Review

Triptolide: A Review of Its Traditional Use, Derivatives, Pharmacology, Antitumor Effect, and Clinical Applications

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Review

Triptolide: A Review of Its Traditional Use, Derivatives, Pharmacology, Antitumor Effect, and Clinical Applications

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Abstract

Triptolide (TPL), a diterpenoid derived from the Chinese medicinal plant Tripterygium wilfordii, exhibits broad-spectrum biological and pharmacological activities, although its clinical translation is limited by systemic toxicity. Recent advances in the development of TPL derivatives have created new therapeutic opportunities. This review summarizes current knowledge of triptolide, with a focus on TPL's toxicity profile, derivative strategies, and antitumor mechanisms. There are at least ten cancer types studied by research. We also summary the plant origin and traditional uses of the plant, TPL's pharmacokinetics (PK), and relevant clinical trials against tumors. The main mechanism of TPL antitumor effect is interfere ATPase of XPB via covalently binding to it, as well as inducing rapid depletion of RPB1 via hyperphosphorylation and ubiquitination. We also reviewed systematic toxicity including neuro, cardio, oto, nephron, hepato, digestive hemato and reproductive toxicity. Finally, we searched the clinical trials through three platforms against tumor and concluded that Minnelide has great potential against solid tumor in clinic. By critically evaluating TPL and its derivatives from multiple dimensions, this review aims to inform future strategies that maximize therapeutic efficacy while minimizing adverse effects.

Keywords: triptolide; derivatives; toxicity; clinical trial; antitumor; mechanism

1. Introduction

Tripterygium wilfordii Hook. f. (TwHF), known in Chinese as "Leigongteng" holds a significant place in traditional Chinese medicine, with documented uses dating back centuries[1]. Despite its historical application in treating conditions including rheumatoid arthritis and skin disorders, the drug's apparent toxicity has limited its wider clinical applications. Triptolide (TPL), a key bioactive diterpenoid triepoxide, was isolated from TwHF in the 1970s and was found to have pharmacological potential, particularly as a potent antitumor agent in medulloblastoma, pancreatic cancer, and leukemia in vivo[2-4]. TPL mechanism of action includes indirect degradation of RNA polymerase II, and inhibition of transcription factor machinery XPB[5]. As such, TPL has shown efficacy in a wide spectrum of cancers, such as glioma, pancreatic cancer, lung cancer, and leukemia. However, the clinical translation of TPL has been hampered by its poor solubility and systemic toxicity[6]. In recent years, extensive research has been dedicated to overcoming these challenges through the synthesis of novel derivatives and the development of advanced drug delivery systems[7]. This review aims to provide a comprehensive and up-to-date synthesis of the traditional uses, chemical derivatization, pharmacology, antitumor mechanisms, and the current status of clinical trials of TPL and its derivatives, highlighting both the promising therapeutic avenues and the persistent challenges in its development as a modern onco-therapeutic drug.

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2. Plant TwHF Characteristics and Geographic Distribution

The plant TwHF (also known as Thunder God Vine) is a traditional Chinese botanical medicine, first documented in the Compendium of Materia Medica in the 16th century[1]. The plant's Chinese name (Leigongteng) alludes to the plant's potent toxicity. The plant is cultivated across Asia, including Korea, Japan, and India. TwHF was introduced to the United States in the 1930s and has since attracted research interest from scientists worldwide. This plant is a deciduous subshrub or climbing semi-woody vine, and its root and rhizome are highly important in traditional Chinese medicine. TwHF belongs to the genus Tripterygium (Celastraceae), which includes several closely related species, such as T. hypoglaucum and T. regelii[8], which are also toxic and exhibit similar antitumor and immunomodulatory effects.

3. Traditional Uses of TwHF and Chemical Structure of TPL

The traditional uses of TwHF were documented in Chinese medical literature as early as the Ming Dynasty. No non-Chinese medicinal use of TwHF was documented prior to modern times, likely due to its restricted geographical distribution. Given its significant toxicity, TwHF was traditionally applied topically rather than orally. A summary of its traditional uses is provided in Table 1.

