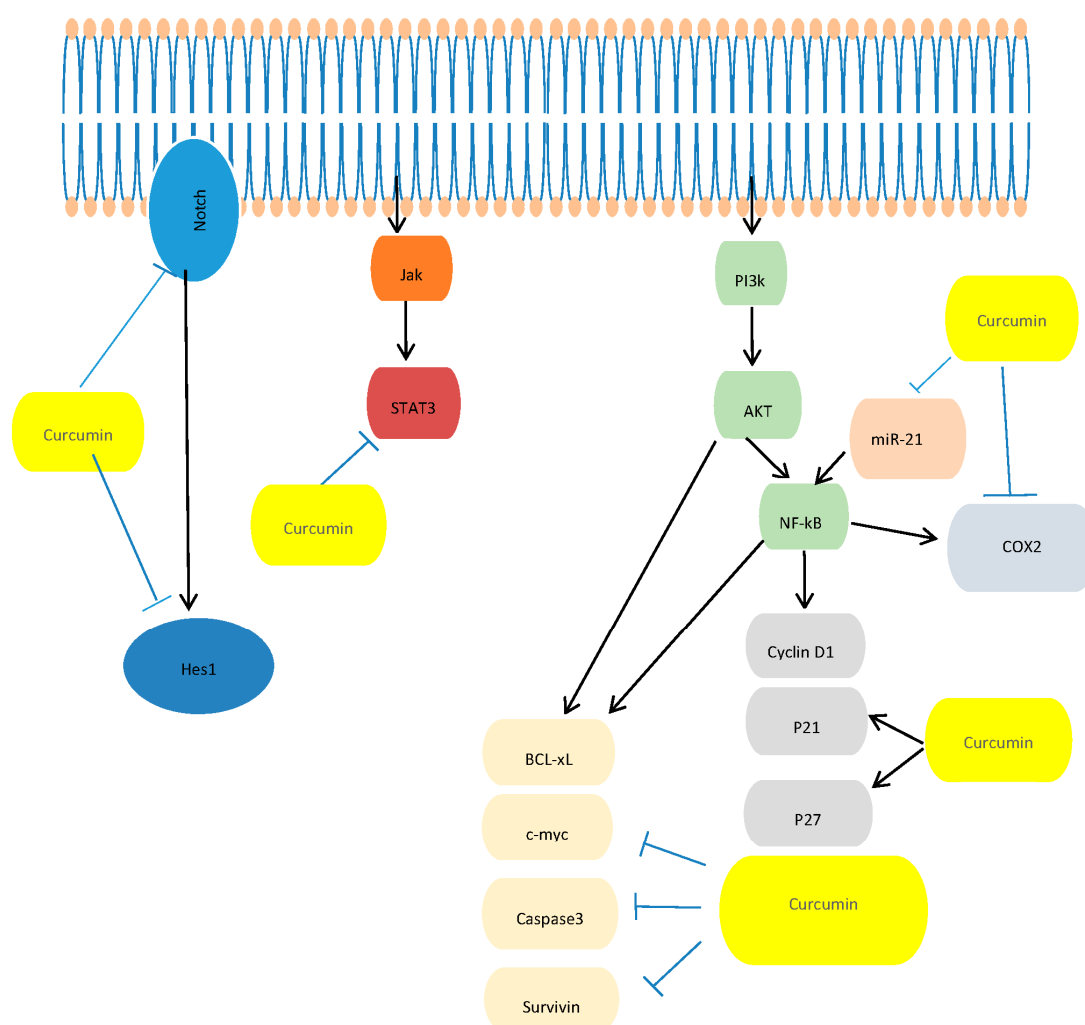


Figure 1. A schematization of molecular targets in PC regulated by curcumin. NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; COX2: Cyclooxygenase 2; Hes-1: Cyclin-dependent kinase 1; Akt: Protein kinase B; Stat3: Signal transducer and activator of transcription 3; PI3K: phosphatidylinositol 3-kinase; Notch-1: Neurogenic locus notch homolog protein-1; c-myc: C-mycproto-oncogene; Jak: Janus kinase. P21: Cyclin-dependent kinase inhibitor; P27: Cyclin-dependent kinase inhibitor; BCL-xL: B-cell lymphoma-extra large.

In order to ameliorate the aqueous solubility of curcumin, different derivatives of this compound or delivery system have been developed [78,79]. One curcumin analogue used in in vitro experiments is the 3,4-difluorobenzylidene curcumin (CDF). This compound has a higher tendency to accumulate in the pancreas than normal curcumin [74,80]. Although it has been demonstrated that CDF

has cytotoxic effects on both resistant and nonresistant pancreatic tumor cell lines with respect to curcumin, this curcumin derivative still presents low aqueous solubility. To bypass this problem, researchers developed a new delivery system based on nanoparticles, such as hyaluronic acid (HA)-conjugated polyamidoamine dendrimers and hyaluronic acid (HA) and styrene-maleic acid-engineered nanomicelles of CDF. Results from studies performed with these systems gained improvements of aqueous solubility, stability, release profile and antitumor effects on PC cells lines with respect to unformulated CDF [56,63,81]. Table 1 summarizes the most relevant in vitro studies on the antitumor effect of curcumin in PC cells.

Table 1. A summary of in vitro studies on the role of curcumin in Pancreatic Cancer cell growth.

Cell Lines	Dose of Curcumin (μM)	Molecular Targets	Reference
MiaPaCa-2; BxPC-3; Panc-1; MPanc-96	≥ 25	NF- κ B \downarrow ; VEGF \downarrow	[71]
MiaPaCa-2	50	NF- κ B \downarrow	[18]
BxPC-3	2.5	Cdk1 \downarrow ; cyclin B1 \downarrow	[29]
Panc-28; L3.6p	≥ 25	NF- κ B \downarrow , Sp-1, Sp-3, Sp4 \downarrow	[59]
Miapaca-E; Miapaca-M; BxPC-3	≥ 4	miR-220 \uparrow ; miR-21 \downarrow	[31]
Panc-1	≥ 25	IAP \downarrow	[42]
L3.6pl; MIA PaCa-2	5–25	NF- κ B \downarrow , Sp-1, Sp-3, Sp4 \downarrow	[34]
PANC-1	10–30	Shh \downarrow , GLI1 \downarrow , E-cadherin \downarrow , vimentin \downarrow	[70]

NF- κ B: Nuclear factor kappa-light-chain-enhancer of activated B cells; VEGF: Vascular endothelial growth factor; Cdk1: Cyclin-dependent kinase 1; Sp-1: Specificity protein 1; Sp-3: Specificity protein 3; Sp4: Specificity protein 4; IAP: inhibitors of apoptosis; Shh: Sonic hedgehog, GLI1: Glioma-associated oncogene homologue 1; E-cadherin: Epithelial cadherin.

