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REVIEW

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Delivery of triptolide: a combination of traditional Chinese medicine and nanomedicine

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Abstract

As a natural product with various biological activities, triptolide (TP) has been reported in anti-inflammatory, anti-tumor and anti-autoimmune studies. However, the narrow therapeutic window, poor water solubility, and fast metabolism limit its wide clinical application. To reduce its adverse effects and enhance its efficacy, research and design of targeted drug delivery systems (TDDS) based on nanomaterials is one of the most viable strategies at present. This review summarizes the reports and studies of TDDS combined with TP in recent years, including passive and active targeting of drug delivery systems, and specific delivery system strategies such as polymeric micelles, solid lipid nanoparticles, liposomes, and stimulus-responsive polymer nanoparticles. The reviewed literature presented herein indicates that TDDS is a multifunctional and efficient method for the delivery of TP. In addition, the advantages and disadvantages of TDDS are sorted out, aiming to provide reference for the combination of traditional Chinese medicine and advanced nano drug delivery systems (NDDS) in the future.

Keywords: Triptolide, Traditional Chinese medicine, Nanomedicine, Passive targeting, Active targeting, Stimuli-responsive targeting

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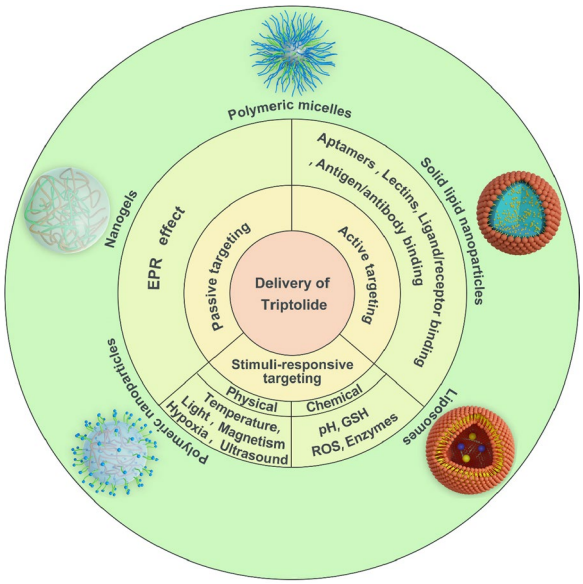
Graphical Abstract



Introduction

As one of the core components of traditional Chinese medicine (TCM), Chinese herbal medicine (CHM) has a long history in China. Under the theoretical guidance of TCM, CHM has been applied in clinical practice and has proven to be a treasure for human civilization for thousands of years. During the recent outbreak of coronavirus disease 19 (COVID-19), TCM has been widely used because of its unique advantages and remarkable curative effects against viral infections [1–3]. Among numerous

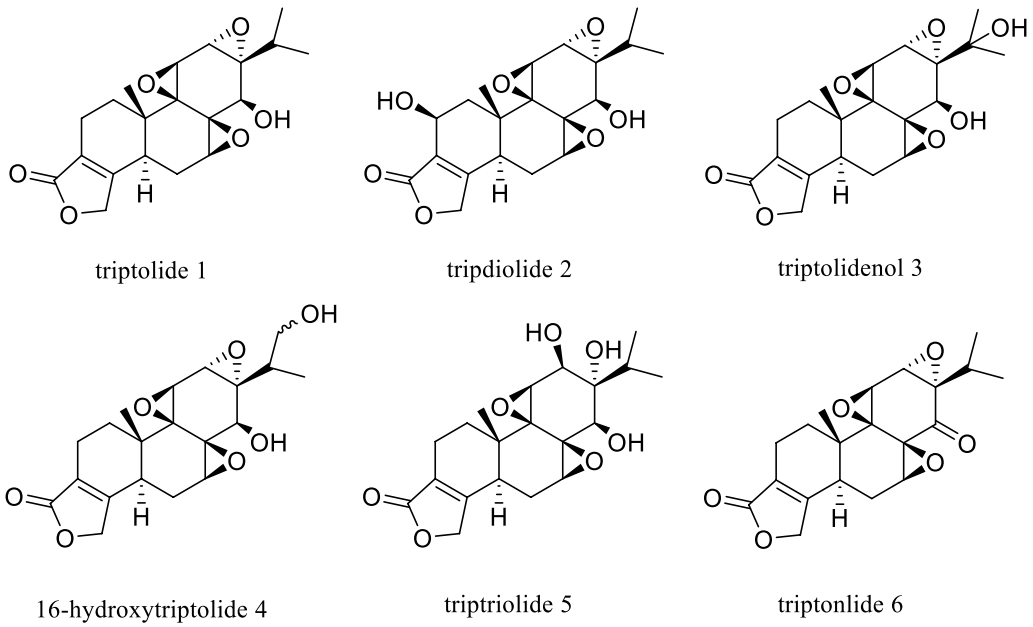


Fig. 1 Triptolide and other compounds isolated from TWHF

CHMs, triptolide (TP) was considered as the most active epoxide diterpene lactone compound isolated by Kupchan et al. from *Tripterygium wilfordii* Hook F. (TWHF) in 1972 [4]. Its molecular structure is depicted in Fig. 1. TP is also considered as one of the main effective components of TWHF [5].

TP has become a research hotspot because of its highly effective anti-inflammatory, anti-autoimmune, and anticancer activities [6–9]. In addition, TP is partly used in the clinical management of rheumatoid arthritis (RA) [10–12]. In recent years, TP has been shown to exert an inhibitory effect on cancer growth, leading to researchers extensively exploring its anti-cancer effects [13–16]. Furthermore, studies have shown that the antitumor mechanism of TP is related to its involvement in the regulation of various molecules and signaling pathways, thereby inhibiting cell proliferation, inducing cell apoptosis, and inhibiting tumor metastasis [15, 16].

