


# The Emerging Potential of Parthenolide Nanoformulations in Tumor Therapy

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**Abstract:** Plant-derived sesquiterpene lactones are promising natural sources for the discovery of anti-cancer drugs. As an extensively studied sesquiterpene lactone, the tumor suppression effect of parthenolide (PTL) has been clarified by targeting a number of prominent signaling pathways and key protein regulators in carcinogenesis. Notably, PTL was also the first small molecule reported to eradicate cancer stem cells. Nevertheless, the clinical application of PTL as an antitumor agent remains limited, owing to some disadvantages such as low water solubility and poor bioavailability. Thus, nanomedicine has attracted much interest because of its great potential for transporting poorly soluble drugs to desired body sites. In view of the significant advantages over their free small-molecule counterparts, nanoparticle delivery systems appear to be a potential solution for addressing the delivery of hydrophobic drugs, including PTL. In this review, we summarized the key anticancer mechanisms underlined by PTL as well as engineered PTL nanoparticles synthesized to date. Therefore, PTL nanoformulations could be an alternative strategy to maximize the therapeutic value of PTL.

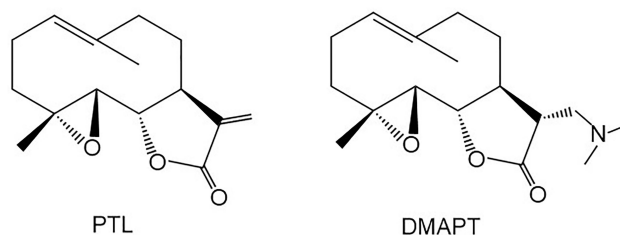
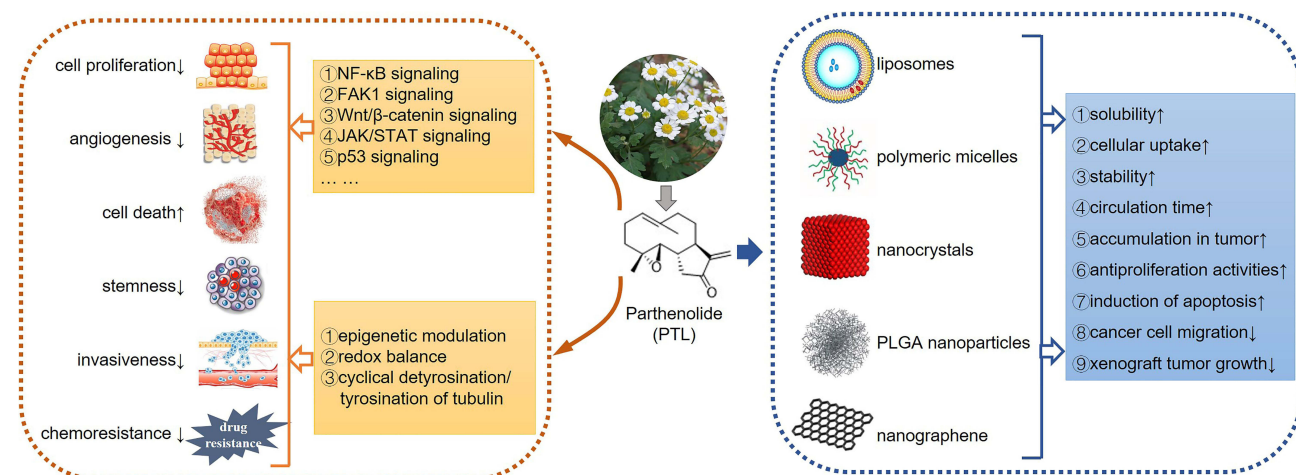
**Keywords:** parthenolide, signaling pathways, cellular processes, nanomedicine, cancer therapy

## Introduction

As a medical herb, Feverfew (*Tanacetum parthenium*) is conventionally used in Europe to treat fever, inflammation, migraines, rheumatoid arthritis, and menstrual irregularities. Parthenolide (PTL, [Figure 1](#)) is a sesquiterpene lactone found in feverfew, which is currently considered to be responsible for the herb's therapeutical potential.<sup>1</sup> Initially, conventional extraction methods using chloroform and petroleum ether were performed to extract PTL; various extraction methods have been developed, such as high-performance liquid chromatography (HPLC), Soxhlet extraction, supercritical fluid extraction (SFE) and microwave-assisted extraction (MAE).<sup>1,2</sup>

The anti-cancer property of PTL was firstly validated in 1973. Furthermore, its patent application for tumor suppression was approved in 2005.<sup>3</sup> Additionally, the in vitro and in vivo antitumor potential of PTL in multiple cancer types has been confirmed by numerous researches, which mainly resulted from its cytotoxicity to the bulk population of cancer cells as well as from selectively targeting cancer stem cells (CSCs); it is a subpopulation currently believed to be responsible for chemotherapy resistance and tumor relapse.<sup>3-10</sup> Further studies revealed a series of direct PTL targets [p65, IκB kinase (IKK), focal adhesion kinase 1 (FAK1), and others] that indirectly affect signaling pathways, which account for cell cycle arrest, apoptosis induction, metastasis suppression, redox imbalance, and epigenetic regulation involved in PTL's antitumor properties.<sup>3,4,11,12</sup> The potential utility of PTL as radio-sensitization agent and complementary therapy against various cancers has also been widely studied and summarized.<sup>13-15</sup> As reviewed by Malgorzata et al, PTL has been combined with various anticancer agents, such as tubulin-directed agents, anthracyclines, antimetabolites, histone deacetylase inhibitors, mTOR inhibitors, and inducers of reactive oxygen species (ROS).<sup>14</sup>

## Graphical Abstract



**Figure 1** Chemical structure of PTL and DMAPT.

Despite its deciphered anticancer potential and mechanisms of action in pre-clinical experiments, the clinical application of PTL remains hindered because of some disadvantages, including weak aqueous solubility, low oral bioavailability, and relative instability under chemical and physiological conditions.<sup>16,17</sup> As a result, various methods for synthesizing PTL derivatives to yield compounds with better hydrophilicity and improved potency have been proposed.<sup>4,6,18</sup> Dimethylamino parthenolide (DMAPT, **Figure 1**), a representative among hydrophilic PTL analogues, showed improved water solubility and oral bioavailability. Thus, it has advanced into the first phase of a clinical trial for the treatment of acute myeloid leukemia (AML).<sup>19</sup>

Nanomedicine is a rapidly developing field that exploits nanoparticles (NPs) to facilitate the diagnosis and treatment of a wide range of diseases. Nanoparticles applied in nanomedicine generally refer to a type of colloidal drug delivery system, which comprises particles with a size range from 10 to 200 nm in diameter.<sup>20</sup> By far, diverse types of nanoparticles have been developed as drug carriers, including but not limited to liposomes, polymeric micelles, carbon nanotubes, mesoporous silica nanoparticles, metal-based nanoparticles, and dendrimers. Moreover, these can be made of diverse materials, including lipids, phospholipids, polymers, proteins, and inorganic materials.<sup>21,22</sup>

