Preclinical studies for the combination of paclitaxel and curcumin in cancer therapy (Review)

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Abstract. Cancer is one of the most common causes of death and remains the first in China and the second in the US. The common treatments for cancer include surgery, radiation, chemotherapy, targeted therapy and immunotherapy, while chemotherapy remains one of the most important treatments. However, the efficacy of chemotherapy is limited due to drug induced-toxicities and resistance, particularly multiple drug resistance (MDR). Therefore, discovery and development of novel therapeutic drugs and/or combination therapy are urgently needed to reduce toxicity and improve efficacy. Paclitaxel has been widely used to treat various cancers including cervical, breast, ovarian, brain, bladder, prostate, liver and lung cancers. However, its therapeutic efficacy is limited and MDR is a major obstacle. Recently, numerous preclinical studies have shown that the combination of paclitaxel and curcumin may be an ideal strategy to reverse MDR and synergistically improve their therapeutic efficacy in cancer therapy. This review mainly focuses on the current development and progress of the combination of paclitaxel and curcumin in cancer therapy preclinically.

Contents

1. Introduction

As one of the most common causes of death, cancer is a serious health problem globally and the mortality remains the first in China and the second in the US (first in 21 states) and other Western countries (1,2). There were 4,292,000 new cases with 2,814,000 deaths of cancers and the incidence and mortality of lung cancer were the highest in China in 2015 (1). The common treatments for cancer include surgery, radiation, chemotherapy, targeted therapy and immunotherapy, while chemotherapy remains one of the most important treatments (3,4). Numerous chemotherapeutic drugs have been developed and used for the treatment of cancer, such as paclitaxel, cisplatin, 5-fluorouraci, cyclophosphamide, irinotecan, mitomycin C and doxorubicin (5-11). However, the effectiveness of chemotherapy as monotherapy is limited in cancer therapy due to low water solubility, lack of convincing anticancer activity and therapeutic selectivity, and drug resistance especially multiple drug resistance (MDR) (12-15). Therefore, the combination of various chemotherapeutic drugs with different mechanisms has become the standard clinical practice for cancer treatment (16-24).

Paclitaxel is a natural plant alkaloid that is isolated from the bark of the pacific yew tree and the active ingredient was firstly isolated and named as Taxol by Wani and Wall (25-27). Paclitaxel is a mitotic inhibitor for targeting tubulin by stabilizing the microtubule polymer and protecting it from disassembly to prevent the metaphase spindle configuration of chromosomes. Thus, it caused abnormality of mitotic spindle assembly, chromosome segregation, and cell division, resulting in blocking the progression of mitosis and prolonging activation of the mitotic checkpoint to trigger cell apoptosis or blocking cell cycle arrest at G2/M without cell division of treated cells (28-33). Although paclitaxel is widely used for the treatment of various cancers including cervical, breast, ovarian, brain, bladder, prostate, liver and lung cancers, the application of paclitaxel in clinic is significantly limited due to MDR (34-39). Many factors may be responsible for the MDR of paclitaxel and the possible mechanisms are proposed in Fig. 1. The multidrug resistance gene 1 encodes the transporter P-glycoprotein (P-gp) leading to MDR (40-46). The activation of protein kinase B (Akt) and nuclear factor-κB (NF-κB) is the important cause for MDR (47,48). The activation of mitogen-activated protein kinases (MAPKs) is also responsible for MDR (49,50). Therefore, in order to improve the therapeutic effect of paclitaxel, it is necessary to reverse its MDR.

Curcumin is an effective monomer component extracted from the roots of Zingiberaceae. It shows many biological

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functions such as antioxidant, anti-inflammation and especially antitumor (51-55). Many previous studies showed that curcumin inhibited cancer cell growth and reversed MDR through various mechanisms including antiproliferation, induction of apoptosis and blocking cell cycle arrest at G2/M of cancer cells (56,57) as shown in Fig. 2. NF-κB is a nuclear protein and a transcription factor; it is in activated status in a variety of cancers (58). NF-κB plays a key role in the aspects of cell proliferation, differentiation, survival, metastasis, and apoptosis. Curcumin inhibits the activation of NF-κB and NF-κB regulated Akt (59-61). Curcumin reduces the expression levels of c-Jun N-terminal kinase (JNK), MAPK p38 and extracellular signal-regulated kinase (ERK) (62,63). Curcumin blocks cell cycle arrest at G2/M of cancer cells (64-67). Curcumin also inhibits the expression of P-gp, therefore, it may not only become a promising anticancer drug but also an excellent agent for MDR reversal (68-71).