(b) *In Vivo Studies: Effects of Curcumin in Mouse Model of PC*

The antitumor effect of curcumin and its analogues on PC has been demonstrated in in vivo experiments on mouse models of PC [18,27,59,71,74,82–88]. The first in vivo study was reported by Kunnumakara et al. [71]. The authors demonstrated that curcumin (1 g/kg orally) potentiated the antitumor activity of gemcitabine (25 mg/kg via intraperitoneal injection) in an orthotopic mouse model of PC [15] through the suppression of proliferation, angiogenesis, and inhibition of NF- κ B-regulated gene products. Our research group also reported similar results. In fact, we demonstrated with the generation of an orthotopic mouse model of PC that tumors from mice injected with MIA PaCa-2 cells and placed on a diet containing curcumin at 0.6% for six weeks were smaller than those observed in controls. We also showed a down-regulation of the NF- κ B-regulated gene products, suggesting that curcumin had great potential in the treatment of human PC, through the modulation of the NF- κ B pathway [18]. Mach et al., in a xenograft human PC model, established the minimum effective dose (MED, 20 mg/kg) and optimal dosing schedule for liposomal curcumin [88]. In another study, the in vivo antitumorigenic activity of curcumin was investigated in athymic nude bearing L36pL cells as xenografts. The authors demonstrated that curcumin (dose of 100 mg/kg/days) inhibited tumor growth and tumor weight by down-regulation of the Sp transcription factor [59]. In order to potentiate the effects of curcumin on PC in vivo, several studies were performed using different forms of curcumin. Bao et al. demonstrated that CDF (2.5 mg/mouse/days; 5 mg/mouse/days; intragastric once daily for three weeks), an analogue of curcumin analogue, inhibited pancreatic tumor growth by switching on suppressor microRNAs and attenuating the expression of histone methyltransferase enhancer of zeste homolog 2, EZH2 [74]. Similar effects were reported for synthetic curcumin analogues EF31 and UBS109. The authors demonstrated, both in vitro and in vivo, that these analogues were potent DNA hypomethylating agents in PC [86]. The efficacy of liposomal curcumin in human PC was also reported by Ranjan et al. The authors showed that in xenograft tumors in nude mice, liposomal curcumin (20 mg/kg i.p. three times a week for four weeks) induced a suppression of tumor growth compared to untreated controls, indicating that this agent could be beneficial in patients with PC [85]. Similar results have been reported by recent studies in which the efficacy of curcuminoids and nanomicelles in treatment of PC

was demonstrated [81,82]. It is important to underline that in all studies performed with curcumin derivatives and or a delivery system, the antitumor effects have been reported to be greater with respect to those observed with conventional curcumin. On the basis of these results, researchers tested the anticancer effects of curcumin in clinical trials, trying to overcome the poor bioavailability of this agent by developing new bioavailable forms of curcumin. Table 2 summarizes preclinical in vivo studies on the anticancer effects of curcumin against PC.

Table 2. Preclinical in vivo studies on the anticancer effects of curcumin against PC.

Animal Models	Drug	Dose of Curcumin	Effects	Reference
Orthotopic mouse model (MIA PaCa-2 cells)	Curcumin + Gemcitabine	1 g/kg (orally)	Suppression of proliferation, angiogenesis, and inhibition of NF- κ B in tumors	[71]
Orthotopic mouse model (MIA PaCa-2 cells)	Curcumin	0.6% for 6 weeks (dietary food)	Tumor growth inhibition and down regulation of the NF- κ B-regulated gene products	[18]
Xenograft mouse model (L36pL cells)	Curcumin	100 mg/kg/days	Tumor growth and Tumor weight inhibition	[59]
Orthotopic mouse model (MIA PaCa-2 cells)	CDF	2.5 mg/mouse/days; 5 mg/mouse/days; intragastric once daily for 3 weeks	Tumor growth inhibition, reduced expression of EZH2	[74]
Xenograft mouse model (MIA PaCa-2 cells)	Liposomal curcumin	20 mg/kg i.p. three-times a week for four weeks	Tumor growth inhibition	[85]

(c) Clinical Trials

In order to translate the preclinical antitumor effects of curcumin into clinical practice, few clinical trials have been performed so far. Healthy volunteers and cancer patients were treated with curcumin, administered orally, in different clinical trials (phase I and pharmacokinetic studies). No dose-limiting toxicity (DLT) of up to at least 12 g/day was observed in patients, although nausea and diarrhea have been reported [48,89,90]. It was established that the daily oral dose of curcumin of 8 g or less is the most commonly used in clinical trials, due to its poor bioavailability.

Several phase II clinical trials on the antitumor effects of curcumin in PC were conducted [91–93]. Dhillon et al. conducted the first trial [91] and successfully tested the safety and the efficacy of curcumin used as a monotherapy in 25 patients of PC. Another group conducted a phase I/II clinical trial of curcumin in 21 patients with PC (resistant to gemcitabine-based chemotherapy), combining gemcitabine-based chemotherapy with curcumin treatment (8 g daily oral dose) [92]. Results from this study indicated that combination therapy using 8 g oral curcumin daily with gemcitabine-based chemotherapy was safe and feasible in patients with PC. Another interesting study tested the efficacy and feasibility of curcumin (8 g daily oral dose) in combination with gemcitabine monotherapy (standard dose and schedule) in 17 chemo-naive patients with PC. Differently from previous studies, increased gastrointestinal toxicity was observed in seven patients treated with this therapy, probably due to the elevated dose of curcumin combined with gemcitabine. For this reason, the dose of curcumin was reduced from 8 to 4 g [93]. From this study emerged the problem of the poor bioavailability of curcumin, which strongly limited its application in clinical practice. To solve this problem, new curcumin analogs and new drug delivery systems have been developed [46–55]. Interesting results have been reported by dose escalation and pharmacokinetic studies performed with Theracurcumin, a nanoparticle-based curcumin [55]. These studies demonstrated that the plasma curcumin levels observed after Theracurcumin ingestion were higher with respect to those obtained with conventional curcumin. The phase I clinical trial involving Theracurcumin (level 1 group: 200 mg oral/daily; level 2 group: 400 mg oral/daily) was conducted on 16 patients with PC resistant to gemcitabine-based chemotherapy [94]. The results from this study showed that repetitive systemic exposure to high concentrations of Theracurcumin did not increase the incidence of side effects in cancer patients receiving gemcitabine-based chemotherapy, indicating that this agent could represent a new agent for PC treatments.