Compared with free drug counterparts, nanoparticles entrapment has displayed distinct advantages, such as improved bioavailability, prolonged circulation time, and ease of functionalization by surface modification. Furthermore, the enhanced permeability and retention (EPR) effect caused by the large amount of leaky vascularization and impaired lymphatic drainage at the tumor site enables non-targeted nanoparticles to accumulate in tumor tissues.<sup>23</sup> Some of these nanoparticles have been approved as cancer therapeutics by the Food and Drug Administration.<sup>21</sup> Besides the chemical modification of PTL for property improvement, the development of nanoscale drug delivery systems offers another promising strategy to overcome the poor water solubility and bioavailability of PTL as well as to determine its efficient

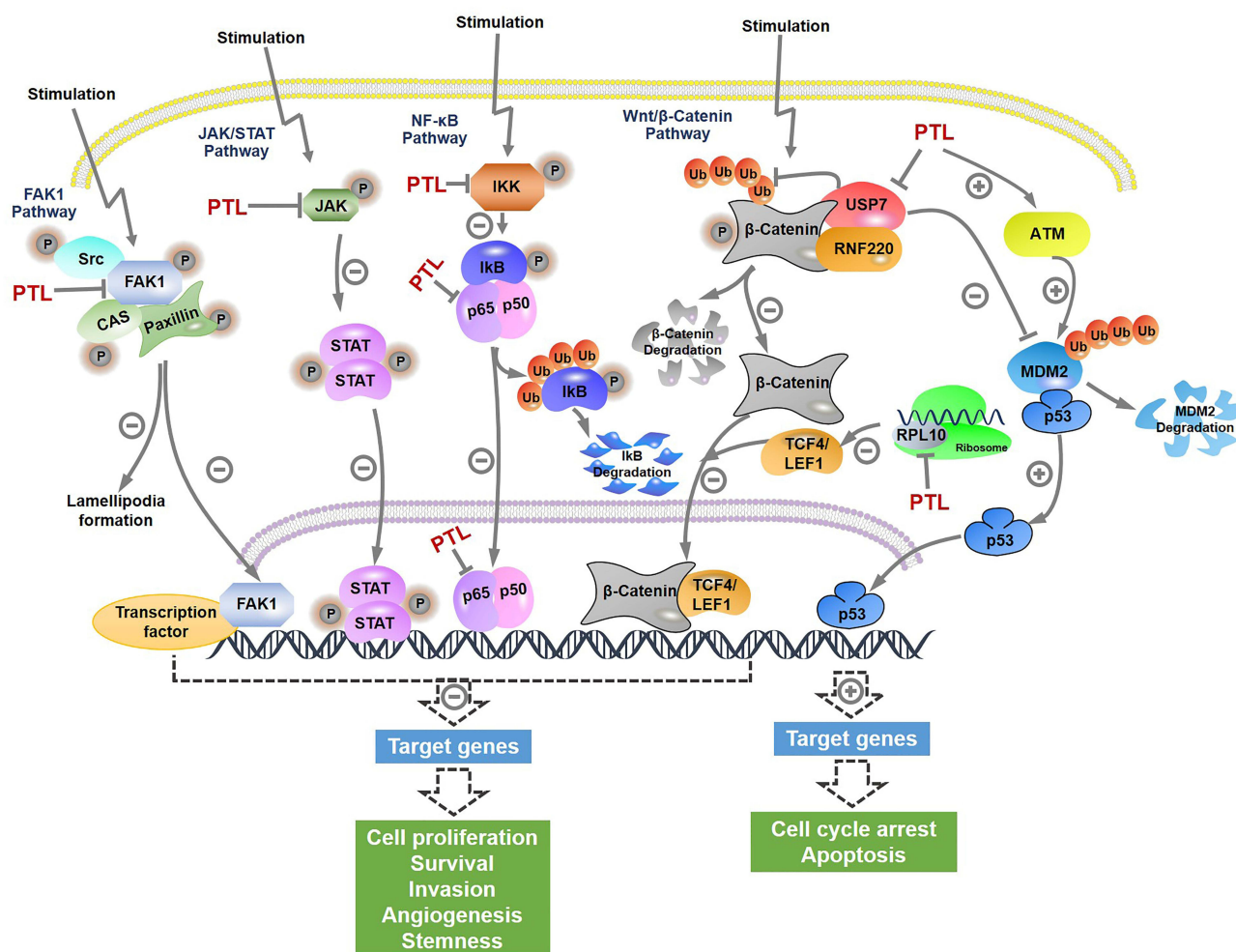
and selective delivery to tumor tissues; the latter of which has not been summarized as compared to the extensively reviewed bioactivities and combination treatments of PTL. Therefore, we focused on the key antitumor mechanisms of PTL as well as its efficiency in being formulated as a nanoparticle delivery system.

## Antitumor Mechanisms of PTL

Current evidence demonstrates that the antitumor mechanism of PTL is multifactorial and complex, due to the high electrophilic reactivity of  $\alpha$ -methylene- $\gamma$ -lactone present in PTL, thereby resulting in the alkylation of various proteins. A number of PTL targets have thus been identified and summarized.<sup>4</sup> Furthermore, newer potential targets of PTL, such as USP7 and EGFR, continue to be reported,<sup>24–27</sup> thereby giving rise to the regulatory effect of PTL on various signaling pathways (Figure 2) and cellular processes (Figure 3) responsible for proliferation, cell cycle regulation, stemness, cell death, angiogenesis and metastasis.<sup>3,4</sup> Thus, it is not surprising that PTL displays diverse anticancer effects, including abrogated cell viability and angiogenesis, cell cycle arrest, cell death induction, and decrease in stemness, invasiveness, and chemoresistance (Table 1).