Based on the mechanisms of anticancer action of curcumin, it is rational and valuable to use the combination of paclitaxel and curcumin for synergistic anticancer activity and reversing MDR of paclitaxel (Table I). Numerous previous studies showed that the combination of paclitaxel and curcumin reversed the MDR of paclitaxel and inhibited cancer cell growth more effectively than paclitaxel alone. This review focuses on the combination of paclitaxel and curcumin in cancer therapy for different types of cancers.

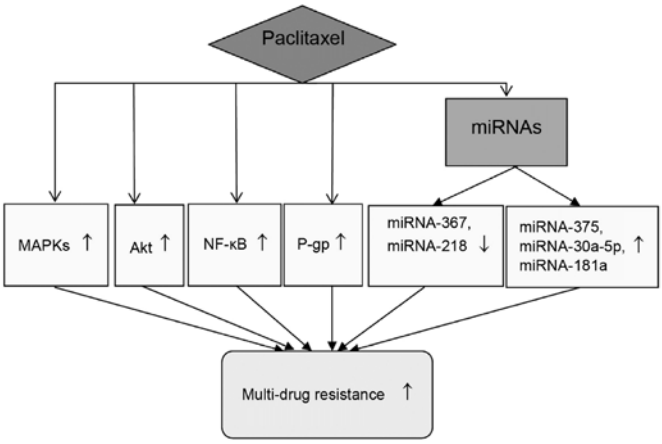

Figure 1. The proposed mechanisms of multiple drug resistance (MDR) of paclitaxel in cancer therapy. ↑ indicates activation, ↓ indicates inhibition. MAPKs, mitogen-activated protein kinases; Akt, protein kinase B; NF-κB, nucleas transcription factor κB; P-gp, P-glycoprotein.

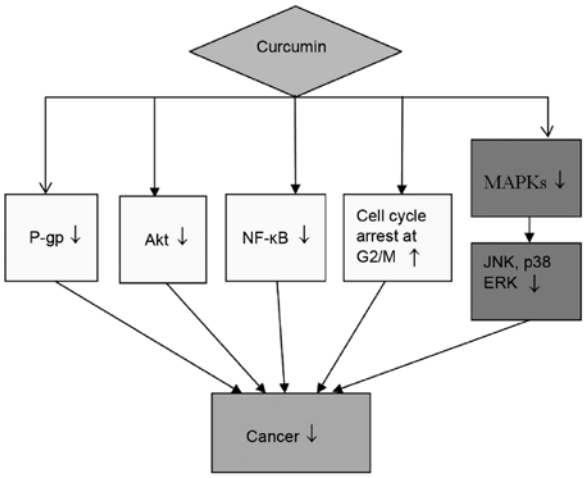

Figure 2. The proposed mechanisms of anticancer activity and multiple drug resistance (MDR) reversal of curcumin in cancer therapy. + indicates activation, - indicates inhibition. P-gp, P-glycoprotein; Akt, protein kinase B; NF-κB, nucleas transcription factor κB; MAPKs, mitogen-activated protein kinases; JNK, c-Jun n-terminal kinase; ERK, extracellular signal-regulated kinase.

2. The combination of paclitaxel and curcumin in cancer therapy

Cervical cancer

Anticancer activity. Cervical cancer is the second most common cancer in female reproductive system and almost 500,000 new cases are diagnosed in women worldwide every year (72). It ranked both the fourth-most common cause of cancer and the fourth-most common cause of death from cancer in women worldwide (73). The commonly used chemotherapeutic drugs for the treatment of cervical cancer include cisplatin, paclitaxel, fluorouracil, gemcitabine, ifosfamide and mitomycin C. Recent studies indicated that the combination of paclitaxel and curcumin was quite effective for the treatment of cervical cancer in preclinical settings (74-78). Studies have demonstrated that curcumin sensitized paclitaxel-induced apoptosis via enhancing the expression of p53, activation of caspase-3, -7, -8 and -9, cleavage of poly(ADP-ribose) polymerase (PARP) and release of cytochrome c by western blot analysis (74,77). Therefore, the combination of paclitaxel and curcumin may have synergistic anticancer effect and be a promising regimen for the treatment of cervical cancer.