In 1972, a compound called TPL was extracted from the roots of the TwHF plant[9]. X-ray crystallography showed that TPL consists of a 5/7/5 tricyclic diterpenoid canonical skeleton, a highly strained and reactive three-membered epoxy bridge (C-12/C-13), and a α,β-unsaturated five-membered lactone ring (Figure 1).

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Table 1. Traditional uses of TwHF.

The name or origin of traditional uses	Main components	Usage	Reference
TwHF	Leaves of TWHF	Skin itchy, external use	Hunan Materia Medica
TwHF	Flower of TWHF, Lindera aggregata (Sims) Kosterm	Skin sores, external use	Hunan Materia Medica
HUO BA HUA GEN Tablet	Root of T. hypoglaucum	Syndrome of wind cold dampness arthralgia	10.3321/j.issn:0253-2670.2001.09.032
Tripterygium glycosides tablets	tripterygium glycosides	Rheumatoid arthritis, nephrotic syndrome,	10.1016/j.eng.2024.04.003
TwHF tablets	Triptolide	Rheumatoid arthritis, nephrotic syndrome, Behçet's triad, leprosy reaction	10.19540/j.cnki.cjcmm.20200710.501
Jin Guan Tablets	TwHF, Dipsacus asper Wall.ex Henry, Chinese yam, Asarum heterotropoides F. Schmidt etc.	Rheumatoid arthritis, ankylosing spondylitis	10.3969/j.issn.1674-7860.2012.24.030
Shuangniu Trauma Medicinal Wine	Root of TwHF, aconitum kusnezoffii, safflower etc	Traumatic injuries, external	Wenke Hu's experience
Kidney disease prescription	TwHF, Chrysanthemum, dandelion, bittercress	Nephrotic syndrome	10.1002/14651858.CD008568.pub2.
Anti-rheumatic wine	TwHF, Clematis chinensis, Rehmannia root, Polygonatum sibiricum	Rheumatoid arthritis	Hebei traditional Chinese medicine (Author translation from Chinese)
God's Response All-Effective Ointment	TwHF, Aconitum kusnezoffii, Linderae sibiricum, Areca catechu	All wind-induced swelling and toxic diseases	Plaster Prescription Collection (Author translation from Chinese)
Insecticide	TwHF	Insecticides to larva	10.1515/znc-2004-5-62410.1515/znc-2004-5-624

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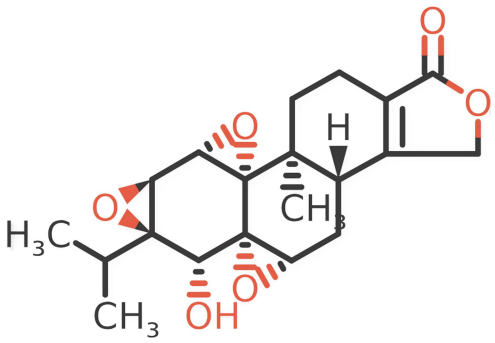

Figure 1. Chemical structure of TPL. (Adopted from FDA website https://precision.fda.gov/home).

4. Pharmacodynamics and PK

4.1 Toxicity

The clinical application of TPL is significantly limited by its dose-limiting organ toxicities, which affect the liver, kidneys, heart, reproductive system, and others (Figure 2). As the primary site of drug metabolism, the liver is particularly susceptible to toxicity from drugs and their metabolites. TPL-induced hepatotoxicity involves multiple intracellular signaling pathways, including the regulation of cytochrome P450 enzymes, immune cell responses, and gut microbiota imbalance. Specifically, TPL has been shown to cause hepatotoxicity by reducing the substrate affinity, activity, and expression (at both transcriptional and protein levels) of CYP450 isoforms, including 3A, 2C9, 2C19, and 2E1[10-12]. Furthermore, TPL sensitizes hepatocytes to exogenous NK-cell-mediated cytotoxicity by inhibiting hepatocyte MHC-I expression[13]. Additionally, TPL-induced liver injury has been linked to Th2 cytokines produced by iNKT cells, which promote the expression of immunoregulatory factors[14]. TPL triggers iron accumulation and lipid peroxidation by modulating Nrf2 expression[15]. Interestingly, TPL perturbs the gut microbiota-bile acid-FXR axis, wherein a reduction in Lactobacillus rhamnosus GG abundance ultimately promotes liver damage[16].