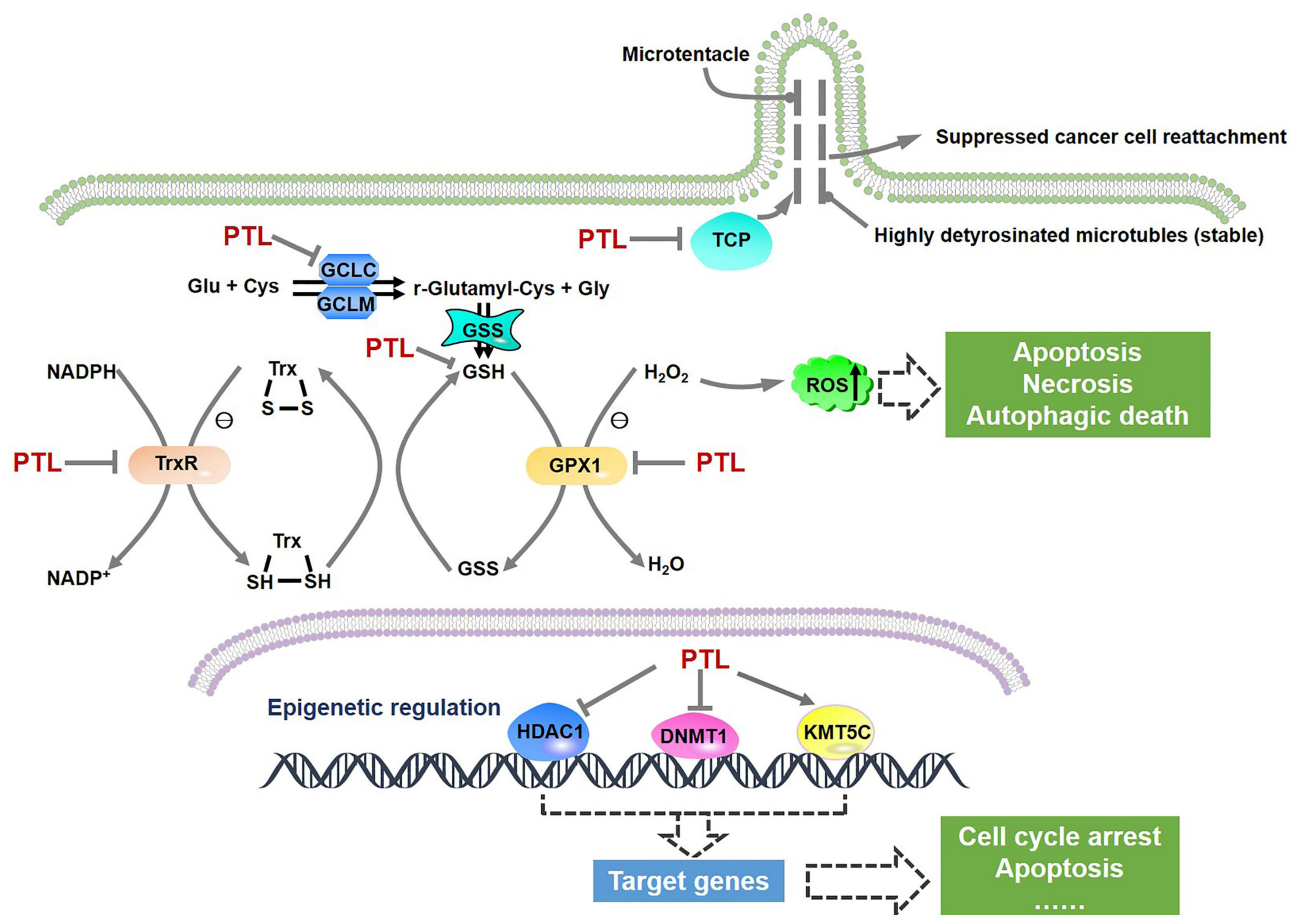
## Signaling Pathways Affected by PTL

As shown in Figure 2, several signaling pathways closely related to tumorigenesis and progression were suppressed by PTL; among these, the prominent NF- $\kappa$ B signaling pathway was the first to be inhibited. Mechanism investigation



**Figure 2** Selected signaling pathways regulated by PTL. The key components and signal transduction cascade reactions in NF- $\kappa$ B signaling, Wnt/ $\beta$ -catenin signaling, JAK/STAT signaling, FAK1 signaling, and p53 signaling were depicted, and the nodes targeted by PTL were labeled.

**Notes:**  $\ominus$  Represents the inhibitory effect, and  $\oplus$  Represents the activation effect.



**Figure 3** Pivotal cellular processes affected by PTL. Schematic diagram showing the formation of microtentacle and major antioxidant machineries were plotted. The targets regulated by PTL were marked.

**Note:** ↑ Represents the accumulation of ROS.

illustrated that PTL inhibited NF- $\kappa$ B signaling by alkylating cysteine 38 in p53 and cysteine 179 in IKK.<sup>28,29</sup> Additionally, a later study predicted that tumor necrosis factor receptor-associated factor 6 (TRAF6) might have been a novel target involved in the PTL-associated inhibition of NF- $\kappa$ B.<sup>30</sup> Moreover, the role of PTL in preventing NF- $\kappa$ B activation contributed to the suppression of hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) signaling.<sup>31</sup> Recent studies have elucidated that PTL inhibited Wnt/ $\beta$ -catenin signaling by targeting ubiquitin specific peptidase 7 (USP7) and ribosomal protein L10 (RPL10), a deubiquitination enzyme stabilizing  $\beta$ -catenin and a ribosomal protein related to the synthesis of the transcriptional regulator 4/lymphoid enhancer binding factor 1 (TCF4/LEF1), respectively.<sup>24,32</sup> Furthermore, FAK1 and janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling were found to be impaired by PTL by covalently modifying specific cysteine molecules.<sup>33,34</sup>

Apart from inhibiting the aforementioned signaling pathways, PTL also activated p53 functions by promoting the ubiquitination of E3 ligase murine double minute 2 (MDM2) in an ataxia-telangiectasia mutated (ATM)-dependent manner, thus leading to either cell cycle arrest or apoptosis.<sup>35</sup> Specially, USP7 was reported to interact with and stabilize MDM2 and p53.<sup>36,37</sup> Thus, the inhibitory effect of PTL on USP7 might be a further step for activating p53 and inhibiting NF- $\kappa$ B. Additionally, the activation of c-Jun N-terminal kinase (JNK) by PTL enhanced the sensitivity of human cancer cells to tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) or tumor necrosis factor-related apoptosis-inducing ligand (TRAIL).<sup>38,39</sup>

## Cellular Processes Influenced by PTL

To date, PTL has been found to exert antitumor effects on several cellular processes, including redox balance and epigenetic modulation; the targets involved in these two processes have also been revealed (Figure 3). Several studies