Effect on MDR reversal. MDR significantly affects the antitumor activity of paclitaxel against cervical cancer, while reversal of MDR improves its anticancer effect. A study by Bava *et al* showed that paclitaxel could activate NF-κB and Akt leading to the development of MDR of paclitaxel, whereas curcumin was able to reverse MDR of paclitaxel via the inhibition of NF-κB (the inhibition of phosphorylation of IKBa and the reduction of p65-NF-κB subunit) and Akt (74). Cyclooxygenase-2 (COX-2) and cyclin D1 are the most important gene products regulated by NF-κB and Akt. Another study by the same group noted that paclitaxel activated the expression levels of COX-2 and cyclin D1, while curcumin downregulated the expression levels of COX-2 and cyclin D1 (75). The combination of paclitaxel and curcumin could inhibit anti-apoptotic proteins including cellular inhibitor of apoptosis 1 (cIAP1), X-linked inhibitor of apoptosis protein (XIAP) and survivin through the inhibition of NF-κB and Akt (76,77). The study also showed that the combination of paclitaxel and curcumin reversed the MDR of paclitaxel by inhibiting JNK, p38 MAPK and ERK (76). Punfa *et al* reported that the encapsulation of curcumin in polylactic-co-glycolic acid nanoparticles could target P-gp and reduce its expression and the combination of paclitaxel and curcumin reversed the MDR of paclitaxel by targeting P-gp in cervical cancer cells (78).

Breast cancer

Anticancer activity. Breast cancer is the most common cancer in women worldwide (2). At present, paclitaxel is approved

Table I. Effects of the combination of paclitaxel and curcumin on MDR reversal in various cancers.

	Cervical cancer	Breast cancer	Ovarian cancer	Brain cancer	Bladder cancer	Prostate cancer	Liver cancer
MAPKs	-						
NF-κB	-	-	-	-	-		-
Akt	-	-	-	-		-	
P-gp	-	-					
MMP-9			-				
TIMP-2			+				
VEGF				-			
b-FGF				-			
hTERT				-			
Lin28							-
References	(6,74-78)	(83-86)	(8,90-93)	(95,96)	(98)	(103)	(107,108)

'+' indicates activation, '-' indicates inhibition. MAPKs, mitogen-activated protein kinases; NF-κB, nucleas transcription factor κB; Akt, protein kinase B; P-gp, P-glycoprotein; MMP-9, matrix metalloprotein-9; TIMP-2, tissue inhibitors of metalloproteinase-2; VEGF, vascular endothelial growth factor; b-FGF, basic fibroblast growth factor; hTERT, human telomerase reverse transcriptase; Lin28, Lin28 homolog.

and widely used for the treatment of breast cancer in clinic. Various studies have reported that the combination of paclitaxel and curcumin more effectively inhibited breast cancer cells than paclitaxel or curcumin alone due to their synergistic effect (79-87). Faião-Flores *et al* showed that the combination of paclitaxel and curcumin exhibited synergistic anticancer effect for the treatment of breast cancer cells by increasing the release of cytochrome c and activation of caspases, especially caspase-3 (79). Banerjee *et al* reported that curcumin significantly enhanced the apoptotic effect of paclitaxel in breast cancer MCF-7 cells via increasing the expression of p53 and p21 (80). Zhan *et al* showed that combination of paclitaxel and curcumin exhibited synergistic growth inhibition and significantly induced apoptosis via increasing Bcl-2 expression, but decreasing Bax expression in breast cancer MCF-7 cells. Furthermore, the combination of paclitaxel and curcumin potentiated antitumor efficacy of paclitaxel in the mouse models of breast cancer (81). Studies also showed that combining paclitaxel and curcumin with β-cyclodextrin triazine exhibited synergistic anticancer effect for the treatment of breast cancer (82,83).

Effect on MDR reversal. MDR of paclitaxel significantly limits its therapeutic effect and clinical application. Royt *et al* demonstrated that the combination of paclitaxel and curcumin significantly improved the anticancer effect by reversing MDR of paclitaxel via inhibition of NF-κB (84). Inhibition of phosphorylation of IKBa contributed to the inhibition of NF-κB and paclitaxel induced the phosphorylation of IKBa to activate NF-κB (85). However, curcumin inhibited the phosphorylation of IKBa to inhibit the activation of NF-κB (86). Paclitaxel activated the gene products of matrix metalloprotein-9 (MMP-9), COX-2, C-myc and cyclin D1, while curcumin inhibited their activation through inhibition of NF-κB and Akt (85,86). Wang *et al* developed a multifunctional anti-cancer nanomedicine loaded with magnetic nanoparticles (MNPs), paclitaxel and curcumin and showed that the nanoparticles reduced the expression of P-gp and increased paclitaxel accumulation in breast cancer MCF-7/ADR cells, thereby, enhancing the therapeutic efficacy of paclitaxel against breast cancer cells and the effect was due to reversing MDR of paclitaxel through inhibition of P-gp by curcumin (87).