New clinical trials are needed to test the therapeutic effects of curcumin and its analogues in patients with PC.

3. Conclusions

Several preclinical studies have demonstrated that curcumin, a naturally occurring polyphenolic compound, has anticancer effects against different types of cancer, including PC, by modulating many molecular targets. On the basis of these results, several researchers tested the anticancer effects of curcumin in clinical trials, trying to overcome the poor bioavailability of this agent, which limited its clinical application. New bioavailable forms of curcumin have been developed and the results from clinical trials on patients with PC suggest that these agents could represent promising new treatments for PC, although more clinical studies will be still needed.

Acknowledgments: I.O.S. and Coleman Srl covered the costs for publication of this paper in OPEN access.

Author Contributions: The present review was mainly written by S.B., A.B. and F.I. and revised and edited by the rest of the authors. M.L., M.P.; A.G., C.D.A., C.V., V.G., R.P. prepared the tables and figure. S.B. and F.I. revised and confirmed the final version of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

PC	Pancreatic cancer
NF- κ B	Nuclear factor kappa-light-chain-enhancer of activated B cells
Cdk1	Cyclin-dependent kinase 1
ATM	Ataxia tel-angiectasia
Chk1	Checkpoint kinase 1
Cdc25C	Cell division cycle 25C
FOXO1	Forkhead box O1
PI3K	Phosphatidylinositol 3-kinase
Akt	Phosphatidylinositol 3-kinase
Sp1	Specificity protein
IAP	Inhibitors of apoptosis
EMT	epithelial-mesenchymal transition
STAT1	Activator of transcription 1
STAT3	Signal transducer and activator of transcription 3
EGFR	Epidermal growth factor receptor
Notch-1	Neurogenic locus notch homolog protein-1
COX2	Cyclooxygenase 2
Hes-1	Cyclin-dependent kinase 1
Akt	Protein kinase B
Stat3	Signal transducer and activator of transcription 3
PI3K	phosphatidylinositol 3-kinase
Notch-1	Neurogenic locus notch homolog protein-1
c-myc	C-mycproto-oncogene
Jak	Janus kinase
P21	Cyclin-dependent kinase inhibitor
P27	Cyclin-dependent kinase inhibitor
BCL-xL	B-cell lymphoma-extra large
CDF	3, 4-difluorobenzylidene curcumin
HA	hyaluronic acid
Sp-3	Specificity protein 3
Sp4	Specificity protein 4
Shh	Sonic hedgehog
GLI1	Glioma-associated oncogene homologue 1
E-cadherin	Epithelial cadherin
EZH2	enhancer of zeste homologue 2
MED	minimum effective dose
DLT	dose-limiting toxicity

References

1. Siegel, R.; Naishadham, D.; Jemal, A. Cancer statistics, 2013. *CA Cancer J. Clin.* **2013**, *63*, 11–30. [[CrossRef](#)] [[PubMed](#)]
2. Stathis, A.; Moore, M.J. Advanced pancreatic carcinoma: Current treatment and future challenges. *Nat. Rev. Clin. Oncol.* **2010**, *7*, 163–172. [[CrossRef](#)] [[PubMed](#)]
3. Burris, H.A., 3rd; Moore, M.J.; Andersen, J.; Green, M.R.; Rothenberg, M.L.; Modiano, M.R.; Cripps, M.C.; Portenoy, R.K.; Storniolo, A.M.; Tarassoff, P.; et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. *J. Clin. Oncol.* **1997**, *15*, 2403–2413. [[PubMed](#)]
4. Berlin, J.D.; Catalano, P.; Thomas, J.P.; Kugler, J.W.; Haller, D.G.; Benson, A.B., 3rd. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern cooperative oncology group trial e2297. *J. Clin. Oncol.* **2002**, *20*, 3270–3275. [[CrossRef](#)] [[PubMed](#)]
5. Lima, C.M.R.; Green, M.R.; Rotche, R.; Miller, W.H., Jr.; Jeffrey, G.M.; Cisar, L.A.; Morganti, A.; Orlando, N.; Gruia, G.; Miller, L.L. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J. Clin. Oncol.* **2004**, *22*, 3776–3783. [[CrossRef](#)] [[PubMed](#)]
6. Louvet, C.; Labianca, R.; Hammel, P.; Lledo, G.; Zampino, M.G.; Andre, T.; Zaniboni, A.; Ducreux, M.; Aitini, E.; Taieb, J.; et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: Results of a gercor and giscad phase III trial. *J. Clin. Oncol.* **2005**, *23*, 3509–3516. [[CrossRef](#)] [[PubMed](#)]
7. Oettle, H.; Richards, D.; Ramanathan, R.K.; van Laethem, J.L.; Peeters, M.; Fuchs, M.; Zimmermann, A.; John, W.; Von Hoff, D.; Arning, M.; et al. A phase III trial of pemetrexed plus gemcitabine versus gemcitabine in patients with unresectable or metastatic pancreatic cancer. *Ann. Oncol.* **2005**, *16*, 1639–1645. [[CrossRef](#)] [[PubMed](#)]
8. Heinemann, V.; Quietzsch, D.; Gieseler, F.; Gonnermann, M.; Schonekas, H.; Rost, A.; Neuhaus, H.; Haag, C.; Clemens, M.; Heinrich, B.; et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J. Clin. Oncol.* **2006**, *24*, 3946–3952. [[CrossRef](#)] [[PubMed](#)]
9. Herrmann, R.; Bodoky, G.; Ruhstaller, T.; Glimelius, B.; Bajetta, E.; Schuller, J.; Saletti, P.; Bauer, J.; Figer, A.; Pestalozzi, B.; et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: A randomized, multicenter, phase III trial of the swiss group for clinical cancer research and the central european cooperative oncology group. *J. Clin. Oncol.* **2007**, *25*, 2212–2217. [[CrossRef](#)] [[PubMed](#)]
10. Poplin, E.; Feng, Y.; Berlin, J.; Rothenberg, M.L.; Hochster, H.; Mitchell, E.; Alberts, S.; O'Dwyer, P.; Haller, D.; Catalano, P.; et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-min infusion) in patients with pancreatic carcinoma e6201: A trial of the eastern cooperative oncology group. *J. Clin. Oncol.* **2009**, *27*, 3778–3785. [[CrossRef](#)] [[PubMed](#)]
11. Ueno, H.; Ioka, T.; Ikeda, M.; Ohkawa, S.; Yanagimoto, H.; Boku, N.; Fukutomi, A.; Sugimori, K.; Baba, H.; Yamao, K.; et al. Randomized phase III study of gemcitabine plus s-1, s-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: Gest study. *J. Clin. Oncol.* **2013**, *31*, 1640–1648. [[CrossRef](#)] [[PubMed](#)]
12. Aggarwal, B.B.; Sundaram, C.; Malani, N.; Ichikawa, H. Curcumin: The Indian solid gold. *Adv. Exp. Med. Biol.* **2007**, *595*, 1–75. [[PubMed](#)]
13. Strimpakos, A.S.; Sharma, R.A. Curcumin: Preventive and therapeutic properties in laboratory studies and clinical trials. *Antioxid. Redox Signal.* **2008**, *10*, 511–545. [[CrossRef](#)] [[PubMed](#)]
14. Kanai, M. Therapeutic applications of curcumin for patients with pancreatic cancer. *World J. Gastroenterol.* **2014**, *20*, 9384–9391. [[PubMed](#)]
15. Pattanayak, R.; Basak, P.; Sen, S.; Bhattacharyya, M. Interaction of kras g-quadruplex with natural polyphenols: A spectroscopic analysis with molecular modeling. *Int. J. Biol. Macromol.* **2016**, *89*, 228–237. [[CrossRef](#)] [[PubMed](#)]
16. Perrone, D.; Ardito, F.; Giannatempo, G.; Dioguardi, M.; Troiano, G.; Lo Russo, L.; A, D.E.L.; Laino, L.; Lo Muzio, L. Biological and therapeutic activities, and anticancer properties of curcumin. *Exp. Ther. Med.* **2015**, *10*, 1615–1623. [[CrossRef](#)] [[PubMed](#)]

