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The Potential Role of Curcumin for Treatment of Pancreatic Cancer

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1. Introduction

Gemcitabine has been the standard chemotherapy for advanced pancreatic cancer since 1997, when a randomized phase III study demonstrated that gemcitabine significantly improved cancer-related symptoms in comparison with 5-fluorouracil (5-FU) (Burris *et al.*, 1997). However, the survival benefit of gemcitabine is modest and the median survival time was 5.7 and 4.4 months for gemcitabine and 5-FU arm, respectively. Thus the prognosis of this disease still remains dismal and the development of a more effective therapy is urgently needed in daily clinical practice. For the past decade, many efforts have been made to improve the overall survival of patients with this disease by adding a second cytotoxic agent to gemcitabine. Several large phase III trials have compared gemcitabine alone with gemcitabine combination therapy (e.g. capecitabine, 5-fluorouracil, irinotecan, oxaliplatin, pemetrexed). However, none of them could demonstrate a significant survival advantage for the gemcitabine combination therapy over the gemcitabine monotherapy, despite a significant improvement in response rates (Berlin *et al.*, 2002; Herrmann *et al.*, 2007; Louvet *et al.*, 2005; Oettle *et al.*, 2005; Rocha Lima *et al.*, 2004). It is likely that the benefit of adding a second cytotoxic agent to gemcitabine is countered by increased toxicity and the decreased dose intensity of gemcitabine. Therefore, a new approach other than adding cytotoxic agents to gemcitabine is warranted. Since pancreatic cancer patients often suffer from cancer-related symptoms (e.g. fatigue, appetite loss, pain), it is very important to maintain a balance between efficacy and quality of life in palliative chemotherapy.

Curcumin is derived from turmeric (Curcuma longa) and is a natural polyphenol (Figures 1 and 2). Curcumin has long been used as a food (e.g. the popular Indian curry), coloring agent and traditional medicine (Aggarwal *et al.*, 2007; Strimpakos & Sharma, 2008).

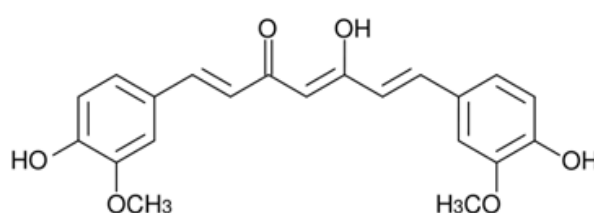Fig. 1. Turmeric (left panel) and curcumin (right panel)

Fig. 2. Chemical structure of curcumin

A number of preclinical studies have demonstrated the anticancer effects of curcumin in a variety of tumors including pancreatic cancer, both *in vitro* and *in vivo,* and these promising data are now attracting the interest of many researchers in developing this agent as a chemopreventive as well as a chemotherapeutic drug (Corson & Crews, 2007). In contrast to conventional cytotoxic drugs, curcumin causes little toxicity, which is a great advantage of developing this agent for the treatment of pancreatic cancer patients, who are often intolerant to cytotoxic combination therapy due to their poor clinical condition. Safety is another advantage of this agent. The safety of curcumin has been approved by the Food and Drug Administration (FDA) and World Health Organization (WHO); however, its safety is most strongly supported by the fact that this agent has been used as a traditional Hindu or Chinese medicine for thousands of years. In this chapter, we highlight the potential role of curcumin for the treatment of pancreatic cancer by reviewing the published preclinical and clinical data.

2. Anticancer effects of curcumin

A Pubmed search using the key words 'curcumin' and 'cancer' demonstrated that more than 1500 articles have been published since 1983 and that this number has rapidly increased over the past 5 years (Figure 3). The potential anticancer effects of curcumin have been reported in a variety of preclinical models including breast, colon, gastric, head and neck, hepatic, ovarian, pancreatic and prostate cancer, leukemia and multiple myeloma, and well described in several review articles (Aggarwal *et al.*, 2007; Shishodia *et al.*, 2007; Strimpakos & Sharma, 2008). Curcumin can modulate a variety of molecules which play an important role in cancer progression. Among these molecules, nuclear transcription factor-κB (NF-κB) is one of the major targets of curcumin. Diverse upstream signals (e.g. growth factors, cytokines, hypoxia) can induce constitutive NF-κB activation in patients with cancer, including those with pancreatic cancer, and its activity is positively correlated with cancer