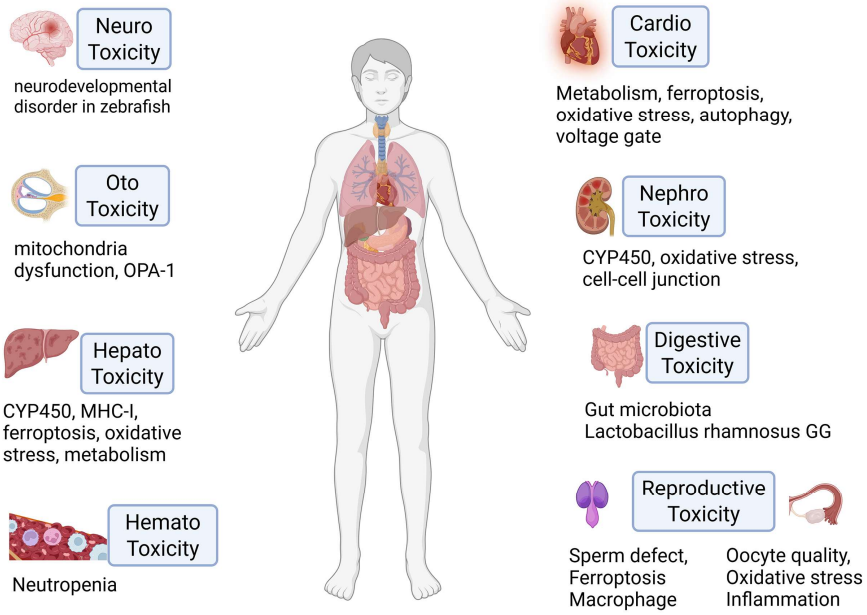

Figure 2. Reported systemic toxicities associated with TPL (Created with BioRender.com).

The kidney is also highly vulnerable to TPL toxicity. Shen et al. demonstrated that the organic cation transporter 2, expressed on the surface of renal tubular epithelial cells, mediates TPL transfer

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from the blood into the renal tubule[17]. Within the tubule, TPL disrupts cell-cell junctions and increases paracellular permeability[18]. The principal mechanisms underlying TPL-induced nephrotoxicity are oxidative stress and inflammation, the severity of which is dose-dependent[19]. Multi-omics analyses have revealed associated alterations in RNA and protein profiles, implicating several pathways in TPL nephrotoxicity. These include the cytochrome P450 protein family, cellular lipolytic activity, and antioxidant nuclear transcription factors, operating through acute-phase response signaling, the antigen presentation pathway, FXR/RXR activation, LPS/IL-1-mediated inhibition of RXR function, and EIF2 signaling[20, 21]. Furthermore, an in vivo study confirmed that oxidative stress-induced mitochondrial DNA damage activates the cGAS-STING signaling pathway, ultimately leading to nephrotoxicity[19].

Research on TPL-induced cardiotoxicity emerged in the 2010s. A predominant finding is that metabolic dysregulation, implicated in approximately half of the related studies, impairs glucose uptake and glycogen metabolism[22, 23], This dysregulation promotes the generation of reactive oxygen species (ROS), inducing oxidative stress that damages cardiac mitochondria, proteins, and DNA through multiple pathways[24, 25], ultimately leading to cardiomyocyte apoptosis and F-actin depolymerization[26]. Mechanistic studies have highlighted several key processes. The mitochondria-targeted antioxidant MitoQ was shown to alleviate TPL-induced cardiotoxicity by restoring NRF2 expression[27]. Similarly, calycosin, a compound known to regulate mitochondrial respiration via PGC-1α activation[28, 29], protected against TPL-induced impairment of PGC-1α/NRF1-dependent mitochondrial biogenesis and respiration[30], suggesting a potential combination strategy to mitigate toxicity. Furthermore, Xu et al. demonstrated, using patch-clamp experiments, that TPL binds to and inhibits the voltage-gated sodium channels Nav1.5 and Nav1.7, contributing to its cardiotoxic effects[31]. Additional reported mechanisms include SLC7A11/GPX4 inactivation-mediated ferroptosis and dysregulated autophagy[25, 32, 33].