17. Li, L.; Aggarwal, B.B.; Shishodia, S.; Abbruzzese, J.; Kurzrock, R. Nuclear factor-kappaB and ikappaB kinase are constitutively active in human pancreatic cells, and their down-regulation by curcumin (diferuloylmethane) is associated with the suppression of proliferation and the induction of apoptosis. *Cancer* **2004**, *101*, 2351–2362. [[CrossRef](#)] [[PubMed](#)]
18. Bimonte, S.; Barbieri, A.; Palma, G.; Luciano, A.; Rea, D.; Arra, C. Curcumin inhibits tumor growth and angiogenesis in an orthotopic mouse model of human pancreatic cancer. *Biomed. Res. Int.* **2013**, *2013*, 810423. [[CrossRef](#)] [[PubMed](#)]
19. Bimonte, S.; Barbieri, A.; Palma, G.; Rea, D.; Luciano, A.; D’Aiuto, M.; Arra, C.; Izzo, F. Dissecting the role of curcumin in tumour growth and angiogenesis in mouse model of human breast cancer. *Biomed. Res. Int.* **2015**, *2015*, 878134. [[CrossRef](#)] [[PubMed](#)]
20. Notarbartolo, M.; Poma, P.; Perri, D.; Dusonchet, L.; Cervello, M.; D’Alessandro, N. Antitumor effects of curcumin, alone or in combination with cisplatin or doxorubicin, on human hepatic cancer cells. Analysis of their possible relationship to changes in Nf-kappaB activation levels and in iap gene expression. *Cancer Lett.* **2005**, *224*, 53–65. [[CrossRef](#)] [[PubMed](#)]
21. Tomita, M.; Kawakami, H.; Uchihara, J.N.; Okudaira, T.; Masuda, M.; Takasu, N.; Matsuda, T.; Ohta, T.; Tanaka, Y.; Ohshiro, K.; et al. Curcumin (diferuloylmethane) inhibits constitutive active Nf-kappaB, leading to suppression of cell growth of human t-cell leukemia virus type I-infected T-cell lines and primary adult T-cell leukemia cells. *Int. J. Cancer* **2006**, *118*, 765–772. [[CrossRef](#)] [[PubMed](#)]
22. Wang, Z.; Zhang, Y.; Banerjee, S.; Li, Y.; Sarkar, F.H. Notch-1 down-regulation by curcumin is associated with the inhibition of cell growth and the induction of apoptosis in pancreatic cancer cells. *Cancer* **2006**, *106*, 2503–2513. [[CrossRef](#)] [[PubMed](#)]
23. Everett, P.C.; Meyers, J.A.; Makkinje, A.; Rabbi, M.; Lerner, A. Preclinical assessment of curcumin as a potential therapy for b-cll. *Am. J. Hematol.* **2007**, *82*, 23–30. [[CrossRef](#)] [[PubMed](#)]
24. Li, M.; Zhang, Z.; Hill, D.L.; Wang, H.; Zhang, R. Curcumin, a dietary component, has anticancer, chemosensitization, and radiosensitization effects by down-regulating the MDM2 oncogene through the PI3K/mTOR/ETS2 pathway. *Cancer Res.* **2007**, *67*, 1988–1996. [[CrossRef](#)] [[PubMed](#)]
25. Lin, Y.G.; Kunnumakara, A.B.; Nair, A.; Merritt, W.M.; Han, L.Y.; Armaiz-Pena, G.N.; Kamat, A.A.; Spannuth, W.A.; Gershenson, D.M.; Lutgendorf, S.K.; et al. Curcumin inhibits tumor growth and angiogenesis in ovarian carcinoma by targeting the nuclear factor-kappaB pathway. *Clin. Cancer Res.* **2007**, *13*, 3423–3430. [[CrossRef](#)] [[PubMed](#)]
26. Bachmeier, B.E.; Mohrenz, I.V.; Mirisola, V.; Schleicher, E.; Romeo, F.; Hohneke, C.; Jochum, M.; Nerlich, A.G.; Pfeffer, U. Curcumin downregulates the inflammatory cytokines CXCL1 and -2 in breast cancer cells via NfkappaB. *Carcinogenesis* **2008**, *29*, 779–789. [[CrossRef](#)] [[PubMed](#)]
27. Kunnumakara, A.B.; Diagaradjane, P.; Guha, S.; Deorukhkar, A.; Shentu, S.; Aggarwal, B.B.; Krishnan, S. Curcumin sensitizes human colorectal cancer xenografts in nude mice to gamma-radiation by targeting nuclear factor-kappaB-regulated gene products. *Clin. Cancer Res.* **2008**, *14*, 2128–2136. [[CrossRef](#)] [[PubMed](#)]
28. Milacic, V.; Banerjee, S.; Landis-Piwowar, K.R.; Sarkar, F.H.; Majumdar, A.P.; Dou, Q.P. Curcumin inhibits the proteasome activity in human colon cancer cells in vitro and in vivo. *Cancer Res.* **2008**, *68*, 7283–7292. [[CrossRef](#)] [[PubMed](#)]
29. Sahu, R.P.; Batra, S.; Srivastava, S.K. Activation of ATM/Chk1 by curcumin causes cell cycle arrest and apoptosis in human pancreatic cancer cells. *Br. J. Cancer* **2009**, *100*, 1425–1433. [[CrossRef](#)] [[PubMed](#)]
30. Glienke, W.; Maute, L.; Wicht, J.; Bergmann, L. Curcumin inhibits constitutive STAT3 phosphorylation in human pancreatic cancer cell lines and downregulation of survivin/BIRC5 gene expression. *Cancer Investig.* **2010**, *28*, 166–171. [[CrossRef](#)] [[PubMed](#)]
31. Ali, S.; Ahmad, A.; Banerjee, S.; Padhye, S.; Dominiak, K.; Schaffert, J.M.; Wang, Z.; Philip, P.A.; Sarkar, F.H. Gemcitabine sensitivity can be induced in pancreatic cancer cells through modulation of mir-200 and mir-21 expression by curcumin or its analogue CDF. *Cancer Res.* **2010**, *70*, 3606–3617. [[CrossRef](#)] [[PubMed](#)]
32. Yang, C.L.; Liu, Y.Y.; Ma, Y.G.; Xue, Y.X.; Liu, D.G.; Ren, Y.; Liu, X.B.; Li, Y.; Li, Z. Curcumin blocks small cell lung cancer cells migration, invasion, angiogenesis, cell cycle and neoplasia through janus kinase-STAT3 signalling pathway. *PLoS ONE* **2012**, *7*, e37960. [[CrossRef](#)] [[PubMed](#)]
33. Yu, L.L.; Wu, J.G.; Dai, N.; Yu, H.G.; Si, J.M. Curcumin reverses chemoresistance of human gastric cancer cells by downregulating the Nf-kappaB transcription factor. *Oncol. Rep.* **2011**, *26*, 1197–1203. [[PubMed](#)]