Ovarian cancer

Anticancer activity. Ovarian cancer is one of the most common cancers in the female reproductive system and the fifth most common cause of cancer deaths in women worldwide; its incidence has been increasing recently (2). Paclitaxel has been used for the treatment of ovarian cancer for many years. Numerous studies have shown that the combination of paclitaxel and curcumin was more effective than paclitaxel alone for the treatment of ovarian cancer preclinically (82,88-93). The expression of potassium channel TREK-1 was increased in ovarian cancer cells and the inhibitors of potassium channels could inhibit the cell growth and proliferation of ovarian cancer cells. A study by Innamaa *et al* showed that curcumin inhibited ovarian cancer cell proliferation via inhibition of TREK-1 and enhanced the anticancer effect of paclitaxel against ovarian cancer (89). Deng *et al* reported that the combination of paclitaxel and curcumin blocked cell cycle arrest at G2/M and showed synergistic anticancer effect against human ovarian cancer cells HO-8910 (90).

Effect on MDR reversal. Paclitaxel is the substrate of P-gp and cytochrome P450 3A2 (CYP3A2). Ganta *et al* reported that curcumin inhibited the expression of P-gp and CYP3A2 to enhance the bioavailability of paclitaxel and sensitized human ovarian cancer cells expressed P-gp and CYP3A2 to paclitaxel treatment (88). The transferrin (TF) receptor is increased in ovarian tumor cells because iron is necessary for DNA synthesis of the cells (91). Therefore, TF-targeted mixed

micelles with paclitaxel and curcumin increased the inhibitory effect on ovarian cancer cells and reversed MDR of paclitaxel via inhibition of NF-κB and Akt (92,93). MMP-9 is involved in cancer cell proliferation and metastasis by promoting tumor angiogenesis and is inhibited by tissue inhibitors of metalloproteinase-2 (TIMP-2). Deng *et al* reported that paclitaxel increased the expression of MMP-9 and reduced the expression of TIMP-2, leading to MDR. However, curcumin reduced the expression of MMP-9 and increased the expression of TIMP-2. Therefore, the combination of paclitaxel and curcumin can inhibit the growth of ovarian cancer cells by reversing MDR of paclitaxel (90).

Brain cancer

Anticancer activity. Brain cancer is the leading cause of death for children under the age of 19 (2). Glioblastoma is the deadliest brain tumor and highly resistant to anticancer drugs (94). Investigations have proved that the combination of paclitaxel and curcumin induced apoptosis of cancer cells and inhibited tumor growth more effectively than paclitaxel alone in a dose-dependent manner for the treatment of brain cancer (95,96). Hossain *et al* demonstrated that the combination of paclitaxel and curcumin activated the expression of caspase-3 and caspase-8 to induce cell apoptosis in human brain cancer LN18 and U138MG cells by western blot analysis (95). Bcl-2 family proteins such as Bax and Bcl-2 are the regulators of apoptosis, Bax promotes apoptosis but Bcl-2 inhibits apoptosis. In this paper, Hossain *et al* also reported that the combination of paclitaxel and curcumin significantly up-regulated the expression of Bax, while greatly downregulated the expression of Bcl-2 in human brain cancer cells (95). Therefore, the results indicate that the combination of paclitaxel and curcumin exhibited synergistic anticancer effect for the treatment of brain cancer. Cui *et al* developed magnetic nanoparticles with the combination of paclitaxel and curcumin, and found that the combination yielded synergistic effects with significant inhibition of brain cancer cell growth compared to the single drug via apoptosis induction and cell cycle arrest. Furthermore, the magnetic nanoparticles with the combination of paclitaxel and curcumin greatly increased the survival rate of mice in an orthotopic mouse model of glioma (97).