progression (Fujioka *et al.*, 2003; Wang *et al.*, 1999). For example, NF-κB activation can up-regulate the expression of a number of genes involved in anti-apoptosis (e.g. Bcl-2, Bcl-xL), proliferation (e.g. cyclin D1, *c*-myc), angiogenesis (e.g. vascular endothelial growth factor (VEGF), interleukin-6), and invasion (e.g. matrix metalloproteinases (MMP)), all of which play a pivotal role in cancer progression (Aggarwal, 2004). Therefore, inhibition of NF-κB activity by curcumin can effectively suppress tumor growth (Figure 4).
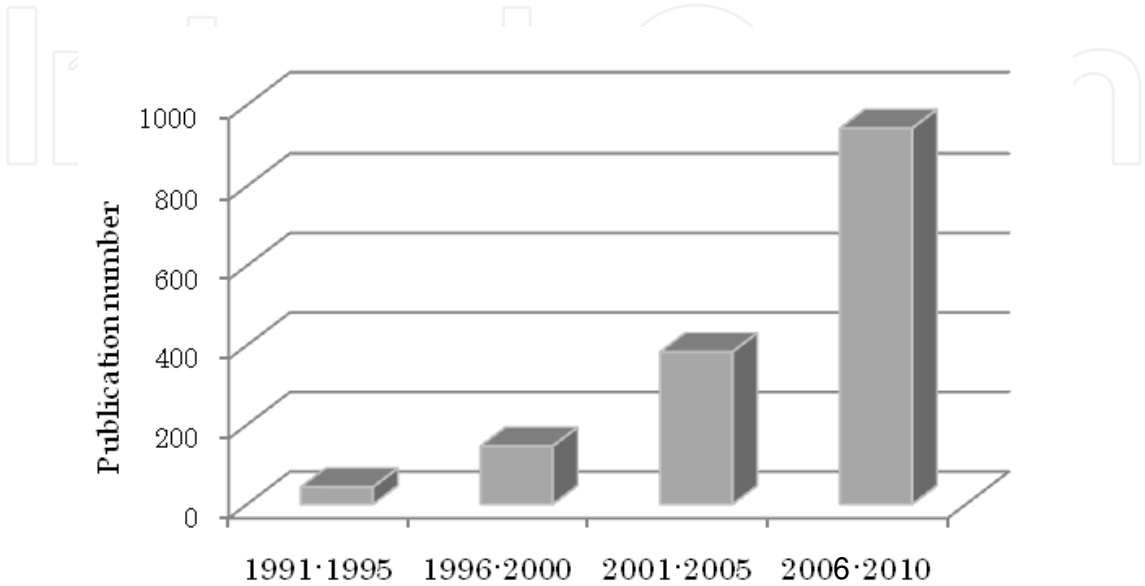

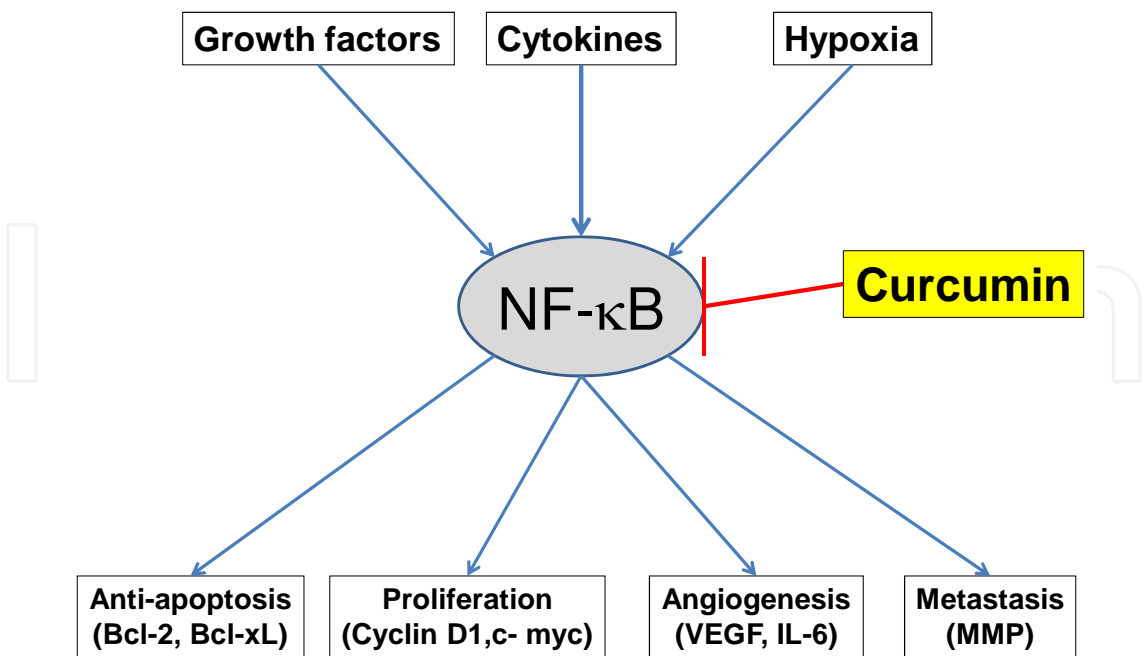Fig. 3. Pubmed search results using the key words 'curcumin' and 'cancer'