34. Basha, R.; Connelly, S.F.; Sankpal, U.T.; Nagaraju, G.P.; Patel, H.; Vishwanatha, J.K.; Shelake, S.; Tabor-Simecka, L.; Shoji, M.; Simecka, J.W.; et al. Small molecule tolfenamic acid and dietary spice curcumin treatment enhances antiproliferative effect in pancreatic cancer cells via suppressing sp1, disrupting Nf- κ B translocation to nucleus and cell cycle phase distribution. *J. Nutr. Biochem.* **2016**, *31*, 77–87. [[CrossRef](#)] [[PubMed](#)]
35. Cao, L.; Xiao, X.; Lei, J.; Duan, W.; Ma, Q.; Li, W. Curcumin inhibits hypoxia-induced epithelialmesenchymal transition in pancreatic cancer cells via suppression of the hedgehog signaling pathway. *Oncol. Rep.* **2016**, *35*, 3728–3734. [[PubMed](#)]
36. Parsons, H.A.; Baracos, V.E.; Hong, D.S.; Abbruzzese, J.; Bruera, E.; Kurzrock, R. The effects of curcumin (diferuloylmethane) on body composition of patients with advanced pancreatic cancer. *Oncotarget* **2016**. [[CrossRef](#)] [[PubMed](#)]
37. Sahebkar, A. Curcumin: A natural multitarget treatment for pancreatic cancer. *Integr. Cancer Ther.* **2016**. [[CrossRef](#)] [[PubMed](#)]
38. Yarla, N.S.; Bishayee, A.; Sethi, G.; Reddanna, P.; Kalle, A.M.; Dhananjaya, B.L.; Dowluru, K.S.; Chintala, R.; Duddukuri, G.R. Targeting arachidonic acid pathway by natural products for cancer prevention and therapy. *Semin. Cancer Biol.* **2016**. in press. [[CrossRef](#)] [[PubMed](#)]
39. Luthra, P.M.; Lal, N. Prospective of curcumin, a pleiotropic signalling molecule from curcuma longa in the treatment of glioblastoma. *Eur. J. Med. Chem.* **2016**, *109*, 23–35. [[CrossRef](#)] [[PubMed](#)]
40. Tsai, C.F.; Hsieh, T.H.; Lee, J.N.; Hsu, C.Y.; Wang, Y.C.; Kuo, K.K.; Wu, H.L.; Chiu, C.C.; Tsai, E.M.; Kuo, P.L. Curcumin suppresses phthalate-induced metastasis and the proportion of cancer stem cell (CSC)-like cells via the inhibition of AhR/ERK/SK1 signaling in hepatocellular carcinoma. *J. Agric. Food Chem.* **2015**, *63*, 10388–10398. [[CrossRef](#)] [[PubMed](#)]
41. Hu, B.; Sun, D.; Sun, C.; Sun, Y.F.; Sun, H.X.; Zhu, Q.F.; Yang, X.R.; Gao, Y.B.; Tang, W.G.; Fan, J.; et al. A polymeric nanoparticle formulation of curcumin in combination with sorafenib synergistically inhibits tumor growth and metastasis in an orthotopic model of human hepatocellular carcinoma. *Biochem. Biophys. Res. Commun.* **2015**, *468*, 525–532. [[CrossRef](#)] [[PubMed](#)]
42. Diaz Osterman, C.J.; Gonda, A.; Stiff, T.; Sigaran, U.; Valenzuela, M.M.; Ferguson Bennit, H.R.; Moyron, R.B.; Khan, S.; Wall, N.R. Curcumin induces pancreatic adenocarcinoma cell death via reduction of the inhibitors of apoptosis. *Pancreas* **2016**, *45*, 101–109. [[CrossRef](#)] [[PubMed](#)]
43. Zhao, Z.; Li, C.; Xi, H.; Gao, Y.; Xu, D. Curcumin induces apoptosis in pancreatic cancer cells through the induction of forkhead box o1 and inhibition of the PI3K/Akt pathway. *Mol. Med. Rep.* **2015**, *12*, 5415–5422. [[PubMed](#)]
44. Azimi, H.; Khakshur, A.A.; Abdollahi, M.; Rahimi, R. Potential new pharmacological agents derived from medicinal plants for the treatment of pancreatic cancer. *Pancreas* **2015**, *44*, 11–15. [[CrossRef](#)] [[PubMed](#)]
45. Sinha, D.; Biswas, J.; Sung, B.; Aggarwal, B.B.; Bishayee, A. Chemopreventive and chemotherapeutic potential of curcumin in breast cancer. *Curr. Drug Targets* **2012**, *13*, 1799–1819. [[CrossRef](#)] [[PubMed](#)]
46. Lao, C.D.; Ruffin, M.T.; Normolle, D.; Heath, D.D.; Murray, S.I.; Bailey, J.M.; Boggs, M.E.; Crowell, J.; Rock, C.L.; Brenner, D.E. Dose escalation of a curcuminoid formulation. *BMC Complement. Altern. Med.* **2006**, *6*. [[CrossRef](#)] [[PubMed](#)]
47. Vareed, S.K.; Kakarala, M.; Ruffin, M.T.; Crowell, J.A.; Normolle, D.P.; Djuric, Z.; Brenner, D.E. Pharmacokinetics of curcumin conjugate metabolites in healthy human subjects. *Cancer Epidemiol. Biomark. Prev.* **2008**, *17*, 1411–1417. [[CrossRef](#)] [[PubMed](#)]
48. Cheng, A.L.; Hsu, C.H.; Lin, J.K.; Hsu, M.M.; Ho, Y.F.; Shen, T.S.; Ko, J.Y.; Lin, J.T.; Lin, B.R.; Ming-Shiang, W.; et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Res.* **2001**, *21*, 2895–2900. [[PubMed](#)]
49. Li, L.; Braiteh, F.S.; Kurzrock, R. Liposome-encapsulated curcumin: In vitro and in vivo effects on proliferation, apoptosis, signaling, and angiogenesis. *Cancer* **2005**, *104*, 1322–1331. [[CrossRef](#)] [[PubMed](#)]
50. Bisht, S.; Feldmann, G.; Soni, S.; Ravi, R.; Karikar, C.; Maitra, A.; Maitra, A. Polymeric nanoparticle-encapsulated curcumin (“nanocurcumin”): A novel strategy for human cancer therapy. *J. Nanobiotechnol.* **2007**, *5*. [[CrossRef](#)] [[PubMed](#)]
51. Antony, B.; Merina, B.; Iyer, V.S.; Judy, N.; Lennertz, K.; Joyal, S. A pilot cross-over study to evaluate human oral bioavailability of BCM-95CG (biocurcumax), a novel bioenhanced preparation of curcumin. *Indian J. Pharm. Sci.* **2008**, *70*, 445–449. [[CrossRef](#)] [[PubMed](#)]