Effect on MDR reversal. MDR of paclitaxel is developed mainly due to the activation of NF-κB and Akt, which are the mediators of cell survival, proliferation and metastasis. The activation of matrix metalloprotein-2 (MMP-2), MMP-9, survivin, human telomerase reverse transcriptase (hTERT), vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (b-FGF) also results in MDR of paclitaxel. MDR is a major problem for paclitaxel in the treatment of brain cancer. Curcumin could inhibit the expression levels of NF-κB, Akt, MMP-2, MMP-9, survivin, hTERT, VEGF, and b-FGF, therefore, the combination of paclitaxel and curcumin could enhance the anticancer effect of paclitaxel for the treatment of brain cancer by reversing MDR of paclitaxel (95). A study by Manju *et al* also showed that the multifunctional magnetic nanoparticles (MNPs) loaded with paclitaxel and curcumin showed stronger anticancer effect than the combination of paclitaxel and curcumin freely by targeting and reducing P-gp for the treatment of brain cancer (96).

Bladder cancer

Anticancer activity. Bladder cancer is the most common cancer in the urinary system and the ninth most common cancer worldwide (72). The common chemotherapeutic drugs for the treatment of bladder cancer include cisplatin, carboplatin, gemcitabine, paclitaxel, docetaxel, doxorubicin, fluorouracil, methotrexate, vinblastine, ifosfamide, and pemetrexed. Kamat *et al* demonstrated that the combination of paclitaxel and curcumin blocked cell cycle arrest at G2/M in human bladder cancer cells and showed synergistic therapeutic effect against bladder cancer (98).

Effect on MDR reversal. Kamat *et al* also reported that curcumin reversed MDR of paclitaxel by inhibiting NF-κB to greatly enhance the effects of paclitaxel on proliferation inhibition and apoptosis induction compared to paclitaxel alone in bladder cancer cells (98).

Prostate cancer

Anticancer activity. Prostate cancer is the most common cause of cancer and the second-most common cause of death from cancer among men worldwide (2,72). Numerous studies have showed that the combination of paclitaxel and curcumin were more effective than paclitaxel alone against prostate cancer through various mechanisms (99-101). Proliferation cell nuclear antigen (PCNA) and MMP-2 are both involved in cell proliferation and invasion of prostate cancer cells. Zhao *et al* have showed that the combination of paclitaxel and curcumin significantly decreased the quantities and expression levels of PCNA and MMP-2 in prostate cancer cells compared to paclitaxel alone (99). Tumor cell immigration from one organ to another contributes to tumor metastasis. Paclitaxel or curcumin alone could reduce the immigration of cancer cells and the combination of paclitaxel and curcumin exhibited synergistic antimetastasis effect in prostate cancer via inhibition of cell immigration (100). The results from the studies of Huang *et al* indicated that the expression of Bcl-2 was inhibited and the expression of Bax was enhanced when prostate cancer cells were treated with the combination of paclitaxel and curcumin (101). The study by Thomas *et al* also showed that the combination of paclitaxel and curcumin could effectively inhibit the growth of prostate cancer cells by activating the expression levels of p21 and p53 to influence cell apoptosis (102).

Effect on MDR reversal. Mathur *et al* reported that the combination of paclitaxel and curcumin reversed MDR of paclitaxel and enhanced anticancer activity by inhibiting PI3K/Akt in prostate cancer cells (103).

Liver cancer

Anticancer activity. Liver cancer is one of the most common cancers and the second (in the USA) or third (worldwide) most common cause of deaths from cancer (2,73,104). China has the highest rates of incidence and mortality of liver cancer in the world (105). The chemotherapeutic drugs such as 5-fluorouracil, doxorubicin, and cisplatin have been used for the treatment of liver cancer for many years. However, the effects of treatment are unsatisfactory because of MDR and other factors, resulting in the average survival time of only

between 6 and 20 months (106). In general, liver cancer cells are highly resistant to paclitaxel (106). However, the studies by Zhou *et al* showed that curcumin significantly enhanced the sensitivity of liver cancer Hep3B cells to paclitaxel and the combination of paclitaxel and curcumin may provide a superior therapeutic index for the treatment of liver cancer (107).

Effect on MDR reversal. Lin28 is an RNA-binding protein that inhibits the process of pre-let-7 miRNAs to reduce tumorigenesis (108). Zhou *et al* found that the expression of Lin28 was directly activated by NF-κB and associated with the resistance of paclitaxel to liver cancer cells (107). Curcumin could down-regulate the expression of Lin28 and NF-κB activation induced by paclitaxel to enhance the sensitivity of liver cancer cells to paclitaxel. Therefore, the combination of paclitaxel and curcumin showed synergistic effects on cell growth inhibition and apoptotic induction against liver cancer cells by reversing MDR of paclitaxel.