Fig. 4. NF-κB is one of the major molecular targets of curcumin

Other mechanisms involved in the anticancer effects of curcumin include the down-regulation of Akt, cyclooxygenase-2 (COX2), prostaglandin E2 or signal transducers and activators of transcription 3 (STAT3) (Aggarwal & Shishodia, 2006), which prevents cancer cells from escaping through alternative signaling pathways. Curcumin can also potentiate the anticancer effects of cytotoxic agents such as cisplatin, 5-fluorouracil and gemcitabine (Du *et al.*, 2006; Kunnumakkara *et al.*, 2007; Tsai *et al.*, 2011).

3. Preclinical data on anticancer effects of curcumin

Li et al. first reported the anticancer effects of curcumin on pancreatic cancer cells *in vitro* (Li *et al.*, 2004). They demonstrated that curcumin can suppress tumor growth of pancreatic cancer cell lines in a time and dose dependent manner through NF-κB inhibition. The efficacy of curcumin *in vivo* has also been demonstrated using an orthotopic mouse model of pancreatic cancer (Kunnumakkara *et al.*, 2007). While treatment with either curcumin (1 g/kg orally) or gemcitabine (25 mg/kg through intraperitoneal injection) demonstrated modest antitumor effects, the combination of curcumin with gemcitabine suppressed tumor growth more effectively than curcumin or gemcitabine alone. As expected, inhibition of NF-κB activity as well as the down-regulation of a variety of NF-κB-dependent gene products (cyclin D1, c-myc, Bcl-2, Bcl-xL, cellular inhibitor of apoptosis protein-1, cyclooxygenase-2, matrix metalloproteinase and VEGF) was observed in orthotopic tumor tissue after administration of curcumin. Other preclinical studies have also demonstrated the anticancer effects of curcumin either alone or in combination with gemcitabine in pancreatic cancer (Ali *et al.*, 2010; Strimpakos & Sharma, 2008; Wang *et al.*, 2006).

Based on these promising preclinical data, the main focus of research has now moved on to demonstrating the anticancer effects of curcumin in clinical trials.

4. Clinical trials using curcumin in patients with pancreatic cancer

Although the number of clinical trials is still limited compared to the numerous preclinical studies, several phase I or pharmacokinetic studies have been conducted with curcumin and found no dose limiting toxicity (DLT) up to at least 12 g/day when administered orally in both healthy volunteers (Lao *et al.*, 2006; Vareed *et al.*, 2008) and cancer patients (Cheng *et al.*, 2001; Garcea *et al.*, 2005; Sharma *et al.*, 2004). Minor toxicities of Grade 1-2 diarrhea and nausea have been reported, probably due to the oral intake of a bulky volume of curcumin at one time. Higher doses than 8 g/day of oral curcumin do not cause any DLT; however, these bulky volumes are unacceptable for daily oral intake. Moreover, doses above 8 g/day did not lead to a further increase in plasma curcumin levels due to poor bioavailability (Cheng *et al.*, 2001; Lao *et al.*, 2006; Vareed *et al.*, 2008). For these reasons, 8 g of daily oral curcumin is accepted to be the optimal dose for clinical trials in cancer patients.