**Table I** Pharmacological Activities of PTL in Tumors (Since 2019)

Tumor Types	Cell Lines and Efficacy [IC <sub>50</sub> , μM (Exposure Time)]	Pharmacological Activities	Mechanisms of PTL Action	In Vivo Model	Ref
Prostate cancer	LNCaP: 8.9±1.9 (72 h); LNCaP—C42B4: 43.8±4.1 (72 h); PC3: 2.7 ±1.1 (72 h); DU145: 4.7±1.9 (72 h); RMI-BT: 3.9±0.4 (72 h); Mat-Ly-Lu: 18.7±2.8 (72 h)	cytotoxicity, induction of apoptosis	Caspase-3 activation	NA	51
Leukemia	AML: HL-60: 3.54 ± 0.44 (72 h); HL-60/ADR (adriamycin resistant): 2.52 ± 1.90 (72 h)	cytotoxicity	NA	NA	52
	ALL: Jurkat: 16.1 (48 h)	cytotoxicity	NA	NA	53
	K562: 18.57 (24 h) and 7.52 (48 h); K562/ADM: 19.75 (24 h) and 8.55 (48 h); LSCs from K562: 32.45 (24 h) and 21.33 (48 h); LSCs from K562/ADM: 32.37 (24 h) and 26.01 (48 h)	Cytotoxicity, apoptosis induction, eliminated drug-resistant LSCs and enhanced the sensitivity of K562/ADM cells to doxorubicin-induced apoptosis	Downregulation of NF-κB activity and mediated P-gp expression; increasing ROS, Bax/Bcl-2 ratio and cytochrome C expression.	NA	64
Breast cancer	MDA-MB-231: 3.48 ± 1.19 (72 h); SUM-159: 3.06 ± 0.94 (72 h); MCF-7: 2.68 ± 0.83 (72 h); Bcap-37: 4.63 ± 1.07 (72 h); 4T-1: 4.09 ± 0.03 (72 h)	cytotoxicity	NA	NA	54
	SUM149: 4.1 (48 h); MDA-MB-468: 4.5 (48 h); MDA-MB-157: 6.8 (48 h); MDA-MB-231: 15.8 (48 h)	cytotoxicity, inhibition of colony formation, and wound healing, induction of apoptosis	targeting both NFκB and IFNα signaling, suppressed expression of IFITM1	SUM149 and MDA-MB-468 tumor xenograft	71
	231MFP and HCC38: 25-50 (48 h)	anti-proliferation/survival, apoptosis-inducing, suppression of migration and tumor xenograft growth	Inhibits FAK1 Activity and FAK1-dependent signaling pathway; activation of caspase3/7	231MFP tumor xenograft	33
	MDA-MB-231: NA	anti-proliferation	Induced expression of miR-29b-1-5p, reduced the p-AKT levels, NRF2 activation, and DNMT expression	NA	55
	MDA-MB-231-pcDNA: 115.8 ± 2.3 (72 h); MDA-MB-231-BCRP (multidrug-resistant cell line): 8.5 ± 1.3 (72 h)	cytotoxicity	bound to IKK, prevented IκB degradation and thus inhibited the NF-κB pathway; Down-regulation of HIF-1α; inhibition of HDAC activity	NA	56
	Pancreatic cancer	SUIT-2: NA	Inhibition of cell migration induced by VASH2	Inhibiting the activity of tubulin carboxypeptidase	NA

(Continued)

Table 1 (Continued).

Tumor Types	Cell Lines and Efficacy [IC <sub>50</sub> , μM (Exposure Time)]	Pharmacological Activities	Mechanisms of PTL Action	In Vivo Model	Ref
Colorectal cancer	HCT-116 (p53 <sup>+/+</sup> ): 17.6 ± 1.8 (72 h); HCT-116 (p53 <sup>-/-</sup> ): 41.6 ± 1.2 (72 h)	cytotoxicity	bound to IKK, prevented IκB degradation and thus inhibited the NF-κB pathway; Down-regulation of HIF-1α; inhibition of HDAC activity	NA	56
	HT-29 and SW480: NA	inhibits cell migration and invasion induced by TGF-β1	inhibits EMT progression	NA	81
	HCT116, SW480, SW620, HT29, and Caco-2: 3-10 (48 h)	anti-proliferation, cell cycle arrest at G <sub>2</sub> /M phase, and induction of apoptosis	Decreased activity of USP7 and Wnt signaling; caspase-8 and-9 activation	NA	24
Hepatocellular carcinoma	Bel-7402: 8.62 ± 1.68 (72 h); Bel-7402/5-FU: 12.98 ± 3.96 (72 h)	cytotoxicity	NA	NA	57
Glioblastoma	U87.MG: 46.0 ± 3.8 (72 h); U87.MGΔEGFR: 32.7 ± 3.8 (72 h)	cytotoxicity	bound to IKK, prevented IκB degradation and thus inhibited the NF-κB pathway; Down-regulation of HIF-1α; inhibition of HDAC activity	NA	56
Uveal melanoma	C918 and SP6.5: 50-100 (48 h)	cytotoxicity, cell cycle arrest at G <sub>1</sub> phase, and induction of apoptosis	Increased expression of p21, Bax, caspase-3, and caspase-9; downregulation of Cyclin D1, Bcl-XL and Bcl-2;	NA	60
Renal cell carcinoma	786-O and ACHN: 4-8 (48 h)	suppressed cell proliferation and metastasis and inhibited the stem cell-like properties	inhibition of EMT, cancer stem cell markers, and the PI3K/AKT pathway	NA	80
Lung cancer	NSCLC (EGFR mutated): H1975: 5.609 (24 h), PC-9: 6.549 (24 h), HCC827: 7.27 (24 h); NSCLC (EGFR wt): H358: 16.27 (24 h), H460: 22.6 (24 h), A549: 11.03 (24 h)	inhibited cell proliferation and colony formation, induction of apoptosis	inhibited phosphorylation of EGFR and its downstream AKT and ERK signaling pathways	H1975 xenograft	27
	A549: 20-30 (48 h); H1299: 30-50 (48 h)	inhibited cell proliferation and migration	inhibition of IGF-1R-mediated PI3K/Akt/FoxO3α signaling	A549 subcutaneous xenograft	58
	LL/2 and H2030BrM: NA	brain metastasis suppression	blocked the nicotine-induced M2 microglial polarization by targeting STAT3	the xenograft model of LL/2 and H2030BrM cell	83

(Continued)

Table 1 (Continued).

Tumor Types	Cell Lines and Efficacy [IC <sub>50</sub> , μM (Exposure Time)]	Pharmacological Activities	Mechanisms of PTL Action	In Vivo Model	Ref
Gastric cancer	SGC7901: 17.48 ± 1.07 (48 h); SGC7901/DDP: 22.61 (48 h); SGC7901/ADR: 20.15 (48 h)	anti-proliferation, induction of apoptosis, reduced drug resistance	decreased NF-κB activity, downregulation of Bcl-2, P-gp, MRP, and cyclin D1; increased caspase-8 activity	NA	78
Squamous Cell Carcinoma	Eca109: 10.3 (48 h); KYSE-510: 13.3 (48 h)	attenuated cell proliferation, migration and xenograft growth, anti-angiogenesis,	reduced the expression level of NF-κB, AP-1 and VEGF	Eca109 xenograft tumor model	79
	KYSE150, KYSE180, KYSE450, and NCI-H2170: NA	anti-proliferation and migration, synthetic lethality toward cells with ARID1A depletion	HDAC1 inhibition and suppression of AKT and ERK signaling pathways	KYSE410 xenograft with or without ARID1A depletion, SCC PDX models with low or high ARID1A expression	59
Thyroid cancer	TPC-1: 8.42 (24 h); TPC-1: 5.26 (48 h)	cytotoxicity, apoptosis-inducing	increase in ROS levels and Bax expression; downregulation of Bcl-2, loss of mitochondrial membrane potential; metabolic imbalance	NA	70

Abbreviation: NA, not available.