52. Shaikh, J.; Ankola, D.D.; Beniwal, V.; Singh, D.; Kumar, M.N. Nanoparticle encapsulation improves oral bioavailability of curcumin by at least 9-fold when compared to curcumin administered with piperine as absorption enhancer. *Eur. J. Pharm. Sci.* **2009**, *37*, 223–230. [[CrossRef](#)] [[PubMed](#)]
53. Anand, P.; Nair, H.B.; Sung, B.; Kunnumakkara, A.B.; Yadav, V.R.; Tekmal, R.R.; Aggarwal, B.B. Design of curcumin-loaded plga nanoparticles formulation with enhanced cellular uptake, and increased bioactivity in vitro and superior bioavailability in vivo. *Biochem. Pharmacol.* **2010**, *79*, 330–338. [[CrossRef](#)] [[PubMed](#)]
54. Sasaki, H.; Sunagawa, Y.; Takahashi, K.; Imaizumi, A.; Fukuda, H.; Hashimoto, T.; Wada, H.; Katanasaka, Y.; Kakeya, H.; Fujita, M.; et al. Innovative preparation of curcumin for improved oral bioavailability. *Biol. Pharm. Bull.* **2011**, *34*, 660–665. [[CrossRef](#)] [[PubMed](#)]
55. Kanai, M.; Imaizumi, A.; Otsuka, Y.; Sasaki, H.; Hashiguchi, M.; Tsujiko, K.; Matsumoto, S.; Ishiguro, H.; Chiba, T. Dose-escalation and pharmacokinetic study of nanoparticle curcumin, a potential anticancer agent with improved bioavailability, in healthy human volunteers. *Cancer Chemother. Pharmacol.* **2012**, *69*, 65–70. [[CrossRef](#)] [[PubMed](#)]
56. Kesharwani, P.; Banerjee, S.; Padhye, S.; Sarkar, F.H.; Iyer, A.K. Parenterally administrable nano-micelles of 3,4-difluorobenzylidene curcumin for treating pancreatic cancer. *Colloids Surf. B Biointerfaces* **2015**, *132*, 138–145. [[CrossRef](#)] [[PubMed](#)]
57. Margulis, K.; Srinivasan, S.; Ware, M.J.; Summers, H.D.; Godin, B.; Magdassi, S. Active curcumin nanoparticles formed from a volatile microemulsion template. *J. Mater. Chem. B Mater. Biol. Med.* **2014**, *2*, 3745–3752. [[CrossRef](#)] [[PubMed](#)]
58. Howells, L.M.; Sale, S.; Sriramareddy, S.N.; Irving, G.R.; Jones, D.J.; Ottley, C.J.; Pearson, D.G.; Mann, C.D.; Manson, M.M.; Berry, D.P.; et al. Curcumin ameliorates oxaliplatin-induced chemoresistance in HCT116 colorectal cancer cells in vitro and in vivo. *Int. J. Cancer* **2011**, *129*, 476–486. [[CrossRef](#)] [[PubMed](#)]
59. Jutooru, I.; Chadalapaka, G.; Lei, P.; Safe, S. Inhibition of NfκB and pancreatic cancer cell and tumor growth by curcumin is dependent on specificity protein down-regulation. *J. Biol. Chem.* **2010**, *285*, 25332–25344. [[CrossRef](#)] [[PubMed](#)]
60. Youns, M.; Fathy, G.M. Upregulation of extrinsic apoptotic pathway in curcumin-mediated antiproliferative effect on human pancreatic carcinogenesis. *J. Cell. Biochem.* **2013**, *114*, 2654–2665. [[CrossRef](#)] [[PubMed](#)]
61. Li, Y.; Revalde, J.L.; Reid, G.; Paxton, J.W. Modulatory effects of curcumin on multi-drug resistance-associated protein 5 in pancreatic cancer cells. *Cancer Chemother. Pharmacol.* **2011**, *68*, 603–610. [[CrossRef](#)] [[PubMed](#)]
62. Ning, X.; Du, Y.; Ben, Q.; Huang, L.; He, X.; Gong, Y.; Gao, J.; Wu, H.; Man, X.; Jin, J.; et al. Bulk pancreatic cancer cells can convert into cancer stem cells(CSCs) in vitro and 2 compounds can target these CSCs. *Cell Cycle* **2016**, *15*, 403–412. [[CrossRef](#)] [[PubMed](#)]
63. Kesharwani, P.; Xie, L.; Banerjee, S.; Mao, G.; Padhye, S.; Sarkar, F.H.; Iyer, A.K. Hyaluronic acid-conjugated polyamidoamine dendrimers for targeted delivery of 3,4-difluorobenzylidene curcumin to cd44 overexpressing pancreatic cancer cells. *Colloids Surf. B Biointerfaces* **2015**, *136*, 413–423. [[CrossRef](#)] [[PubMed](#)]
64. Osterman, C.J.; Lynch, J.C.; Leaf, P.; Gonda, A.; Ferguson Bennit, H.R.; Griffiths, D.; Wall, N.R. Curcumin modulates pancreatic adenocarcinoma cell-derived exosomal function. *PLoS ONE* **2015**, *10*, e0132845. [[CrossRef](#)] [[PubMed](#)]
65. Gundewar, C.; Ansari, D.; Tang, L.; Wang, Y.; Liang, G.; Rosendahl, A.H.; Saleem, M.A.; Andersson, R. Antiproliferative effects of curcumin analog 149H37 in pancreatic stellate cells: A comparative study. *Ann. Gastroenterol.* **2015**, *28*, 391–398. [[PubMed](#)]
66. Fiala, M. Curcumin and omega-3 fatty acids enhance nk cell-induced apoptosis of pancreatic cancer cells but curcumin inhibits interferon-gamma production: Benefits of omega-3 with curcumin against cancer. *Molecules* **2015**, *20*, 3020–3026. [[CrossRef](#)] [[PubMed](#)]
67. Ma, J.; Fang, B.; Zeng, F.; Pang, H.; Zhang, J.; Shi, Y.; Wu, X.; Cheng, L.; Ma, C.; Xia, J.; et al. Curcumin inhibits cell growth and invasion through up-regulation of mir-7 in pancreatic cancer cells. *Toxicol. Lett.* **2014**, *231*, 82–91. [[CrossRef](#)] [[PubMed](#)]
68. Duarte, V.M.; Han, E.; Veena, M.S.; Salvado, A.; Suh, J.D.; Liang, L.J.; Faull, K.F.; Srivatsan, E.S.; Wang, M.B. Curcumin enhances the effect of cisplatin in suppression of head and neck squamous cell carcinoma via inhibition of ikkβ protein of the NfκB pathway. *Mol. Cancer Ther.* **2010**, *9*, 2665–2675. [[CrossRef](#)] [[PubMed](#)]