TPL systemic toxicity has been studied in a number of preclinical in vivo models. In zebrafish embryos, TPL exposure caused a concentration-dependent reduction in mean swimming distance, suggesting neurobehavioral toxicity[34]. Paradoxically, other studies have reported neuroprotective effects in models of neurodegenerative diseases, attributed to its anti-inflammatory action on microglia[35, 36]. In male reproduction, TPL induced significant testicular damage and impaired spermatogenesis, characterized by reduced sperm concentration and aberrant morphology. These effects were mediated by elevated ROS and malondialdehyde production, coupled with decreased glutathione levels and glutathione peroxidase 4 (GPX4) expression[37]. In females, TPL exposure diminished ovarian function and fertility, an effect driven by mitochondrial DNA release and subsequent activation of the cGAS-STING pathway[38]. Additionally, TPL administration perturbed the gut microbiota composition, notably reducing the abundance of Lactobacillus rhamnosus GG[16]. TPL induced mitochondrial dysfunction and ROS production, causing systemic inflammatory response in the kidney and liver[39], as well as inner ear stem cells[40].

4.2. PK

A comprehensive review published in 2019 summarized the PK profile of TPL[41]. Briefly, TPL is rapidly and extensively absorbed after oral administration, exhibiting a bioavailability of approximately 75% in dogs and reaching peak plasma concentration (Tmax) within 10 minutes. Following oral dosing, TPL distributes extensively into major organs, including liver, heart, spleen, lung, and kidney. TPL is metabolized primarily by human CYP2C19 and CYP3A4 enzymes, with less than 4% of the administered dose recovered unchanged in feces, bile, and urine within 24 hours. It is eliminated rapidly, with reported terminal half-lives of 0.42 hours (oral) and 0.19 hours (intravenous) in rats. Notably, nearly 39% of the parent drug is cleared via biliary excretion post-absorption[41]. In 2020, Zhu et al developed a strategy for synchronous measuring of TPL both in blood and brain based on mass spectrometry[42]. They found the Tmax to be 55.0±12.3min and Cmax of 15.1±5.3ng/ml after oral gavage 0.5mg/kg for normal rats, and area under the curve increased to 1.5-fold in rat models of Alzheimer's disease.

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Subsequent studies include TPL co-administration with paeoniflorin, which resulted in reduced peak concentration (Cmax) and delayed the Tmax of TPL[43]. The uptake and efflux of TPL in the rat duodenum were shown to be mediated by Oatp1a5 and P-glycoprotein, respectively[44]. Pretreatment with antibiotics increased the Cmax and relative bioavailability of TPL by approximately 50%, attributable to an elevated inflammatory response[45].

TPL Derivations and Delivery System

5.1. Chemical Structure of TPL's Derivation

Due to its significant systemic toxicity (described below) and poor aqueous solubility, numerous derivatives have been synthesized to overcome these limitations. To the best of our knowledge, at least 20 TPL derivatives with confirmed in vitro cytotoxic effects have been reported (Table 2). The paramount common advantages of these derivatives are reduced toxicity and improved solubility[46]. Beyond these shared benefits, several derivatives exhibit specific mechanistic advantages: TRC102 potently reduces tRXRα expression and inactivates AKT[47]; LLDT-8 and LLDT-67 demonstrate neuroprotective effects against ischemic injury and Parkinson's disease, respectively[48, 49]; and MRx102 downregulates XIAP and Mcl-1, inhibits RNA transcription, and suppresses the Wnt signaling pathway[50].

5.2. TPL Delivery

A 2019 review elaborately summarized TPL delivery systems into five types, including nanoparticle encapsulation, oligonucleotide, peptide, sugar, and antibody conjugates[51]. Herein, we review the progress achieved from 2019 (summarized in Table 2).