have indicated that PTL disrupted intracellular redox homeostasis by depleting glutathione (GSH) and inhibiting its metabolic enzymes, including glutamate-cysteine ligase catalytic subunit (GCLC), thioredoxin reductase 1/2 (TrxR1/2), and GSH peroxidase 1 (GPX1), thus leading to increased ROS level.<sup>40–42</sup> Moreover, ROS enhancement by PTL seemed to elicit different forms of cell death, such as necrosis, apoptosis, and autophagic cell death, depending on the tumor cell type.<sup>40,41,43</sup> Meanwhile, the action of PTL on ROS partially accounts for its distinctive ability to selectively induce cell death in cancer cells, while sparing the equivalent normal cells. This is due to the fact that oxidative stress in cancer cells is more frequently elevated than that in normal cells. Thus, additional ROS produced by PTL may promote tumor cell death, whereas normal cells may maintain redox homeostasis by adaptive antioxidant responses.<sup>44</sup> Moreover, the epigenetic targets of PTL consist of various enzymes, including histone deacetylase 1 (HDAC1), DNA methyltransferase 1 (DNMT1), and lysine methyltransferase 5C (KMT5C); these regulate the transcription of various genes, such as *p21* and high in normal-1 (*HIN-1*).<sup>45–47</sup> In addition, PTL disrupted the cyclical detyrosination/tyrosination of tubulin by inhibiting tubulin carboxypeptidase (TCP), which led to a reduced frequency of microtentacles and suppressed tumor cell reattachment to endothelial layers (Figure 2).<sup>48,49</sup>

Interactions between signaling pathways and cellular processes may be affected by PTL. For instance, the stimulated generation of ROS by PTL was able to induce autophagy and cause NF-κB downregulation.<sup>40,43</sup> Furthermore, NF-κB inhibition contributed to epigenetic regulation,<sup>47</sup> thereby further complicating the antitumor mechanism of PTL.

## Pharmacological Effects of PTL

To understand the pharmacological effects of PTL, in vitro studies on its efficacy, pharmacological activities, and potential molecular mechanisms in a variety of cancer cells as well as available in vivo models since 2019 are tabulated in Table 1, thus further extending and qualifying existing reviews of its biological activities.<sup>3,4,50</sup> As shown in Table 1,

PTL modulation toward the aforementioned signaling pathways and cellular processes exerts multiple pharmacological effects against a myriad of tumor cell types.

The antiproliferative activity of PTL was detected in almost all studies; the results indicated that PTL exhibited half-maximal inhibitory concentration ( $IC_{50}$ ) between the range of 2.5–25  $\mu$ M for most tumor cells listed, thus showcasing its cytotoxicity to different cancer cells.<sup>51–59</sup> Cell cycle arrest, induction of cell death, and changes in related proteins were further detected, thus further supporting the cytotoxic potential of PTL. Overall, PTL was shown to induce different effects depending on the cell type, which can be illustrated by its ability to induce cell cycle arrest at different phases as well as several types of cell death in various cancer cells. For example, PTL arrested uveal melanoma cells in the  $G_1$  phase by upregulating p21 and downregulating cyclin D1, which are two  $G_1$  phase cell cycle regulatory proteins.<sup>60</sup> On the other hand, PTL decreased the expression of survivin promoting  $G_2/M$  cell cycle transition, thereby triggering  $G_2/M$  cell cycle arrest in glioblastoma cells.<sup>61</sup> Apoptosis, necrosis, and autophagy are the three forms of cell death caused by PTL,<sup>62</sup> among which, apoptosis is the most studied. It is well known that apoptosis is elicited by two distinct pathways, the extrinsic and mitochondria-mediated intrinsic pathways; it culminates in the activation of caspases, which function as the main apoptotic effectors.<sup>63</sup>

Numerous studies demonstrated that PTL treatment could induce extrinsic or intrinsic apoptosis in tumor cells by inhibiting the activities of the NF- $\kappa$ B, STAT3, Wnt and JNK signaling pathways, activating the p53 signaling pathway, regulating the Bcl-2 family members, and generating ROS.<sup>24,62,64–71</sup> Furthermore, PTL-induced cell death of breast cancer and multiple myeloma cells was dramatically attenuated by co-treatment with the pan-caspase inhibitor, Q-VD-OPh or Z-VAD-fmk, thus indicating that caspases are involved in PTL-induced apoptotic cell death; it also concurs the presence of other forms of cell death.<sup>33,72</sup> Indeed, a large number of studies reported that PTL was capable of inducing autophagic or necrotic cell death.<sup>50,62</sup> For instance, PTL mediated cell death through ROS-mediated autophagy in human osteosarcoma (Saos-2 and MG-63) and triple-negative breast cancer (MDA-MB-231) cells.<sup>40,43</sup> In particular, PTL was capable of simultaneously inducing mixed forms of cell death, as evidenced by observations of PTL-induced apoptosis and autophagy in HeLa and HepG2 cells as well as apoptosis and necrosis in HL60 cells.<sup>73–75</sup> Additionally, the role of autophagy in cell death involves the fact that its inhibition significantly blocked PTL-induced apoptosis in pancreatic cancer cells,<sup>76</sup> but potentiated PTL-induced apoptosis in human breast cancer cells.<sup>77</sup>

Although previous studies have elucidated the selective targeting effect of PTL on CSCs from primary or sensitive cancer cells,<sup>3</sup> a recent study by Yi et al suggested that PTL also effectively eliminated leukemia stem cells (LSCs) from adriamycin (ADM)-resistant K562 cells (K562/ADM) by suppressing aberrantly activated NF- $\kappa$ B.<sup>64</sup> In addition, NF- $\kappa$ B inactivation by PTL sensitized gastric tumor and esophageal squamous cell carcinoma (ESCC) cells to chemotherapeutic drugs including ADM and cisplatin.<sup>78,79</sup> PTL exerted its anti-angiogenic effects by inhibiting the NF- $\kappa$ B-mediated VEGF expression in ESCC cells.<sup>79</sup> Moreover, several studies have pointed out that PTL inhibits migration, invasion, and metastasis, which benefits from its abilities to regulate epithelial-to-mesenchymal transition (EMT) and to inhibit FAK1, TCP, and STAT3.<sup>33,80–83</sup>

In short, the ultimate outcomes resulting from the affected signaling pathways and cellular processes by PTL include, but are not limited to, impaired cell proliferation and angiogenesis, induction of cell death, and reduced stemness, invasiveness, and chemoresistance. This has been confirmed by a large body of research, thus providing a sufficient basis for studies investigating and developing a wide range of PTL nanoformulations for various cancer therapies.

## Nanoformulations of PTL for Tumor Therapy

To the best of our knowledge, several types of PTL nanocarriers, including liposomes,<sup>84–89</sup> polymeric micelles,<sup>90–96</sup> nanocrystals,<sup>97</sup> PLGA nanoparticles,<sup>98</sup> and nanographene,<sup>99</sup> have been synthesized to deliver PTL and ameliorate its anti-cancer efficacy. Whether PTL is co-encapsulated into nanoparticles with other drugs or small molecules and whether the nanoparticles are modified for targeted therapy, these studies can be classified into three types. Furthermore, the types, materials, and properties of nanocarriers mentioned in these studies, as well as the *in vitro* and *in vivo* models employed to evaluate the anticancer effects of nanoformulations, are separately tabulated in [Tables 2–4](#).