Dhillon et al. were the first to report a phase II clinical trial, using 8 g of daily oral curcumin in patients with pancreatic cancer (Dhillon *et al.*, 2008). Twenty-five patients were enrolled in this study and 22 patients (88%) had a history of prior chemotherapy. Out of the 22 patients evaluable for response, 2 patients demonstrated some clinical benefit. One patient had stable disease for more than 18 months and the other patient achieved a partial response in a liver metastasis (73% decrease in the size), although it lasted for only 1 month. Curcumin was safe in patients with pancreatic cancer and no toxicity associated with

curcumin intake was reported. Furthermore, inhibition of NF-κB activity after curcumin intake was demonstrated using peripheral mononuclear cells from patients.

We also conducted a phase I/II clinical trial using curcumin for patients with pancreatic cancer who had become resistant to gemcitabine-based chemotherapy (Kanai *et al.*, 2010). In contrast to the study by Dhillon et al. which tested the safety and efficacy of curcumin monotherapy, our study evaluated the safety and feasibility of adding curcumin to gemcitabine-based chemotherapy, because no previous studies had demonstrated the safety and feasibility of this combination. In the phase I study, the safety of 8 g of daily curcumin in combination with gemcitabine-based chemotherapy was evaluated. In line with previous reports evaluating curcumin monotherapy, the first 3 assessable patients enrolled for the phase I study completed their first cycle without a predefined DLT (Grade 4 leucopenia; Grade 4 neutropenia; Grade 3 or more thrombocytopenia; non-hematological of Grade 3 or more; patient refusal due to the intolerability of curcumin intake). Therefore, we selected this dose as the recommended dose for the following phase II study. In total, 21 patients who showed disease progression during gemcitabine-based chemotherapy (gemcitabine/S-1 combination therapy for 19 patients and gemcitabine monotherapy for 2 patients) were enrolled. Adding curcumin did not increase the risk of clinically relevant toxicity, and the toxicity profile was comparable with that observed in pancreatic cancer patients treated with gemcitabine-based chemotherapy. No patients showed intolerance to 8 g of daily oral curcumin, and the median compliance rate was as high as 100% (range 79-100%), indicating that there was little toxicity due to curcumin even if administered concurrently with cytotoxic agents. Cumulative toxicity due to curcumin was not observed and 4 patients were able to continue this intake for more than 6 months, which indicates the safety of this agent for long-term use. Albeit the preliminary results from a small sample size, the median survival time (MST) of 161 days (95% CI 109-223 days) and a 1-year survival rate of 19% (95% CI 4.4-41.4%) were encouraging considering the poor prognosis of pancreatic cancer patients for whom gemcitabine-based chemotherapy has failed (Figure 5).
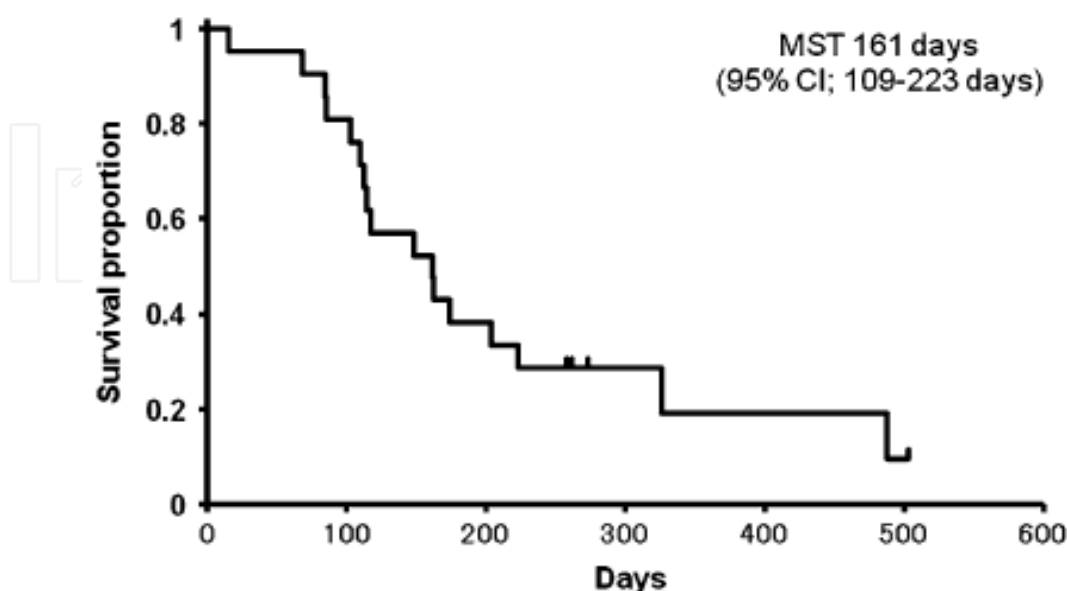