69. Sarkar, S.; Dubaybo, H.; Ali, S.; Goncalves, P.; Kollepara, S.L.; Sethi, S.; Philip, P.A.; Li, Y. Down-regulation of mir-221 inhibits proliferation of pancreatic cancer cells through up-regulation of pten, p27(kip1), p57(kip2), and puma. *Am. J. Cancer Res.* **2013**, *3*, 465–477. [[PubMed](#)]
70. Sun, X.D.; Liu, X.E.; Huang, D.S. Curcumin reverses the epithelial-mesenchymal transition of pancreatic cancer cells by inhibiting the hedgehog signaling pathway. *Oncol. Rep.* **2013**, *29*, 2401–2407. [[PubMed](#)]
71. Kunnumakkara, A.B.; Guha, S.; Krishnan, S.; Diagaradjane, P.; Gelovani, J.; Aggarwal, B.B. Curcumin potentiates antitumor activity of gemcitabine in an orthotopic model of pancreatic cancer through suppression of proliferation, angiogenesis, and inhibition of nuclear factor-kappaB-regulated gene products. *Cancer Res.* **2007**, *67*, 3853–3861. [[CrossRef](#)] [[PubMed](#)]
72. Parasramka, M.A.; Gupta, S.V. Synergistic effect of garcinol and curcumin on antiproliferative and apoptotic activity in pancreatic cancer cells. *J. Oncol.* **2012**, *2012*, 709739. [[CrossRef](#)] [[PubMed](#)]
73. Lin, L.; Hutzen, B.; Zuo, M.; Ball, S.; Deangelis, S.; Foust, E.; Pandit, B.; Ihnat, M.A.; Shenoy, S.S.; Kulp, S.; et al. Novel STAT3 phosphorylation inhibitors exhibit potent growth-suppressive activity in pancreatic and breast cancer cells. *Cancer Res.* **2010**, *70*, 2445–2454. [[CrossRef](#)] [[PubMed](#)]
74. Bao, B.; Ali, S.; Banerjee, S.; Wang, Z.; Logna, F.; Azmi, A.S.; Kong, D.; Ahmad, A.; Li, Y.; Padhye, S.; et al. Curcumin analogue CDF inhibits pancreatic tumor growth by switching on suppressor micrnas and attenuating EZH2 expression. *Cancer Res.* **2012**, *72*, 335–345. [[CrossRef](#)] [[PubMed](#)]
75. Sureban, S.M.; Qu, D.; Houchen, C.W. Regulation of mirnas by agents targeting the tumor stem cell markers DCLK1, MSI1, LGR5, and BMI1. *Curr. Pharmacol. Rep.* **2015**, *1*, 217–222. [[CrossRef](#)] [[PubMed](#)]
76. Bao, B.; Ali, S.; Kong, D.; Sarkar, S.H.; Wang, Z.; Banerjee, S.; Aboukameel, A.; Padhye, S.; Philip, P.A.; Sarkar, F.H. Anti-tumor activity of a novel compound-cdf is mediated by regulating mir-21, mir-200, and pten in pancreatic cancer. *PLoS ONE* **2011**, *6*, e17850. [[CrossRef](#)] [[PubMed](#)]
77. Sun, M.; Estrov, Z.; Ji, Y.; Coombes, K.R.; Harris, D.H.; Kurzrock, R. Curcumin (diferuloylmethane) alters the expression profiles of micrnas in human pancreatic cancer cells. *Mol. Cancer Ther.* **2008**, *7*, 464–473. [[CrossRef](#)] [[PubMed](#)]
78. Grandhi, B.K.; Thakkar, A.; Wang, J.; Prabhu, S. A novel combinatorial nanotechnology-based oral chemopreventive regimen demonstrates significant suppression of pancreatic cancer neoplastic lesions. *Cancer Prev. Res.* **2013**, *6*, 1015–1025. [[CrossRef](#)] [[PubMed](#)]
79. Bisht, S.; Mizuma, M.; Feldmann, G.; Ottenhof, N.A.; Hong, S.M.; Pramanik, D.; Chenna, V.; Karikari, C.; Sharma, R.; Goggins, M.G.; et al. Systemic administration of polymeric nanoparticle-encapsulated curcumin (nanocurc) blocks tumor growth and metastases in preclinical models of pancreatic cancer. *Mol. Cancer Ther.* **2010**, *9*, 2255–2264. [[CrossRef](#)] [[PubMed](#)]
80. Padhye, S.; Banerjee, S.; Chavan, D.; Pandye, S.; Swamy, K.V.; Ali, S.; Li, J.; Dou, Q.P.; Sarkar, F.H. Fluorocurcumins as cyclooxygenase-2 inhibitor: Molecular docking, pharmacokinetics and tissue distribution in mice. *Pharm. Res.* **2009**, *26*, 2438–2445. [[CrossRef](#)] [[PubMed](#)]
81. Kesharwani, P.; Banerjee, S.; Padhye, S.; Sarkar, F.H.; Iyer, A.K. Hyaluronic acid engineered nanomicelles loaded with 3,4-difluorobenzylidene curcumin for targeted killing of CD44+ stem-like pancreatic cancer cells. *Biomacromolecules* **2015**, *16*, 3042–3053. [[CrossRef](#)] [[PubMed](#)]
82. Halder, R.C.; Almasi, A.; Sagong, B.; Leung, J.; Jewett, A.; Fiala, M. Curcuminoids and omega-3 fatty acids with anti-oxidants potentiate cytotoxicity of natural killer cells against pancreatic ductal adenocarcinoma cells and inhibit interferon gamma production. *Front. Physiol.* **2015**, *6*, 129. [[CrossRef](#)] [[PubMed](#)]
83. Nagaraju, G.P.; Zhu, S.; Ko, J.E.; Ashritha, N.; Kandimalla, R.; Snyder, J.P.; Shoji, M.; El-Rayes, B.F. Antiangiogenic effects of a novel synthetic curcumin analogue in pancreatic cancer. *Cancer Lett.* **2015**, *357*, 557–565. [[CrossRef](#)] [[PubMed](#)]
84. Ali, S.; Ahmad, A.; Aboukameel, A.; Ahmed, A.; Bao, B.; Banerjee, S.; Philip, P.A.; Sarkar, F.H. Deregulation of mir-146a expression in a mouse model of pancreatic cancer affecting egfr signaling. *Cancer Lett.* **2014**, *351*, 134–142. [[CrossRef](#)] [[PubMed](#)]
85. Ranjan, A.P.; Mukerjee, A.; Helson, L.; Gupta, R.; Vishwanatha, J.K. Efficacy of liposomal curcumin in a human pancreatic tumor xenograft model: Inhibition of tumor growth and angiogenesis. *Anticancer Res.* **2013**, *33*, 3603–3609. [[PubMed](#)]
86. Nagaraju, G.P.; Zhu, S.; Wen, J.; Farris, A.B.; Adsay, V.N.; Diaz, R.; Snyder, J.P.; Mamoru, S.; El-Rayes, B.F. Novel synthetic curcumin analogues EF31 and UBS109 are potent DNA hypomethylating agents in pancreatic cancer. *Cancer Lett.* **2013**, *341*, 195–203. [[CrossRef](#)] [[PubMed](#)]