However, the anticancer mechanism of TP is not fully understood. In various known signaling pathways, as those depicted in Fig. 2, [17] the experimental results obtained by different researchers, such as Chang et al., showed that TP further leads to tumor necrosis factor-α (TNF-α)-induced apoptosis by inhibiting NF-κB [13]. In addition, Bing et al. found that caspase-dependent apoptosis of leukemia cells was induced by the mitochondrial pathway at low concentrations of TP [18]. Furthermore, Tan et al. verified that TP-induced extracellular signal-regulated kinase (ERK) activation regulated the expression of the Bcl-2 protein family members, whereas the activation of ERK indicated that excessive reactive oxygen species (ROS) in the endoplasmic reticulum caused oxidative stress and induced apoptosis [19]. It is well known that the invasion and metastasis of cancer complicate the prognosis after surgical treatment. Furthermore, disease progression is related to many factors, such as cathepsin and matrix metalloproteinases (MMPs). Yang demonstrated that TP could reduce the expression of human fibrosarcoma HT-1080 cell matrix metalloproteinase-9 (MMP-9), thereby inhibiting cancer metastasis to a certain extent [20]. In addition, some studies have reported that triptolide can inhibit the expression of interferon-γ (IFN-γ)-induced programmed death-1 ligand-1 (PD-L1) on the surface of tumor cells and reverse the inhibitory effect of tumor cells on CD4+ T cells. It has the potential to target PD-L1 anti-tumor therapy [21, 22]. Gao demonstrated that triptolide has the ability to reshape the immune microenvironment of colon cancer, and its main mechanism is to reduce tumor-associated macrophage infiltration and M2 polarization by inhibiting tumor-derived CXCL12 [23].

Despite being a natural product with a variety of bioactivities, the clinical applications of TP are limited because of its poor water solubility, adverse effects, narrow therapeutic window, and severe toxicity affecting organs and organ systems, such as the liver kidneys, spleen, and the

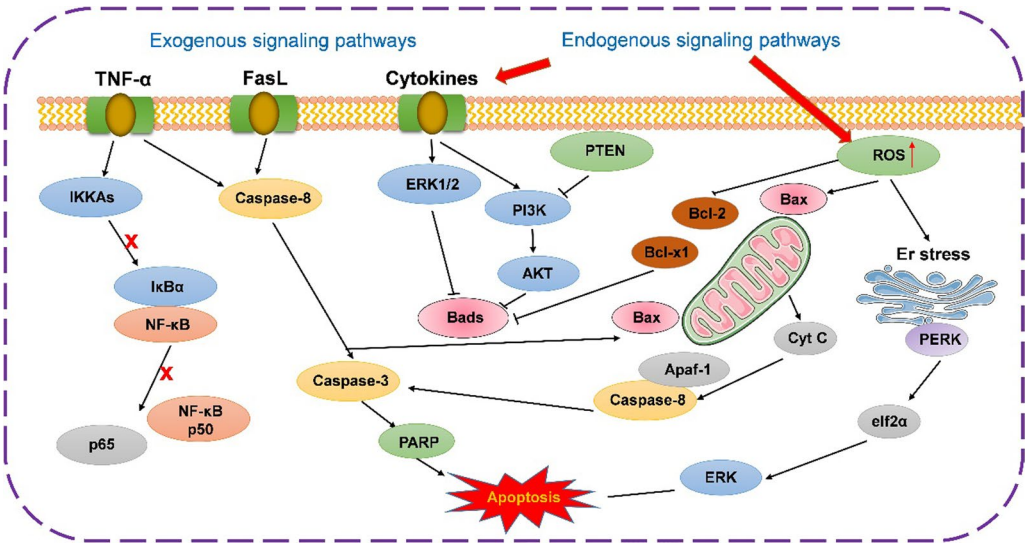


Fig. 2 Schematic diagram of tumor apoptosis induced by TP. TNF-α receptor mediated exogenous signaling pathways, mitochondrial and endoplasmic reticulum (Er) stress mediated endogenous signaling pathways. Exogenous signaling pathways: (1) TNF-α—induced apoptosis was enhanced by inhibition of NF-κB. (2) Both TNF-α and FasL simultaneously activated caspase-8/3 signaling pathway and induce apoptosis. Endogenous signaling pathways: (1) By enhancing Bax/Bad and inhibiting the expression of Bcl-2, it further promotes the release of cytochrome C (Cyt C) and mediates apoptosis after activating the Caspase pathway. (2) By disrupting the mitochondrial membrane potential, the release of Cyt C causes oxidative stress on its surface to mediate apoptosis. (3) Er stress induces Er ROS generation, leading to mitochondrial dysfunction and enhanced mitochondrial ROS production

reproductive system [24]. Therefore, it is imperative to design various drug delivery systems including structural modification of the molecule, to effectively deliver TP to the targeted sites of action to decrease the amount of free drugs in other tissues and organs, which will reduce the toxic adverse effects and dosage and enhance its therapeutic efficacy.

Targeted drug delivery systems (TDDS) are a viable solution to the aforementioned problems. In particular, chemotherapeutic agents cannot be effectively enriched, and most of these drugs distribute to other normal organs throughout the body, leading to serious adverse effects. Nano-drug delivery systems (NDDS), which stem from TDDS, can enrich drugs passively through enhanced permeability and retention (EPR) effects at the tumor site [25, 26]. In addition, more accurate active targeting can make the drug effectively bind to the tumor tissue microenvironment or the specific receptor on the cell surface, thereby achieving a more effective outcome in destroying cancer cells [27, 28]. The two above-mentioned drug targeting methods, viz. passive and active targeting, will be discussed herein. During the past decade, various drug delivery systems have demonstrated remarkable promise for controlled release and targeted drug delivery (Fig. 3), such as polymeric micelles (PMs) [29–32], liposomes [33–36], solid lipid nanoparticles (SLNs) [37], microemulsions [38–40], and polymeric nanoparticles (PNPs) [41–44].

Thus, there is an urgent need to develop NDDS to encapsulate TP, which would likely increase its therapeutic efficiency and reduce its adverse effects. As an ideal drug carrier, it needs to have good biocompatibility, biodegradability [45–47] and avoid triggering the autoimmune defense mechanism of humans or animals [48, 49]. This review focuses on the research and design of targeted delivery systems for TP in recent years, especially in cancer treatment, to provide a reference for further exploration of more intelligent methods to improve the delivery of this molecule and other CHMs and expand the clinical applications of these compounds in the future.