**Table 2** Unmodified Nanoparticles Solely Incorporated with PTL

Carriers	Materials	Co-Delivery with PTL	Properties	In vitro Cell Lines	In vivo Model	Ref
Polymeric micelles	PSMA- <i>b</i> -PS or PSMA- <i>b</i> -PBA	NA	Improved cellular uptake	Multidrug resistant ovarian carcinoma cells	NA	[90]
Polymeric micelles	PSMA- <i>b</i> -PS	NA	Decreased cell viability; NF-κB inhibition	MV4-11 cells	NA	[91]
Liposomes	EPC; Cholesterol; DSPE-PEG <sub>2000</sub>	NA	The effect of stealthy liposomal PTL alone is not significant; Co-treatment with stealthy vinorelbine decreased viability of both cancer and cancer stem cells and inhibited in vivo tumor growth.	MDA-MB-231; MCF-7 cells	MCF-7 BALB/c nude xenograft	[89]
Polymeric micelles	PEG-PTMC	NA	Decreased cell viability; ROS Induction and Inhibition of NF-κB	CB cells; T- and BCP-ALL patient cells	NA	[92]
Polymeric micelles	F127	NA	Decreased cell viability	hMSCs; primary T-ALL cells	NA	[93]
Nanocrystals	Poloxamer 188; Lecithin		Decreased cell growth and migration	HepG2 cell lines	BALB/c nude HepG2 xenograft	[97]
Nanographene	Carboxyl-functionalized Graphene	NA	Decreased cell viability; increases in ROS formation; disruption of mitochondrial membrane potential; apoptosis	Panc-1 cells	NA	[99]

**Abbreviations:** PSMA-*b*-PS, poly(styrenealt-maleic anhydride)-*b*-poly(styrene); EPC, egg phosphatidylcholine; DSPE-PEG<sub>2000</sub>, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine poly(ethylene glycol) 2000; F127, poloxamer 407; hMSCs, human mesenchymal stem cells; CB, cord blood; NA, not available.

## PTL is Solely Incorporated into Unmodified Nanoparticles

Baranello et al synthesized different types of micelles formed from amphiphilic diblock copolymers of PSMA-*b*-PS or PSMA-*b*-PBA; PTL was successfully loaded into these micelles. However, PTL exhibited the greatest loading efficiency and capacity in PSMA<sub>100</sub>-*b*-PS<sub>258</sub> micelles, thereby indicating that the composition and hydrophobic core chemistry of micelles were significant parameters for optimization.<sup>90</sup> Although subsequent studies suggested that PTL-loaded PSMA<sub>100</sub>-*b*-PS<sub>258</sub> micelles did not exhibit better cytotoxic ability toward MV4-11 cells than free PTL, it protected sequestered PTL from damage by both cells and deactivating chemicals, such as GSH.<sup>91</sup> Similarly, the application of stealthy liposomes and micelles fabricated by F127 or biodegradable PTL-PTMC as nanocarriers of PTL did not appear to efficiently increase its cytotoxicity against MCF-7, MDA-MB-231, and patient T-lineage acute lymphoblastic leukemia (T-ALL) or B-cell precursor acute lymphoblastic leukemia (BCP-ALL) cells.<sup>89,92,93</sup> However, the combination of stealthy liposomal PTL slightly sensitized the antitumor effects of stealthy liposomes loaded with vinorelbine.<sup>89</sup>

Unlike the nanocarriers mentioned above, the carboxyl-functionalized nanographene (fGn) as well as the PTL-nanocrystal delivery system showed improved antiproliferation activities in comparison with individual PTL. The IC<sub>50</sub> of PTL and PTL-fGn for Panc-1 cells were 39 and 9.5 μM respectively, whereas the IC<sub>50</sub> of PTL for HepG2 cells decreased from 50.891 μM to 33.618 μM when delivered with nanocrystals.<sup>97,99</sup> Interestingly, there was no significant difference in cytotoxic activity between DMAPT and DMAPT-fGn; this inefficacy may be due to the lack of a hydrophobic interaction between DMAPT and fGn.<sup>99</sup> Thus, whether incorporation of DMAPT into other nanovectors

**Table 3** Undecorated Nanovectors Encapsulated PTL and Other Agents

Carriers	Materials	Co-Delivery with PTL	Properties	In vitro Cell Lines	In vivo Model	Ref
Polymeric micelles	DSPE-PEG <sub>2000</sub> ; vitamin E-TPGS	Paclitaxel	Decreased cell viability	A549 and taxol resistant A549-T24 cell lines	NA	[94]
Liposomes	Phosphatidylcholine; DSPE-PEG <sub>2000</sub> ; Cholesterol	Betulinic acid; Honokiol; Ginsenoside Rh2	Cytotoxicity; Proliferation inhibition; cell cycle arrested; Ca <sup>2+</sup> distribution; cell apoptosis; metastasis inhibition	A549 cells	A549-bearing nude mice model	[84]
Liposomes	DPPC; DSPC; Cholesterol	Indocyanine green	Thermosensitive liposomes responded to near-infrared radiation; Synergistic effects of generation of ROS by PTL and increased temperature by ICG; cell cycle arrest at S phase; apoptosis	MDA-MB-231 cells	BALB/c nude MDA-MB-231 xenograft	[85]

**Abbreviations:** DSPE-PEG<sub>2000</sub>, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine poly(ethylene glycol)<sub>2000</sub>; DPPC, dipalmitoyl phosphatidyl choline; DSPC, distearoyl phosphatidyl choline; NA, not available.

could enhance its cytotoxicity is worth exploring. Furthermore, the in vitro and in vivo combination of PTL-nanocrystals and sorafenib achieved remarkable synergistic anti-cancer effects, as reflected by the MTT, wound-healing and HepG2 xenograft assays.<sup>97</sup>

## Co-Delivery of PTL and Other Agents in Undecorated Nanovectors

Given the molecular complexity of cancer, combination therapy has attracted tremendous attention because of its ability to increase drug efficacy, improve drug resistance, and reduce systemic toxicity. Kanwaldeep et al constructed a paclitaxel and PTL co-delivery system of PEG<sub>2000</sub>-DSPE/vitamin E-TPGS mixed micelles, which retained a high encapsulation efficiency (>95%) and chemical stability over a storage period of 45 days. Furthermore, co-encapsulation of these two drugs significantly suppressed the viability of sensitive and taxol-resistant A549 cells compared to their free drug counterparts in solutions and single drug-loaded micelles.<sup>94</sup> In addition, as a component of these mixed micelles, it is noteworthy that vitamin E-TPGS aided in not only maintaining high encapsulation efficiency due to its bulky structure and large surface area, but also enhanced chemosensitization by inhibiting P-glycoprotein (P-gp) efflux.<sup>94,100</sup> Recently, a liposome system loaded with betulinic acid, PTL, honokiol and ginsenoside Rh2 displayed in vitro and in vivo antitumor activity comparable to cisplatin, the first-line therapy for lung cancer. In addition, this cocktail liposome therapy circumvented obvious kidney damage induced by cisplatin, as revealed by hematoxylin and eosin (H&E) staining. It also did not cause any significant damage to other major organs, including the heart, liver, spleen, and lungs, thereby indicating that this cocktail is a safer alternative for lung cancer treatment.<sup>84</sup>