87. Yallapu, M.M.; Ebeling, M.C.; Khan, S.; Sundram, V.; Chauhan, N.; Gupta, B.K.; Puumala, S.E.; Jaggi, M.; Chauhan, S.C. Novel curcumin-loaded magnetic nanoparticles for pancreatic cancer treatment. *Mol. Cancer Ther.* **2013**, *12*, 1471–1480. [[CrossRef](#)] [[PubMed](#)]
88. Mach, C.M.; Mathew, L.; Mosley, S.A.; Kurzrock, R.; Smith, J.A. Determination of minimum effective dose and optimal dosing schedule for liposomal curcumin in a xenograft human pancreatic cancer model. *Anticancer Res.* **2009**, *29*, 1895–1899. [[PubMed](#)]
89. Sharma, R.A.; Euden, S.A.; Platton, S.L.; Cooke, D.N.; Shafayat, A.; Hewitt, H.R.; Marczylo, T.H.; Morgan, B.; Hemingway, D.; Plummer, S.M.; et al. Phase I clinical trial of oral curcumin: Biomarkers of systemic activity and compliance. *Clin. Cancer Res.* **2004**, *10*, 6847–6854. [[CrossRef](#)] [[PubMed](#)]
90. Garcea, G.; Berry, D.P.; Jones, D.J.; Singh, R.; Dennison, A.R.; Farmer, P.B.; Sharma, R.A.; Steward, W.P.; Gescher, A.J. Consumption of the putative chemopreventive agent curcumin by cancer patients: Assessment of curcumin levels in the colorectum and their pharmacodynamic consequences. *Cancer Epidemiol. Biomark. Prev.* **2005**, *14*, 120–125.
91. Dhillon, N.; Aggarwal, B.B.; Newman, R.A.; Wolff, R.A.; Kunnumakkara, A.B.; Abbruzzese, J.L.; Ng, C.S.; Badmaev, V.; Kurzrock, R. Phase II trial of curcumin in patients with advanced pancreatic cancer. *Clin. Cancer Res.* **2008**, *14*, 4491–4499. [[CrossRef](#)] [[PubMed](#)]
92. Kanai, M.; Yoshimura, K.; Asada, M.; Imaizumi, A.; Suzuki, C.; Matsumoto, S.; Nishimura, T.; Mori, Y.; Masui, T.; Kawaguchi, Y.; et al. A phase I/II study of gemcitabine-based chemotherapy plus curcumin for patients with gemcitabine-resistant pancreatic cancer. *Cancer Chemother. Pharmacol.* **2011**, *68*, 157–164. [[CrossRef](#)] [[PubMed](#)]
93. Epelbaum, R.; Schaffer, M.; Vizel, B.; Badmaev, V.; Bar-Sela, G. Curcumin and gemcitabine in patients with advanced pancreatic cancer. *Nutr. Cancer* **2010**, *62*, 1137–1141. [[CrossRef](#)] [[PubMed](#)]
94. Kanai, M.; Otsuka, Y.; Otsuka, K.; Sato, M.; Nishimura, T.; Mori, Y.; Kawaguchi, M.; Hatano, E.; Kodama, Y.; Matsumoto, S.; et al. A phase I study investigating the safety and pharmacokinetics of highly bioavailable curcumin (theracurmin) in cancer patients. *Cancer Chemother. Pharmacol.* **2013**, *71*, 1521–1530. [[CrossRef](#)] [[PubMed](#)]



© 2016 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC-BY) license (<http://creativecommons.org/licenses/by/4.0/>).