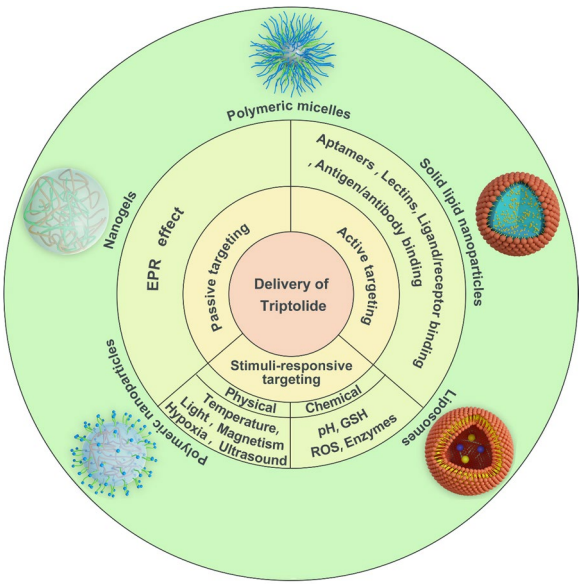


Fig. 3 Schematic diagram of triptolide targeted preparation classification

TDDS for TP

This review classifies and summarizes the recent researches on the combination of TP and nanocarriers according to passive targeting, stimuli-responsive targeting and active targeting. The specific nanocarriers include polymeric micelles, solid lipid nanoparticles, liposomes, polymeric nanoparticles, and nanogels.

Passive TDDS

Polymeric micelle-based TP delivery

As a common nano drug delivery system, polymer micelles (PMs) have become a hot spot in the research of anticancer drug delivery because of their advantages of reducing toxicity caused by free drugs, prolonged blood circulation and selectively accumulating at the tumor tissues [50, 51]. These carriers typically have diameters less than 100 nm [52]. PM with a high density of polyethylene glycol (PEG) shells have been shown to avoid recognition by the reticuloendothelial system and preferentially accumulate in solid tumors because of their enhanced EPR effect [51].

Many studies have shown that TP encapsulated in PMs can significantly enhance anti-tumor efficacy compared with free drugs [53]. By detecting thymus index, serum TNF-α and IL-2 levels, Xu et al. not only confirmed that TP- PMs showed no immunosuppressive activity compared with free drugs, but also that the anticancer activity of TP was not weakened after encapsulation. These results indicate that PMs are promising carriers for cancer therapy using TP [54].

As one of the cancers with the highest incidence, 5-fluorouracil has been used as first-line therapy for colorectal cancer in recent decades. However, its side effects and low tumor targeting result in an unanticipated prognosis for patients [55, 56]. Cui et al. designed polymeric micelles loaded with TP derivative LA67 (LA67-PMs) to improve drug accumulation in tumor. In vitro and in vivo experimental results showed that compared with LA67, LA67-PMs not only solved the problem of poor water-solubility of drugs, but also had higher accumulation

capacity and good therapeutic effect in tumor cells and tissues by means of EPR effect [57].

Although vascular endothelial growth factor (VEGF) blockers can effectively inhibit angiogenesis, the single target of the drug and the serious toxic side effects caused by the lack of selectivity make it difficult to achieve a good therapeutic effect after administration [58, 59]. According to published in vitro studies, TP inhibits angiogenesis [60, 61]. Using methoxypoly (ethylene glycol)-block poly(ε-caprolactone) as an excipient, Wang et al. encapsulated TP into PMs to prepare a nanoformulation. The pharmacokinetic results indicated that the drug concentration at the tumor site was selectively increased due to the EPR effect of PMs. After TP-PMs treatment, the tumor inhibition rate was increased, and the serum VEGF content was significantly decreased. In addition, immunohistochemical results indicated that the density and diameter of tumor vessels were decreased after TP-PM treatment compared with the control group [62].

Despite the aforementioned results suggesting that TP-PMs has remarkable potential for cancer targeted therapy, can overcome drug toxicity and inhibit angiogenesis, the disadvantages of PMs, such as low drug loading efficiency and poor stability, still require further study and refining.

Solid lipid nanoparticle-based TP delivery

Solid lipid nanoparticles (SLNs) are nanocarriers prepared from solid natural or synthetic lipids with particle sizes usually between 50 and 1000 nm. SLNs has been widely studied and applied in recent years due to its characteristics of high drug load, wide applicability, controlled drug release, good biosafety and stability [63–65].

Studies have shown that TP can play a therapeutic effect by significantly enhancing the level of ROS. However, because ROS can damage DNA and induce lipid peroxidation in cells, TP is highly toxic to normal metabolic organs, such as liver and kidney. Mei et al. prepared and characterized tp-loaded SLNs, and observed through a series of experiments that TP-SLNs can effectively reduce liver toxicity while possessing anti-inflammatory activity [64]. The experiment of treating rat foot swelling induced by carrageenan showed that the therapeutic effect of TP-SLNS group was stronger than free TP group. The results of serum physiology and biochemical analysis demonstrated that the hepatotoxicity of the TP-SLNs group was significantly lower than that of the free TP group. The above results indicated that TP encapsulated by SLNs had a good effect of toxicity reducing and efficacy enhancing.

To better elucidate SLNs-based therapy, TP-SLNs were also prepared by Xue et al. The in vivo behavior of SLNs was investigated by tracking and comparing the tissue distribution of free drug and nanoparticles in rats [66]. Through the data analysis of toxicokinetics and tissue distribution results, it was found that the nanoformulation could promote the absorption of TP and control drug release, indicating that one of the reasons for the enhanced efficacy of the nanoformulation may be the change of toxicokinetics. Although SLNs are suitable for drug administration in many ways and have a wide range of drug adaptability, the problems of low drug loading, easy formation of supercooled melts, and drug precipitation must be solved. More specifically, it remains to be studied whether the excipients of SLN affect the efficacy of TP [64, 67]. In addition, after oral administration, SLN is mainly excreted with feces by adhering to the mucosa. However, it should be noted that the particle size of nanoparticles and the characteristics of excipients will directly affect its metabolism and excretion process [68, 69].

Liposome-based TP delivery

As one of the most mature nanodelivery carriers, liposomes are one of the few nanoformulation that have been applied in clinical treatment, and their particle size ranges from 50–1000 nm [70]. Due to the special lipid bilayer structure, the water-soluble drugs can be encapsulated in the core and the lipid-soluble drugs can be encapsulated between the lipid bilayers [71–73]. The properties of liposomes, such as amphiphilicity, biocompatibility and biodegradation, are very valuable for the delivery of TCM. In addition, these carriers provide improved therapeutic efficacy and safety, increased bioavailability, sustained release, and localized drug delivery [74].