Lung cancer

Anticancer activity. Lung cancer is the most common cancer and most common cause of death from cancer worldwide (2,73). The mortality of lung cancer has declined and survival rate has increased in the United Kingdom and the United States (109). However, the incidence and mortality of lung cancer are still increase in the developing countries, therefore, substantial efforts are needed to decrease the mortality of lung cancer. The studies by Boztas *et al*, found that the combination of paclitaxel and curcumin synergistically improved paclitaxel induced apoptosis in lung cancer H1299 cells, and enhanced the cell growth inhibition for a low IC_{50} values for the combination compared to paclitaxel or curcumin alone (82). Therefore, the combination of paclitaxel and curcumin may be an excellent choice for the treatment of lung cancer due to the synergistic anticancer effect. Muthoosamy *et al* developed a drug delivery system loaded with paclitaxel and curcumin by functionalizing reduced graphene oxide with an amphiphilic polymer PF-127 via hydrophobic assembly. Cell proliferation assay showed highly potent synergistic effect with the combination to inhibit the cell growth of lung cancer cells A549 with IC_{50} ~13.24 μg/ml (110). The possible mechanism may be associated with increased reactive oxygen species, mitochondrial membrane potential depletion and cell apoptosis (110).

Effect on MDR reversal. Study by Su *et al* showed that several drugs could induce drug resistance with increased expression of the multidrug resistance-associated protein (MRP1) but paclitaxel reversed drug-induced drug resistance in small cell lung cancer cells (111). Since curcumin also could reverse MDR induced by paclitaxel and other chemotherapeutic drugs in various cancers, the combination of paclitaxel and curcumin may have synergistic effects in reversing MDR in lung cancer cells.

3. Conclusion

Paclitaxel has been widely used for the treatment of various cancers including cervical, breast, ovarian, brain, prostate, liver and lung cancers. However, MDR greatly limits the anticancer efficacy and clinical application of paclitaxel. As we discussed in this review that curcumin alone or in combination with chemotherapeutic drugs may alter the signaling pathways and molecular interactions which regulate MDR. Numerous cell and animal studies have showed that the combination of paclitaxel and curcumin exhibited synergistic anticancer effect and reverse MDR of paclitaxel in various cancers therapy. Therefore, it is speculated that the combination of paclitaxel and curcumin may be an ideal strategy in clinical practice for cancer treatment. However, owing to the low water solubility of curcumin and paclitaxel, the combination of paclitaxel and curcumin may not be suitable to be administered as an intravenous infusion. Moreover, the formulation suitable for parenteral administration of the original product Taxol has to contain additional surfactants such as Cremophor EL that may cause acute hypersensitivity reactions and peripheral neuropathy. Therefore, the dosage for easy dissolution and absorption is the most serious challenge in clinical practice.

The prospect of the combination of paclitaxel and curcumin in clinical application for cancer therapy appears to be promising but also challenging. Therefore, the feasibility and effectiveness of the combination should be further evaluated in clinical studies. To our knowledge, there is no report of the combination of paclitaxel and curcumin in clinical setting for cancer treatment from the literature up to date. However, paclitaxel has been widely used for the treatment of patients with different cancers. Clinical trials of curcumin alone or in combination with other anticancer drugs have been reported and the safety and tolerability of curcumin in patients have been well-established in clinical studies (112-116). Dhillon *et al* reported a phase II trial of curcumin in patients with advanced pancreatic cancer (112). The results showed that oral administration of 8 g curcumin to the patients daily is well tolerated and has biological activity in some patients with pancreatic cancer (112). The combination of curcumin and gemcitabine in patients with advanced pancreatic cancer has also been reported (113). In addition, a randomized control trial has been conducted for the combination of curcumin with standard care FOLFOX (oxaliplatin + fluorouracil + folinic acid) chemotherapy in patients with inoperable colorectal cancer (114). Noteworthy, there are studies on the combination of docetaxel (a taxane derivative with similar chemical structure of paclitaxel) and curcumin in patients with advanced and metastatic breast cancer or castration-resistant prostate cancer (115,116). The results indicate that some improvements were observed for biological and clinical responses in most breast cancer patients and a high response rate, good tolerability and patient acceptance were achieved in prostate cancer patients. Furthermore, the low bioavailability of curcumin could be markedly improved via the use of structural analogues or special formulations such as highly bioavailable curcumin (Theracurmin) and/or liposomal curcumin (117,118). In addition, paclitaxel and curcumin could be encapsulated in biodegradable nanoparticles to avoid acute hypersensitivity reactions and peripheral neuropathy from Cremophor EL.

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