The field of nanomaterials has witnessed explosive growth in recent years, attracting extensive research interest. Exosomes, as endogenous delivery systems that have gained prominence in recent years, exhibit targeted effects, reduced toxicity, and immune evasion capabilities. Liu et al. were the first to construct a TPL-loaded exosome delivery system, demonstrating superior antitumor efficacy compared with free TPL, along with reduced liver and spleen toxicity[52]. Another report combined exosomes and liposomes with oligonucleotides to co-deliver miR-497 and TPL, overcoming cisplatin resistance in ovarian cancer by activating the PI3K/AKT/mTOR pathway[53]. Similarly, Gu et al. developed hybrid nanoparticles encapsulating exosomes, liposomes, and CYP3A4-siRNA, which effectively inhibited melanoma growth with negligible toxicity in a mouse model[54].

Recently, biomimetic nanoparticles have shown considerable potential in prolonging circulation time, enhancing membrane penetration, and improving the solubility and stability of loaded drugs. Li et al. developed cancer cell membrane-camouflaged biomimetic Poly(lactic-co-glycolic acid) (PLGA) nanoparticles loaded with TPL for the treatment of hepatocellular carcinoma (HCC), which promoted tumor-site accumulation and reduced TPL toxicity[55]. Another study utilized a cancer cell-platelet hybrid membrane to co-deliver sorafenib and TPL, leveraging the advantages of both long circulation and homologous targeting[56]. Metal-organic frameworks (MOFs) have recently emerged as promising drug-delivery platforms due to their tunable pore sizes, large surface areas, and ease of functionalization. In one study, a TPL-loaded MOF coated with methotrexate enabled effective tumor accumulation and deep penetration, thereby remodeling the tumor microenvironment in triple-negative breast cancer[57].

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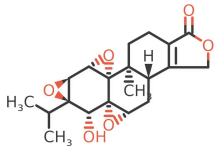
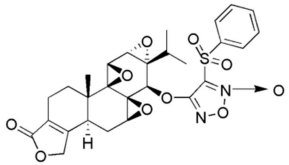
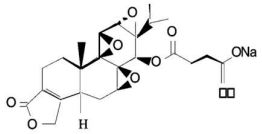
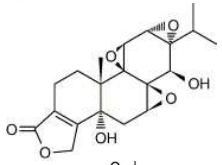
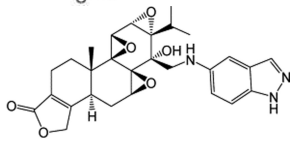
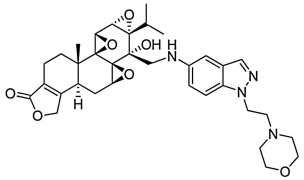
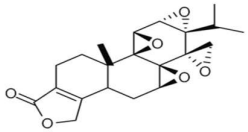
Table 2. The derivation and delivery system for TPL

Name	Molecular formula*	Advantage	Reference
TPL			[9]
ZT01		Strong anti-inflammatory effects and low toxicity; an obviously beneficial effect on DSS-induced colitis	[58]
PG490-88 (Omtriptolide)		Highly effective in prevention of murine GVHD via inhibition of alloreactive T cell expansion through interleukin-2 production	[59]
LLDT-8		Inhibiting T cell activation; reduce toxic	[60]
LLDT-246		Suppresses NF-κB signaling by interpreting AKT/GSK3β/mTOR pathway on HCT-116 cells	[61]
LLDT-288		Efficacy in human prostate xenograft mice model with obviously low toxicity; No inhibitory effects on CYP450 isoforms	[62]
LLDT-67		Neuroprotective effect: enhance NGF synthesis in astrocytes in the midbrain and rescue dopaminergic neurons indirectly through TrkA activation	[48]