As a new therapeutic method, photosensitizer-based therapy has received extensive attention from researchers in recent years. Photodynamic therapy (PDT) is one of the two main methods of light therapy, which is based on the fact that a photosensitizer in a tumor is irradiated by a specific wavelength of laser light, which produces a large amount of ROS, thereby causing apoptosis [75]. In order to co-administer TP and PDT to achieve the purpose of enhancing the anti-tumor effect. Yu et al. designed a light-activated liposome (TP/Ce6-LP) combining photosensitizers Ce6 and TP to synergistically treat hepatocellular carcinoma (HCC) using the controlled drug release properties of liposomes and photodynamic therapy [76]. The results of anti-tumor activity studies showed that the combination therapy group induced apoptosis by up-regulating the expression of Caspase-3/PARP protein, and had a good therapeutic effect on patient-derived hepatocellular carcinoma xenografts (PDX^{HCC}) after irradiation.

In the field of TCM, TP is mostly used to treat RA. To improve the efficacy of transdermal drug delivery in collagen-induced arthritis (CIA) rats, Chen et al. prepared a microneedle patch to deliver tp-loaded liposome hydrogel (TP-LHP) for administration, and the experimental results were used to evaluate the pharmacokinetics and pharmacodynamics. All treatment dose groups of TP-LHP could reduce the degree of joint swelling, and the high dose group had the best effect after 1 week of treatment (Fig. 4). Since TP-LHP can continuously and stably release TP, the effect is significant after 4 weeks of continuous treatment. TP-LHP combined with microneedle administration strategy had a good effect in the treatment of RA [77].

In the field of translational medicine, liposomes have attracted more and more attention because of their good stability and biocompatibility. However, their shortcomings, which include low envelopment rate require further improving. In particular, for TCM, compound administration can often play a synergistic role; nevertheless, limited studies on their delivery using liposomes have been carried out. Therefore, the development of liposomes is one of the core contents of TCM pharmaceutics.

Polymeric nanoparticle-based TP delivery

Polymer nanoparticles (PNPs) with a particle size range of 10–1000 nm are a kind of carrier prepared by biocompatible and biodegradable polymer [78–80]. PNPs is a promising drug delivery vehicles with a simple manufacturing process that can deliver drugs to specific targets, thereby improving drug safety [81–83]. To increase the therapeutic benefit while minimizing side effects. More and more polymers have been used as excipients for the preparation of nanoparticles, such as poly (lactide-co-glycolic) acid [84], chitosan [85], phosphatidylcholine [86], poly (caprolactone) [87], and carboxymethyl chitosan [88].

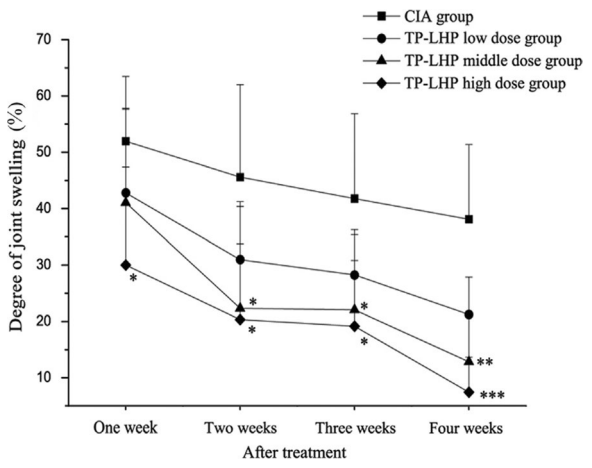


Fig. 4 Changes in the degree of joint swelling in the CIA and TP-LHP treated groups. $^{*}P < 0.01$, $^{**}P < 0.01$, $^{***}P < 0.001$ *vs.* CIA group, n = 9. Reproduced with permission from [77]

Poly (D, L-lactic acid)(PLA) has been widely used in the preparation of nanocarriers for drug delivery systems due to its good biocompatibility and biodegradability, and has been approved by the Food and Drug Administration for clinical application. Liu et al. prepared TP-PNPs with PLA using TP as a model drug, and investigated the renal toxicity of oral administration in rats [89]. In addition, urine samples from 5 groups of rats treated with TP-PNPs and free TP at day 5, 10, and 15 were analyzed. The results showed that compared with free drugs, TP-PNPS could effectively alleviate renal toxicity.

In order to reduce the toxic and side effects of TP during RA treatment, Zhang et al. encapsulated TP into nanoparticles prepared by poly-γ-glutamic acid-grafted l-aspartate di-tert-butyl ester (PAT) [90]. In vivo treatment experiment, nanoparticles accumulated in the inflammatory joint site, and played a good anti-inflammatory effect. In addition, the adverse effect of TNF-α was less than that of free TP. In addition, Liu et al. established a rat model of arthritis induced by complete Freund's adjuvant, prepared TP-PLA nanoparticles, and studied the anti-inflammatory effect after administration [91]. In vivo experiment results showed that TP-PLA nanoparticles had a significant inhibitory effect on adjuvant—induced arthritis. Compatibility is a key characteristic of multi herb prescriptions. TCM formulations which contain two or more herbs can often result in better curative outcomes and fewer adverse effects than formulations with single herbs [92, 93]. Studies have shown that co-loaded nanocarrier systems could allow for the encapsulated drugs to exert a synergistic antitumor effect [94, 95]. Some studies have reported that the combination of curcumin and TP at low concentrations has a synergistic antitumor effect on ovarian cancer [96]. Liu et al. co-loaded TP and curcumin into nanoparticles prepared by mPEG-DPPE (TP/Curc-NPs). Through prescription screening, it was found that when TP and curcumin concentrations were 25.22 ng/mL and 6.62 g/mL, respectively, the synergistic killing effect of the two drugs on SKOV-3 tumor cells reached the maximum [97]. The synergistic anti-tumor mechanism of TP and Curc is mainly through the activation of caspase-3/9 and the inhibition of heat shock protein (HSP) expression to induce cellular apoptosis. After combined administration, TP/Curc-NPs reduced HSP70 mRNA levels while maintaining HSP90 mRNA levels. Since TP will produce excessive ROS in the liver and kidney, which leads to toxicity and damage to normal tissues, the combination of TP and curcumin can