To exploit the advances in photothermal therapy, Jin Xin and co-workers constructed thermosensitive liposomes (TSLs), in which PTL and the photosensitizer indocyanine green (ICG) were co-loaded. ICG converts light energy into heat energy upon near-infrared light irradiation. Compared to groups treated with paclitaxel, a combination of free drugs with or without laser, or PTL-ICG TSLs without laser, groups treated with PTL-ICG TSLs with laser exhibited lower cell viability, higher ROS induction and apoptosis, and better in vivo anti-cancer effects. According to these results, the two benefits of heat energy released by ICG under near-infrared radiation at the tumor location were validated. On the one hand, the heat-promoted phase transition of these liposomes enhanced their fluidity and permeability, thus allowing loaded drugs to effectively diffuse to tumor tissues at high concentrations. On the other hand, the maximum temperature of tumor tissues treated with PTL-ICG TSLs with laser reached 47.4°C± 2.68°C, which led to irreversible damage and further synergized with the oxidative stress of PTL.<sup>85</sup>

**Table 4** Targeted Nanocarriers Encapsulated PTL with or without Other Agents

Carriers	Materials	Co-Delivery with PTL	Properties	In vitro Cell Lines	In vivo Model	Ref
Nanoparticles conjugated with antiCD44	PLGA	NA	Decreased cell viability; greater uptake	Kasumi-1; KG-1a; and THP-1 cells	NA	[98]
Multistage vector combined micelles with porous silicon particles and ESTA	mPEG-PLA micelles; porous silicon particles	NA	Inhibition of NF- $\kappa$ B; activation of $\gamma$ -H2AX; impair leukemia stem cells and decrease AML tumor burden in vivo	Primary AML cells	Patient-derived AML xenografts; secondary AML engraftment	[95]
Liposomes with targeted tLyp-1 ligand	Lecithin, cholesterol, DSPE-PEG2000	Ginsenoside CK	Greater uptake; decreased cell viability; increased accumulation in the tumor region; enhanced ROS level; impaired MMP; increased Ca <sup>2+</sup> level; apoptosis; migration inhibition	A549 cells	A549-bearing nude mice model	[87]
Polymeric micelles modified with $\Delta$ WVAP peptides	Mal-PEG <sub>3000</sub> -PLA <sub>2000</sub>	NA	BBB and BBTB penetrating capacity in vitro and the brain and glioma targeting ability in vivo; no immunogenicity; cytotoxicity; inhibition of vessel-like structure formation and NF- $\kappa$ B	U87 and HUVEC cells	Intracranial U87 glioma-bearing nude mice model	[96]
Liposomes coated with magnetic nanoparticles	SPC; Cholesterol; magnetic nanoparticles	Indocyanine green	Higher heating rate and drug release; decreased cell viability; greater uptake; increased intratumoral concentration	HeLa cells	Kunming mice bearing U14 (mouse cervix cancer cells) xenograft	[86]
Liposomes coated with magnetic nanoparticles	Soya phosphatidylcholine; Cholesterol; chitosan magnetic nanoparticles	Glucose oxidase	Multifunctional antitumor drug delivery system for chemotherapy, chemodynamic therapy, starvation therapy and magnetic targeting synergistic therapy	HeLa cells	Kunming mice bearing U14 (mouse cervix cancer cells) xenograft	[88]

**Abbreviations:** PLGA, poly lactide co-glycolide; mPEG-PLA, methoxypoly(ethylene glycol)-poly(lactic acid); ESTA, E-selectin thioaptamer; SPC, soya lecithin; BBB, blood-brain barrier; BBTB, blood-brain tumor barrier; NA, not available.

## Nanocarriers Encapsulated with PTL Were Modified to Enhance Their Targeting Ability

To further improve drug delivery and selective targeting toward cancer cells, targeted nano-encapsulation of PTL with or without other agents was developed according to the characteristics of specific types of tumor cells and their micro-environment or the suction of the magnetic field. CD44 is a pivotal receptor involved in myelopoiesis; its specific variant isoforms have been reported to be overexpressed in AML cells, thus indicating that CD44 can serve as a promising receptor for targeted delivery of anti-AML drugs.<sup>101,102</sup> As a result, an intervention was developed by encapsulating PTL into PLGA nanoparticles conjugated with antiCD44 with higher tumor targeting efficiency than PLGA-PTL nanoparticles. Although the cytotoxic abilities of PLGA-antiCD44-PTL and PLGA-PTL nanoparticles were not compared, PLGA-antiCD44-PTL nanoparticles exhibited stronger cytotoxicity than free PTL.<sup>98</sup>

Leukemia stem cells (LSCs) within the bone marrow (BM) microenvironment are thought to be the primary mediators of relapse and chemotherapy resistance in AML. Furthermore, E-selectin expressed in the BM endothelium provides a feasible approach for targeted BM delivery. In view of the remarkable capability of PTL to eradicate cancer

stem cells including LSCs, a multistage vector system (MSV) was developed by entrapping PTL in mPEG-PLA micelles coated with protective degradable porous silicon particles and an E-selectin thioaptamer. In contrast to the negligible therapeutic efficacy of PTL-loaded micelles, MSV-PTL significantly reduced the tumor burden of patient-derived AML xenografts, concurrent with the inhibition of NF- $\kappa$ B and activation of  $\gamma$ -H2AX; this supports the effectiveness of the MSV system for targeted BM delivery. Moreover, the decreased level of secondary xenotransplants implied that the directed delivery of PTL to the BM using the MSV system led to the elimination of LSCs.<sup>95</sup>

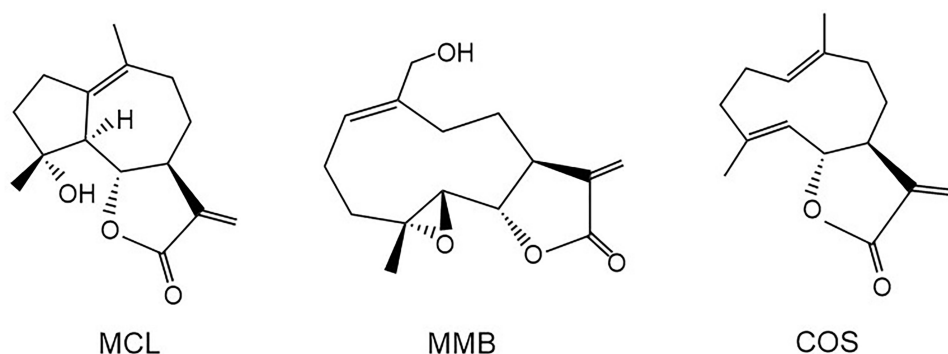
The tLyP-1 peptide has been verified to possess cell-penetrating ability and tumor-targeting capacity, which are derived from its C-terminal structure and affinity to the neuropilin-1 receptor overexpressed in several kinds of cancer cells (eg glioma and lung cancer).<sup>103</sup> In which tLyP-1-modified liposomes entrapped in PTL and ginsenoside compound K (CK) were synthesized, the level of ROS and induced apoptosis of A549 cells in vitro significantly increased. Besides, PTL/CK tLyP-1 liposomes exhibited greater anticancer efficacy than the combined administration of these two compounds in A549 tumor-bearing mice.<sup>87</sup> In addition, Ran et al developed PTL-loaded PEG-PLA micelles decorated with a “Y”-shaped <sup>D</sup>WVAP peptide, which could guide micelles across multiple biological barriers and ultimately target glioma and its associated stem cells. Moreover, combined therapy of PTL-loaded, <sup>D</sup>WVAP-modified PEG-PLA micelles with temozolomide or <sup>D</sup>WVAP-modified PEG-PLA micelles loaded with paclitaxel achieved outstanding anti-glioma efficacy, according to the Kaplan–Meier survival analysis.<sup>96</sup>