Fig. 5. Overall survival of patients with advanced pancreatic cancer treated with gemcitabine-based chemotherapy plus curcumin (n = 21) (adapted from Kanai et al. 2011)

Interestingly, several patients reported an improvement in cancer- or chemotherapy-related symptoms (e.g. fatigue, pain, constipation). We cannot rule out the placebo effect; however, several preclinical studies demonstrating that curcumin can improve fatigue, depression or neuropathic pain support our current observation (Gupta *et al.*, 2011; Sharma *et al.*, 2006; Xu *et al.*, 2005). Therefore, curcumin could improve the quality of life of patients with pancreatic cancer by alleviating cancer-related symptoms, and this could indirectly contribute to the improved overall survival.

Recently, another clinical trial has been reported by Epelbaum et al., who investigated the efficacy and feasibility of curcumin in combination with gemcitabine monotherapy in patients with advanced pancreatic cancer (Epelbaum *et al.*, 2010). Seventeen chemo-naïve patients were enrolled and received a standard dose and schedule of gemcitabine in combination with 8 g of daily oral curcumin. In contrast to our results showing a good compliance rate and low toxicity using 8 g of daily oral curcumin, this study reported that 5 patients (29%) discontinued curcumin after a few days to 2 weeks due to intractable abdominal fullness or pain. Furthermore, the dose of curcumin was reduced to 4 g/day because of abdominal complaints in 2 other patients. They discussed the possibility that increased gastrointestinal toxicity could be caused by the combination of curcumin and gemcitabine and concluded that 8 g of oral curcumin is not feasible when combined with gemcitabine in patients with pancreatic cancer. The reasons for the discrepancy between our study and that of Epelbaum et al. are unclear at this moment. Ethnic differences may exist in compliance to the combination therapy of curcumin and gemcitabine. Another possible explanation is that the patients' clinical condition at base line was poorer in Epelbaum's study than in ours, and abdominal fullness or pain could therefore be mainly attributable to cancer-related symptoms.

Table 1 summarizes the published clinical trials using curcumin in patients with pancreatic cancer.

	Dhillon et al.	Epelbaum et al.	Our study
Sample size	25	17	21
Study design	Phase II	Phase II	Phase I/II
Study period	2008*	2004-2006	2008-2009
Dose of curcumin	8 g/day	8 g/day	8 g/day
Prior history of chemotherapy	22	none	21
Combination with gemcitabine	no	yes	yes
Toxicity attributable to curcumin	none	7 (Abdominal discomfort)	none

* Publication year

Table 1. Comparison of the published clinical trials using curcumin in patients with pancreatic cancer

5. Development of a new form of curcumin with improved bioavailability

Several investigators, including ourselves, have tested plasma curcumin levels in clinical trials, and most studies report that plasma curcumin levels remained at low ng/ml levels in spite of taking gram doses of curcumin (Cheng *et al.*, 2001; Garcea *et al.*, 2005; Kanai *et al.*, 2010; Sharma *et al.*, 2004; Shoba *et al.*, 1998) (Table 2). As described in the previous section, the intake of more than 8 g of oral curcumin did not lead to a further increase in plasma curcumin levels in human subjects (Cheng *et al.*, 2001; Lao *et al.*, 2006; Vareed *et al.*, 2008). Thus, poor bioavailability is the major weak point of curcumin and has been the main challenge for physicians seeking to verify the therapeutic efficacy of this promising agent in clinical trials. Therefore, many efforts have been made to improve its bioavailability through several approaches including innovative drug delivery systems (liposomes, nanoparticles and phospholipids) (Anand *et al.*, 2010; Antony *et al.*, 2008; Bisht *et al.*, 2007; Das *et al.*, 2010; Gupta *et al.*, 2009; Koppolu *et al.*, 2010; Li *et al.*, 2005; Liu *et al.*, 2006; Marczylo *et al.*, 2007; Mukerjee & Vishwanatha, 2009; Sahu *et al.*, 2008; Shaikh *et al.*, 2009; Sou *et al.*, 2008; Takahashi *et al.*, 2009), or the development of new curcumin analogues (Lin *et al.*, 2011; Mosley *et al.*, 2007; Ohori *et al.*, 2006; Sato *et al.*, 2011). A nanoparticle-based drug delivery system is effective in improving the water solubility of hydrophobic agents like curcumin, and the development of at least 8 different types of nanoparticle-based curcumin have been published up to this point (Anand *et al.*, 2010; Bisht *et al.*, 2007;