reduce ROS to achieve the purpose of attenuating toxicity and enhancing efficacy. In conclusion, TP/Curc-NPs has a good synergistic therapeutic effect, and curcumin can also alleviate the toxicity of TP to a certain extent. Therefore, TP/Curc-NPs may be a potential platform for ovarian cancer treatment. TP and celastrol (CL) are two monomers of TCM with various bioactivities isolated from TWHF. Silk fibroin protein is a kind of natural protein with many characteristics and is an ideal excipient for the preparation of nanoparticles. Ding et al. used SF as carrier material to prepare TP and CL loaded nanoparticles (TP-SFNPs and CL-SFNPs) respectively, and studied the synergistic therapeutic effect on pancreatic cancer cells (PC) [98]. Compared with free TP and CL, TP-SFNPs and CL-SFNPs can induce a large number of apoptosis of tumor cells due to the controlled release of TP and CL by SFNP during treatment. It showed good antitumor activity at the cellular level. The above results also reflect that the synergistic effect of TP-SFNPs and CL-SFNPs has a good therapeutic effect on PC.As one of the most widely used natural chemotherapy agents [99], paclitaxel (PTX) has long been a first-line drug for many cancers, such as non-small-cell lung cancer [100], glioblastoma [101], breast cancer [102], and However, long-term use causes cancer cells to develop resistance; thus, it has been reported that TP has anti-multidrug resistance in A549/Taxol cell lines mainly through inhibition of NF-κB signaling pathway and selective regulation of mitogen-activated protein kinase signaling pathway [103, 104]. Lipomeric hybrid nanoparticles (LPN) is a special nano carrier, which has the characteristics of both liposomes and polymerized nanoparticles [105, 106]. In view of this, in order to reduce drug resistance and then achieve the purpose of combined therapy, Liu et al. designed LPN as a combined drug delivery system of PTX and TP [107]. Compared with the control group, the nanoparticle group showed better anti-tumor effect. In vivo and in vitro experiments showed that PTX/TP-LPN had synergistic effects on lung cancer xenograft tumor, and the systemic toxicity was minimal. Although nanoparticles show great potential in TP delivery due to their controlled release of drugs, good biosafety and therapeutic effects [90, 91, 97], problems in mass production such as rigorous design and quality control still need to be thoroughly studied [108, 109].

Nanogels-based TP delivery

Hydrogels are three-dimensional network structures interwoven by hydrophilic polymers. Because of its good biocompatibility and drug delivery capacity, it is often injected directly into the site of the lesion for therapeutic purposes [110, 111]. In addition to preventing the drug from diffusing to normal tissues and causing side effects, it also has the effect of controlling the release and maintaining the concentration of the drug at the target site [112, 113] Considering the characteristics of hydrogels and nanoparticles, loading nanoparticles into the three-dimensional network structure of hydrogels can sustain drug release. This is one of the current main therapeutic strategies for hydrogels.

Due to the unique drug storage capacity of the hydrogel and the anti-inflammatory effect of TP, the combination of them can be used to treat RA and other diseases through transdermal administration. He et al. prepared the triptolide-loaded reduced graphene oxide hydrogel. Graphene nanosheets have good transdermal penetration while loading TP. Because of the strong π–π interaction between graphene oxide and triptolide, in vitro release studies showed that the release time of graphene hydrogels could be extended to 14 h (63.64–96.78%). The results of in vivo pharmacokinetic experiments showed that the relative bioavailability of graphene hydrogels was increased (3.3 fold) in comparison to the control hydrogels [114]. Analgesia and anti-inflammatory are two goals of RA treatment. Chen et al. cleverly brought them together using the gel as a platform [115]. In vitro and in vivo results showed that the pain threshold was increased and the inflammatory factors were effectively reduced after administration to the arthritis model rats.

In terms of anti-tumor therapy, Li et al. synthesized a triptolide-loaded injectable peptide hydrogel for in situ treatment of hepatocellular carcinoma [116]. In vitro results showed that the sustained release time of TP reached 14 days. Compared with human normal hepatocyte L-02, the liver cancer cell Bel-7402 has better cellular uptake and toxicity after administration. After in situ injection of nanogels into the tumor, TP was continuously released for more than 13 days and mainly accumulated in the target site, and the tumor inhibition rate was as high as 99.7%. Interesting, Zhang et al. designed a thermosensitive nano-hydrogel containing TP using a biodegradable material (poly (*N*-isopropylacrylamide). It is liquid at room temperature. After local injection into the tumor site, the gel is formed due to temperature rise, and TP released further mediates tumor apoptosis while anti-angiogenesis, which plays a good synergistic therapeutic effect [117].

Although nanohydrogels have the advantages of prolonged drug release, good biocompatibility, and biodegradability. However, for some special diseases that require drugs to quickly reach the plateau threshold, it is best to cooperate with other modes of administration.

Stimuli-responsive nanoparticle-based TP delivery

Stimuli-responsive drug release and targeted drug delivery are two high-profile directions in cancer research, which have potential in intelligent and personalized cancer treatment [118]. In recent years, drug stimulus-responsive delivery systems have been extensively studied and have shown irreplaceable advantages in the diagnosis or treatment of various diseases. Researchers can design intelligent drug delivery systems based on physical or chemical factors, such as temperature, light, magnetism, hypoxia, glucose, pH, ultrasound, enzymes, and redox potential) and other lesion microenvironments or external interventions [119, 120]. Nanocarriers prepared using materials with stimuli-responsive release can deliver drugs to target sites or target cells and release them according to the responsive properties [121].

Due to the increase of ROS caused by chronic inflammation and the high expression of glutathione (GSH) caused by self-protection mechanisms, the microenvironment of tumor tissue is very different from that of normal tissue [122, 123]. Wang et al. used the special conditions of the tumor microenvironment to co-dissolve dithiodiacetic acid with PEG-2000-linoleic acid (mPEG2000-LD) in ethanol to develop a prodrug conjugated with TP and vitamin E (VE). In vitro release results showed that pegylated nano prodrug had a certain redox reaction, and the combination of PEGylated nano prodrug with TP prodrug had good targeting, sustained release and safety [27].

Based on the red fluorescence and good antitumor activity of doxorubicin (DOX), Wu et al. designed a stimuli-responsive release nano-drug delivery strategy [124]. Using a reduction-responsive polymer (mPEG-S–S-C16) and other excipients, a lipopolymer nanoparticle co-encapsulating DOX and TP was prepared. The results of in vitro drug release and cell internalization showed that the nanoparticles could successfully release the two drugs. In vitro and in vivo experiments showed that DOX/TP co-loaded LPNP (DOX/TP-LPNP) had a strong synergistic effect, and the combination index was low.