Recently, by virtue of the magnetic field, magnetic nanoparticles (MNPs) were chosen to modify the surface of liposomes (lips) loaded with PTL by Gao and co-workers.<sup>86,88</sup> In one study, PTL-ICG-Lips, similar to PTL-ICG TSLs mentioned above, were coated with MNPs. In terms of in vitro heating efficiency and drug release, there was no significant difference between the PTL-ICG-Lips@MNPs group treated only with laser and PTL-ICG-Lips@MNPs group treated with laser plus magnet, which were stronger than non-laser irradiation treated groups. These results suggested the dominant role of photothermal conversion mediated by ICG in these processes. However, the presence of the magnetic field increased the heating rate and percentage of drug release at an earlier stage. In addition, cells treated with ICG-C6-Lips@MNPs (magnet plus laser) exhibited the highest cellular uptake. Consistently, in vivo studies also showed that the PTL-ICG-Lips@MNPs (magnet plus laser) group displayed the fastest heating rate, highest temperature, and highest intratumoral PTL concentration.<sup>86</sup> These findings indicated that the magnetic field could enrich the magnetic liposomes in the irradiated area, thus further enhancing the efficiency of photothermal conversion and facilitating the release and uptake of PTL.

Another multifunctional delivery system generated by Gao et al was the encapsulation of PTL and glucose oxidase (GOD) into nanomagnetic liposomes coated with chitosan, named GOD-PTL-Lips@MNPs. The addition of chitosan endowed GOD-PTL-Lips@MNPs with the capability to release drug at a slightly acidic pH, which was characteristic of the tumor microenvironment. As a result, this increased the targeting ability of the system together with the magnetic field. By consuming glucose, GOD in this system lowers the pH and generates H<sub>2</sub>O<sub>2</sub> as well as starves the cancer cells to death. A lower pH further promotes drug release; H<sub>2</sub>O<sub>2</sub> can be subsequently catalyzed by iron ions in MNPs to produce hydroxyl radicals ( $\bullet$ OH), a noxious ROS. Meanwhile, PTL protects  $\bullet$ OH from scavenging by depleting GSH,<sup>40</sup> which amplifies the intracellular oxidative stress and thus leads to cell apoptosis. Under an extra magnetic field, the GOD-PTL-Lips@MNPs demonstrated prominent antitumor effects in vitro and in vivo through the integration of chemo-, chemodynamic, starvation and magnetic-targeting therapies.<sup>88</sup>

As discussed above, the incorporation of PTL into nanocarriers results in increased solubility, cellular uptake and stability, prolonged circulation time, and enhanced accumulation at tumor sites. Therefore, the majority of nanocarriers encapsulated with PTL, especially when combined with other agents such as photosensitizers, anticancer drugs, and MNPs, demonstrated higher anticancer efficiency than free PTL. These mechanisms are reflected by better antiproliferative activities, more effective induction of apoptosis, higher suppression rate of migration, and xenograft tumor growth. Histological examination demonstrated the low toxicity of this novel therapeutic agent.

In addition, a variety of naturally occurring sesquiterpene lactones structurally related to PTL with anticancer efficiency, as represented by micheliolide (MCL, Figure 4), melampomagnolide B (MMB, Figure 4), and costunolide (COS, Figure 4) have been reported.<sup>104–106</sup> Similar with PTL, most of current researches focus on structural modification of these compounds to improve their antitumor effects, stability, and sustainable release.<sup>107–111</sup> Several studies started to investigate the incorporation



**Figure 4** Chemical structure of MCL, MMB and COS.

of MCL analogs and COS into nanoparticles.<sup>112,113</sup> Bone-targeted PSMA-b-PS NPs entrapped with triazole MCL analog exhibited excellent serum stability and significantly reduced LSC burden in leukemic mice.<sup>112</sup> Another study demonstrated that COS and COS-NPs, in combination with doxorubicin (DOX), stimulated the activity of caspase-3 and induced apoptosis of HCT116 and MDA-MB-231-Luc. They also suppressed the tumor growth of HCT116 and MDA-MB-231-Luc implants in nude mice. There was no significant difference in the anti-tumor activity of COS and COS-NPs; the authors deemed that this may have been due to the dose-selective approach for determining the optimal anti-cancer activity for both COS and Nano-COS. Thus, dose-response relationship will be investigated in future studies.<sup>113</sup> In addition, Niu et al constructed pH-responsive mesoporous silica nanoparticles (MSNs) loaded with COS, which increased stability and enhanced anti-fibrotic effect of pure COS.<sup>114</sup> In short, above-mentioned results implied that nanoparticles entrapped with sesquiterpene lactones show great promise in the treatment of cancer and other diseases.

## Conclusion

Studies from the past decades have validated the great potential of PTL as an anticancer agent with extremely intricate bioactivities. However, poor aqueous solubility, instability, low bioavailability, and drug-targeting property of PTL limit its *in vivo* anticancer efficacy and clinical application.<sup>86</sup> As such, the development of nanoparticle-based platforms has been utilized in multiple biomedical fields, including hydrophobic drug delivery, which undoubtedly provides a promising strategic improvement.<sup>115</sup> Indeed, several natural product-derived anticancer nanodrugs, including nanoparticle albumin-bound (NAB)-paclitaxel and liposomal vincristine, have been used in clinical practice.<sup>21</sup> However, no clinical trials have been reported for nanocomposites of PTL and its structurally related sesquiterpene lactones. Furthermore, despite multiple *in vitro* and *in vivo* experiments that have reported the benefits of nanoparticle-based formulations of other natural anti-cancer drugs in the treatment of various cancer types, including quercetin, curcumin, resveratrol, and andrographolide, only a few clinical trials have been performed, thus, suggesting that the investigation of these nanocarriers is still in its relative infancy.<sup>116–118</sup> Further optimization can be performed because the efficiency of nanoparticles can be influenced by many parameters, such as nanocarrier types, compositions (eg materials, ligand modification, co-encapsulated agents), and physical properties (eg size, shape, surface charge).<sup>21</sup> As such, PTL and other natural product-based nanoformulations with improved properties will undoubtedly emerge; clinical trials need to be encouraged to further validate the security and therapeutic efficiency of these nanoparticles for cancer. Finally, PTL has been recently predicted to be a possible agent for the treatment of other diseases, such as Hutchinson-Gilford Progeria syndrome and hypertrophic cardiomyopathy.<sup>119,120</sup> Thus, the therapeutic value of PTL nanoparticles for these diseases deserves further study.

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## Disclosure

The authors declare that they have no conflicts of interest in this work.

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