Subjects	Dose of curcumin	Sample size	Plasma curcumin level (mean ± SE)	Reference
Healthy volunteers	2 g/day	8	6 ± 5 ng/ml	(Shoba *et al.*, 1998)
Patients with precancerous lesions	8 g/day	2	651 ± 688 ng/ml	(Cheng *et al.*, 2001)
Patients with colorectal ca.	3.6 g/day	3	4 ± 0.2 ng/ml	(Sharma *et al.*, 2004)
Healthy volunteers	12 g/day	3 (1)	57 ng/ml[*1]	(Lao *et al.*, 2006)
Patients with colorectal ca.	3.6 g/day	3	below 1 ng/ml	(Garcea *et al.*, 2005)
Healthy volunteers	8 g/day	6	2300 ± 260 ng/ml	(Vareed *et al.*, 2008)
Patients with pancreatic ca.	8 g/day	5	134 ± 70 ng/ml	(Kanai *et al.*, 2010)
Healthy volunteers	0.03 g/day[*2]	7	29.5± 13 ng/ml	(Sasaki, 2011)
Healthy volunteers	0.21 g/day[*2]	6	275 ± 67 ng/ml	(Kanai *et al.*, 2011)

[*1] Plasma curcumin was detected in only one subject.

[*2] THERACURMIN®was used in these studies

Table 2. Comparison of the published plasma curcumin levels in human subjects (adapted from Kanai et al. 2011)

Das *et al.*, 2010; Gupta *et al.*, 2009; Mukerjee & Vishwanatha, 2009; Sasaki, 2011; Shaikh *et al.*, 2009; Sou *et al.*, 2008).

Out of these new forms of nanoparticle-based curcumin, we chose to focus on THERACURMIN®, which demonstrated a more than 30-fold higher bioavailability compared to that of conventional curcumin in rat models (Sasaki, 2011). We conducted a dose-escalation and pharmacokinetic study using this newly developed nanoparticle curcumin to verify its improved bioavailability in human subjects. Six healthy human volunteers were recruited and received THERACURMIN® at a single oral dose of 150 mg. After an interval of 2 weeks, the same subjects then received THERACURMIN® at a single oral dose of 210 mg. C_{max} for THERACURMIN® at 150 mg and 210 mg was 189 ± 48 and 275 ± 67 ng/ml (mean ± S.E.M.), respectively and the area under the curve for 24 h was estimated to be 2649 ± 350 and 3649 ± 430 ng/ml × h (mean ± S.E.M.), respectively (Figure 6. Kanai, 2011).