Negatively charged nanoparticle surfaces in the blood circulation have been reported to enhance stability, while conversion to positive charges in a slightly acidic tumor microenvironment enhances cellular uptake of the particles [125–127]. Based on this, Xu et al. designed a nanocarrier for pH-responsive charge switching and redox-responsive drug release [128]. The prepared nanoparticles were named DA-SS-DT. When DA-SS-DT reaches the tumor tissue due to the EPR effect after intravenous administration, the slightly acidic environment reversed its surface charge, which enhances the uptake of tumor cells. After cellular uptake, the drug begins to be released from the nanoparticles due to its redox-sensitive properties, which in turn exerts an antitumor effect (Fig. 5).

Stimulus-responsive drug delivery systems are multifunctional and smart; however, current developments

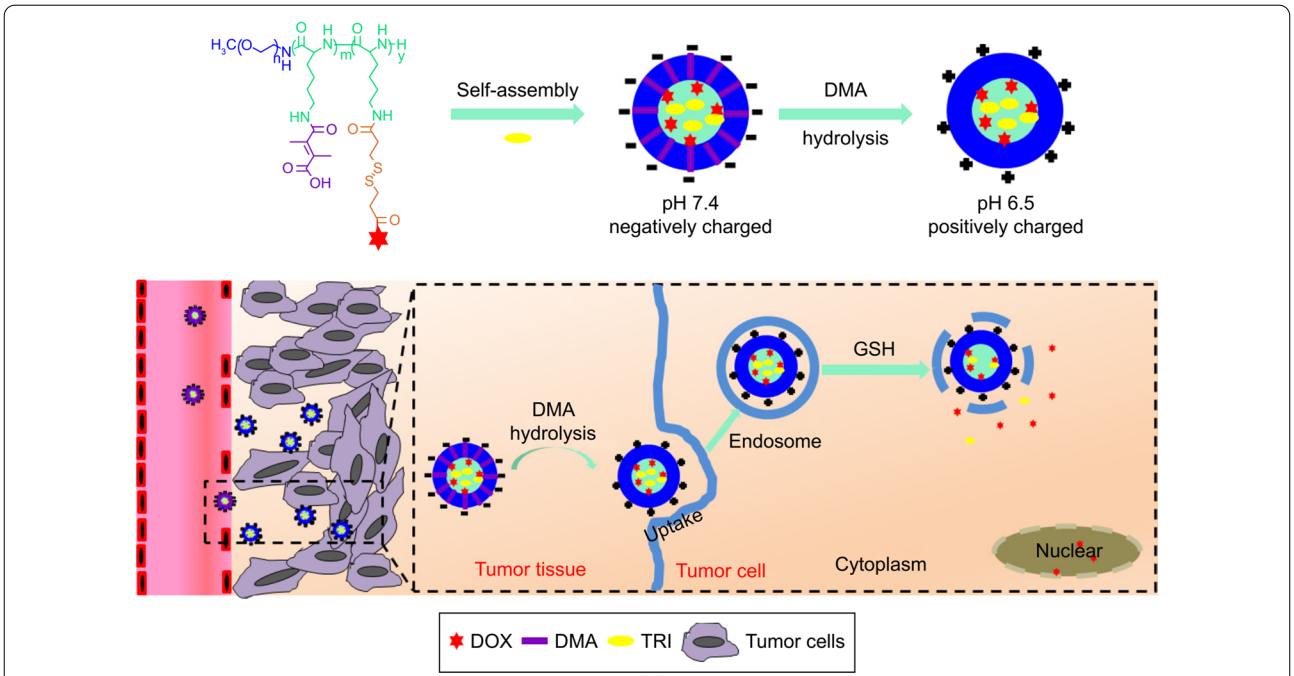


Fig. 5 Schematic diagram of the structure and treatment of DA-SS-DT nanoparticles. Reproduced with permission from [128]

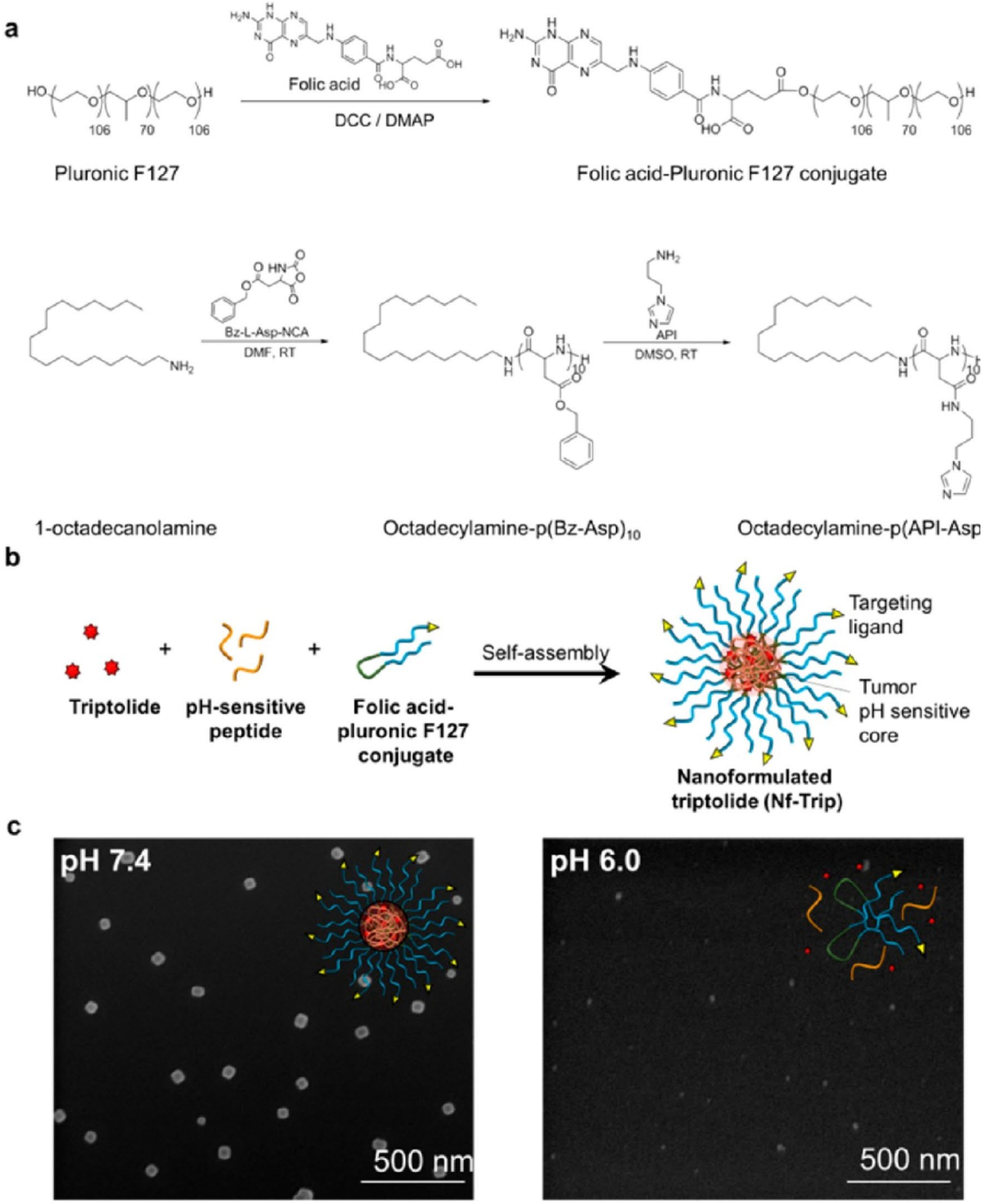


Fig. 6 Synthesis and characterization of nano-formulated triptolide (Nf-Trip). **a** Synthetic scheme of Pluronic F127-folate conjugate and octadecylamine-p (API-Asp)10. **b** Fabrication of Nf-Trip through self-assembly. **c** SEM images of Nf-Trip at pH 7.4 and pH 6.0. Reproduced with permission from [138]

in science and technology are not capable of mass production for clinical application. Therefore, a balance should be reached between application and research and development, striving to ensure that stimulus-responsive nanocarriers will eventually become practical in the near future.

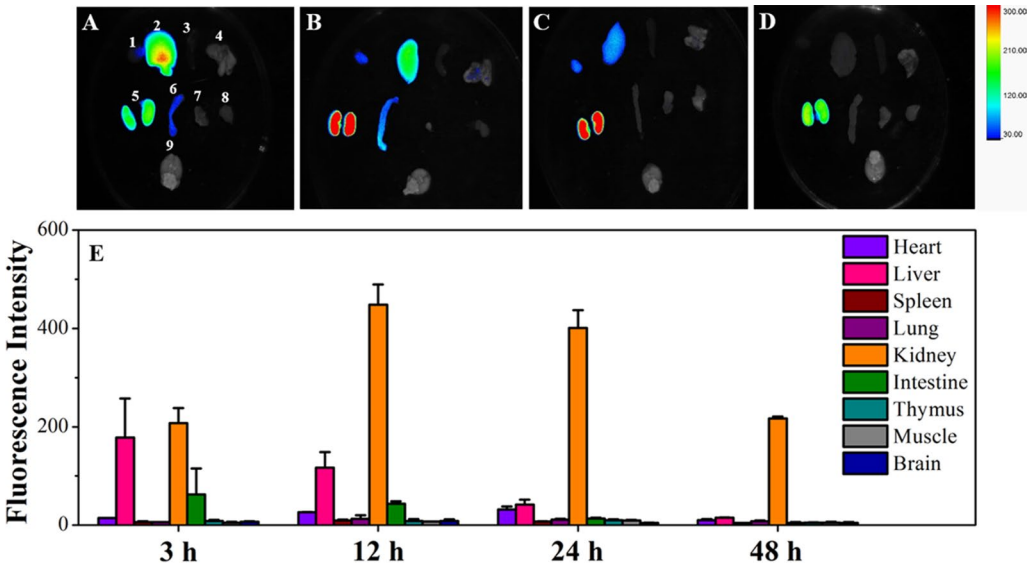


Fig. 7 Ex vivo fluorescence images and biodistribution of Cy7 in organs (1–9: heart, liver, spleen, lung, kidneys, intestine, thymus, muscle, and brain) of mice after Cy7-FPNP injection at **A** 3, **B** 12, **C** 24, and **D** 48 h. **E** Corresponding fluorescence intensity of Cy7 distribution in each organ is examined (**A**–**D**). Data are expressed as mean ± SD (n = 3). Reproduced with permission from [148]

Active TDDS

Passive targeting utilizes the phenomenon of increased vascular permeability and decreased lymphatic return in tumor tissue to make nanoparticles accumulate in the tumor, namely EPR effect. Active targeting uses ligands modified on the surface of nanocarriers to bind to highly expressed receptors on the surface of target cells, followed by receptor-mediated endocytosis so that nanoparticles can selectively accumulate in target cells. The advantage of the active targeted drug delivery strategy is that in addition to increasing the concentration of the drug at the target site, it also reduces the accumulation of the drug in non-target organs, thereby reducing toxicity and enhancing efficacy [129–133].

Because of its insensitivity and resistance to conventional chemotherapy drugs, HCC is one of the tumors with the worst prognosis [134, 135]. The combination of active targeting and stimulus reactivity does not only promote the specific accumulation of nanoparticles at the tumor site, but also improves the release of drugs at the target site, thereby improving therapeutic efficacy and reducing adverse effects [136, 137]. Through comparison and screening, Ling et al. found that the natural product TP has better antitumor activity than the current first-line drugs sorafenib, doxorubicin and daunorubicin. Considering some disadvantages of TP, the researchers synthesized tumor pH-sensitive TP nanoformulations containing folate for folate receptor (FA-R) overexpressed HCC [138]. The synthesis and characterization of nano-formulated TP (Nf-TP) are shown in Fig. 6. In vivo experiments indicated that the nanoparticles connected to folate ligands could specifically bind to FA-R on the surface of HCC, and receptor-mediated endocytosis resulted in the hydrolysis of the pH-responsive lipid core and the release of TP in cancer cells. The observed tumor inhibition effect was significantly better than that in the other groups, and the toxicity and adverse effects of TP were effectively controlled.