These results indicate that an intake of 150 mg of THERACURMIN® could lead to similar or even higher plasma curcumin levels in comparison with those observed after the intake of 8 g of conventional curcumin (Table 2). As for the safety, only one subject reported grade 1 diarrhea lasting from day 1 to day 4 after 150 mg of THERACURMIN® intake. However, diarrhea did not recur after the second, 210 mg dose of THERACURMIN® intake in this subject. No other adverse events were observed. These results suggest that THERACURMIN® can safely increase plasma curcumin levels in a dose dependent manner up to at least 210 mg without saturating the absorption system. If we can achieve higher plasma curcumin levels, there is a greater chance that patients will benefit from this agent. Therefore, we consider that this new form of curcumin could be a promising tool when testing the potential anticancer effects of curcumin in clinical trials, and we are now conducting clinical trials to test this new agent in patients with pancreatic cancer.
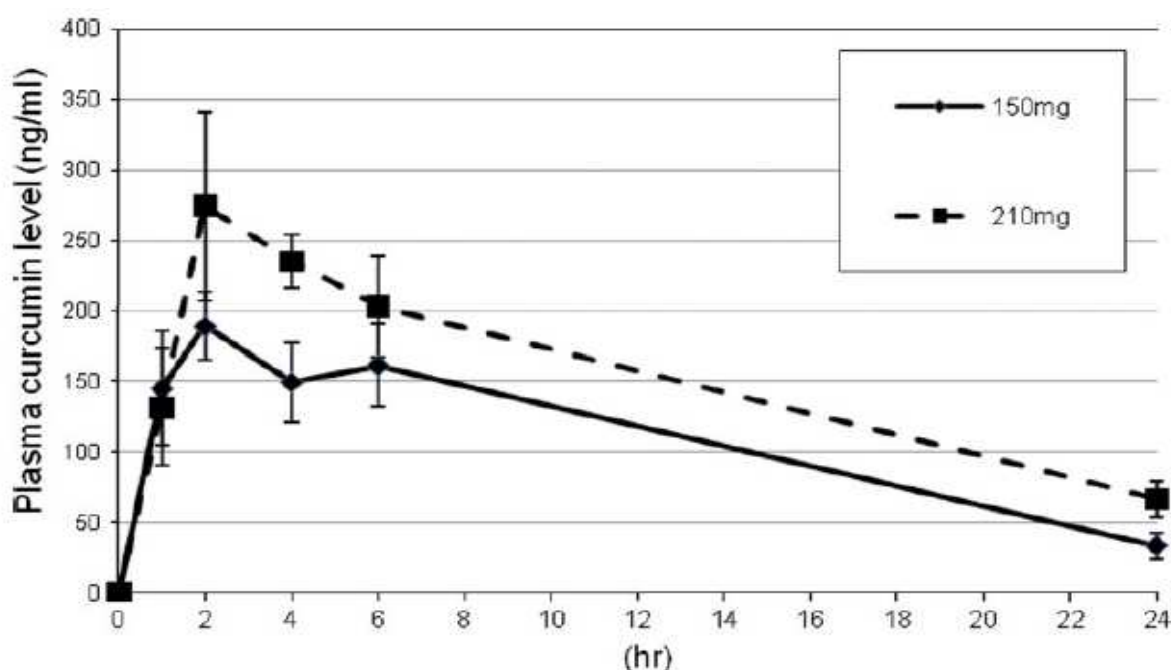

Fig. 6. Time course of plasma curcumin levels after intake of 150mg (solid line) and 210 mg (dash line) of THERACURMIN® (n = 6). Error bar represents S.E.M. (adapted from Kanai et al. 2011)

6. Conclusion

More and more data support the idea that curcumin could be a promising anticancer drug. Curcumin can exhibit anticancer effects through inhibiting diverse signaling pathways with minimal toxicity. On the other hand, poor bioavailability has been the main challenge in demonstrating the benefits of this promising agent in clinical trials. This problem has now been overcome by the development of nanoparticle curcumin and we can achieve higher plasma curcumin levels without saturating the absorption system. We are now conducting clinical trials to test the safety and efficacy of this new form of curcumin in patients with pancreatic cancer.

7. Acknowledgements

8. References

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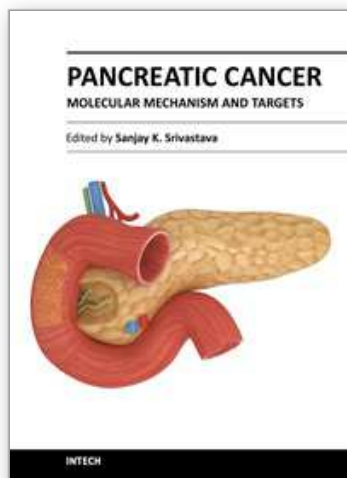
Pancreatic Cancer - Molecular Mechanism and Targets

Edited by Prof. Sanjay Srivastava

This book provides the reader with an overall understanding of the biology of pancreatic cancer, hereditary, complex signaling pathways and alternative therapies. The book explains nutrigenomics and epigenetics mechanisms such as DNA methylation, which may explain the etiology or progression of pancreatic cancer. Book also summarizes the molecular control of oncogenic pathways such as K-Ras and KLF4. Since pancreatic cancer metastasizes to vital organs resulting in poor prognosis, special emphasis is given to the mechanism of tumor cell invasion and metastasis. Role of nitric oxide and Syk kinase in tumor metastasis is discussed in detail. Prevention strategies for pancreatic cancer are also described. The molecular mechanisms of the anti-cancer effects of curcumin, benzyl isothiocyante and vitamin D are discussed in detail. Furthermore, this book covers the basic mechanisms of resistance of pancreatic cancer to chemotherapy drugs such as gemcitabine and 5-flourouracil.

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