Unlike the FA-R on the surface of most solid tumor cells, the asialoglycoprotein receptor (ASGP-R) is specifically located on the surface of HCC cells [139, 140]. Aiming at this unique target, Zhang et al. developed a galactose-modified TP nanoparticle (GC-TP-NP), which can specifically target HCC for anti-tumor therapy. [141].

GC-TP-NP not only has a sustained release effect on drugs, but also galactose can specifically bind to ASGP-R, actively targeting liver cancer cells, improving drug efficacy and reducing systemic side effects. The researchers further studied and found that GC-TP-NP mainly induces cancer cell apoptosis by blocking the TNF-α/NF-κB/Bcl-2 signaling pathway. Compared with HCC, breast cancer is one of the most fatal cancers in women due to its rapid growth and rapid metastasis. In order to improve the tumor delivery rate and anti-metastatic effect of chemotherapy, Zhang et al. designed a CD44-targeting and pH/redox-sensitive nanosystem, which can actively target CD44 overexpressed on the cell surface through hyaluronic acid and release the drug in response to the tumor microenvironment, improving the antitumor effect. At the same time, lung metastasis of tumor

Table 1 Summary of different delivery systems for triptolide

Nano-carriers	Targeting category	Treatment of type	Refs.
Polymeric micelles	Passive targeting	Anti-cancer	[53, 54, 57, 62]
Solid lipid nanoparticles	Passive targeting	Anti-inflammatory	[64, 68]
Liposomes	Redox-responsive	Anti-cancer	[76]
	Passive targeting	Anti-inflammatory	[77]
Polymeric nanoparticles	Passive targeting	Anti-cancer	[96–98, 107]
	Passive targeting	Anti-inflammatory	[90, 91]
	Redox-responsive	Anti-cancer	[27, 32, 124]
	Redox-responsive and pH-triggered charge-switchable	Anti-cancer	[128]
	Active targeting	Anti-cancer	[138, 141]
	Active targeting	Anti-renal ischemia/reperfusion injury	[148]
	Active targeting	Anti-cancer	[142]
Nanogels	Passive targeting	Anti-inflammatory	[114, 115]
	Thermo-responsive	Anti-cancer	[117]
	Passive targeting	Anti-cancer	[116]

was inhibited [142]. The results in vitro and in vivo indicated that the preparation had good effect on promoting tumor cell apoptosis and anti-tumor metastasis.

Acute kidney injury (AKI) is a kidney disease with high morbidity and mortality [143, 144]. Renal ischemia/reperfusion injury (Renal ischemia/reperfusion injury, IRI) is often caused after renal transplantation, cardiopulmonary resuscitation and aortic bypass surgery, trauma, hemorrhage, and is the main cause of AKI [145]. TP is an important bioactive compound with a variety of pharmacological activities, including the effective treatment of nephritis and renal IRI [146]. It is well known that the FA-R is highly expressed in tumors. However, FA-R is also commonly expressed in normal tissues and organs, such as the placenta, kidneys, and intestinal membranes [147].

To reduce toxicity and increase the effectiveness of TP, Huang et al. reported a biocompatible and high-efficiency renal-targeting nano-platform for IRI therapy, in which the toxic drug, TP, was encapsulated into FA-modified Pluronic F127/P123 nanoparticles (FPNP) [148].

In vitro organ imaging results showed that FPNP had higher renal selectivity and longer retention time, as shown in Fig. 7. Systemic toxicity test showed that the nephrotoxicity, hepatotoxicity and reproductive system toxicity of TP-FPNP were significantly lower than those of free TP. Although there are many advantages of active targeted NDDS, the clinical application for disease treatment is very limited because of the following reasons: (1) the single target drug does not achieve the ideal targeting performance; (2) quality control of the complex system is difficult to carry out; and (3) high research and development costs lead to unaffordable medical bills. With the progress in science and technology, it is believed that there will be more stable, reliable, and low-cost active TDDS in clinical settings in the foreseeable future for the benefit of humankind.

The examples of TP combined with nano delivery system are shown in the Table 1, which are summarized and summarized according to nano-carrier, targeting category and treatment of type. The above summarizes the application of the combination of TP and TDDS in the medical field. Whether it is passive targeting, stimuli-responsive targeting or active targeting, all have their own advantages and characteristics. However, no one is perfect. In the selection of TDDS, we should make full use of the specific characteristics of diseases and drugs to avoid weaknesses. For example, some diseases require nanocarriers to quickly release drugs, some diseases require nanocarriers to have a sustained-release effect, and some diseases require nanocarriers to rapidly release drugs to the plateau threshold before sustained release. Therefore, for the problems currently faced, TDDS technology urgently needs to be upgraded and developed. There is still a long way to go in terms of safety and quality control for mass production, beyond the use of functional nanocarriers for therapeutic purposes.

Conclusions

With a long history spanning over more than a thousand years, TCM still plays an irreplaceable role as an important part of human medical treatment. As a CHM, TP is a classic diterpenoid epoxide with a variety of pharmacological activities, such as anti-inflammatory, anti-autoimmunity, anti-cancer, and anti-fertility effects. Although TP has a good curative effect, its clinical application is

limited by its severe toxicity, adverse effects, and poor water solubility. To reduce toxicity and increase efficacy, numerous drugs are delivered using advanced nano drug delivery systems. Based on the numerous examples of NDDS available in literature, this review systematically introduced passive and active targeting methods of TP administration, and preliminarily discussed their advantages and disadvantages. Whether using passive or active targeting, single or combined drug delivery approaches, the nano-targeted drug carriers containing TP have been reported to show site targeting, safety, and superior therapeutic effect compared with free TP. Moreover, stimulus-responsive drug carriers have demonstrated the advantage of intelligent drug delivery. Overall, these targeted delivery strategies could be used as a starting point for future utilization of TP and other TCMs in experimental therapy. Despite the limitations of NDDS and a large number of drug delivery systems are still in the pre-clinical research stage, especially for TCM preparations; however, advances in technology might prompt researchers to pay attention to the development of TCM into novel drug delivery systems.

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RS and JYD drafted and wrote the manuscript. LY and MJL collected the related reports, and helped revise the manuscript. ZQY and LGT provided direction and guidance throughout the preparation of this manuscript. All authors reviewed the final version of the manuscript. All authors read and approved the final manuscript.

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Declarations

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Competing interests
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