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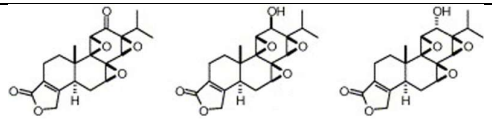
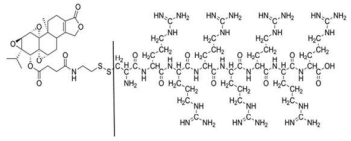
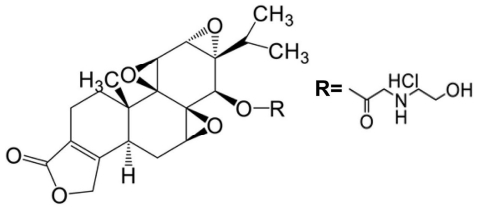
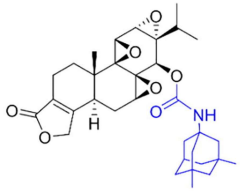
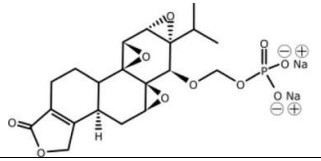
Epoxide-transposition analogues of triptolide	 Not available	Cytotoxicity to A549+HT29	[63]
MRx-102		Decreased leukemia burden and increased survival time in mouse; Inhibited Wnt pathway in lung cancer	[50, 64]
TP-disulfide-CR7 (TP-S-S-CR7)	 Not available	Reduce toxicity to skin and organ; No effect on the intracelluar ROS;	[65]
Triptolidyl 2-(1-methylpiperidine-1-yl) acetate and a series of C-14 triptolide derivatives (17 types)		Decrease toxicity and increase water-solubility; Efficacy on imatiniv-resistance CML	[66]
TRC4		decrease the nuclear retinoid X receptor-α; inactivate AKT and induce apoptosis	[47]
TPL-memantine		neuroprotective effect against Aβ1–42 toxicity; an inhibitory effect against LPS-induced TNF-α production	[67]
Minnelide		Increase water-solubility and bioavailablity; reduce systemic toxicity; clinical trial for pancreatic cancer and medullablastoma	[2, 68]

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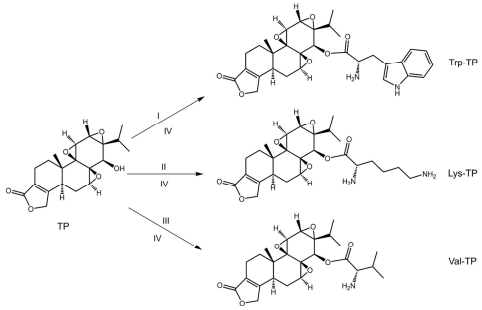
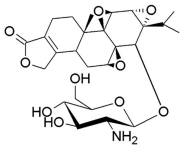
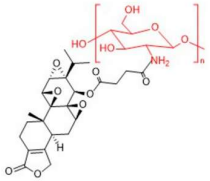
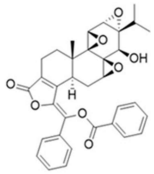
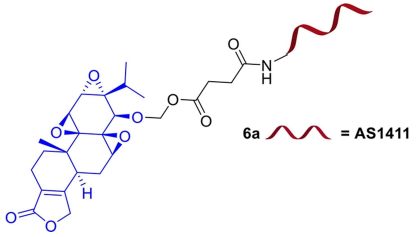
Tryptophan (Trp), Valine (Val), and Lysine (Lys) conjugated to TPL		pancreatic cancer-selective delivery system and increase cytotoxicity	[69]
triptolide aminoglycoside (TPAG)		Increase kidney-targeting efficiency; Protective effect against renal ischemia/reperfusion injury; Low systemic toxicity	[70]
TP-CSO		Increase water-solubility; reduce systemic toxicity; Increase half-life in the blood circulation	[3]
CK21		inhibit NF-kB pathway; increase intracelluar ROS; reduce toxicity in vivo	[71]
AS1411-triptolide conjugate (AS-TP)		in-situ triptolide release and increase intra-tumor triptolide accumulation; increase anti-TNBC efficacy and reduce toxicity in vivo	[72]
TPL loaded nanoparticle platform composed of L-ascorbate palmitate	Not available	Increase the water solubility; reduces the systemic toxicity; Inhibit the erosion of synovitis and bone tissue	[73]

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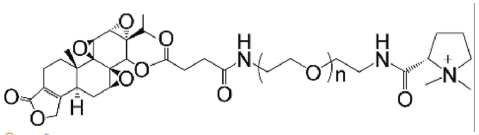
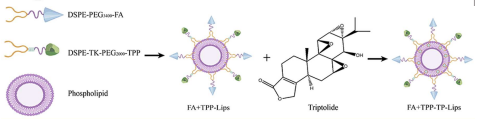
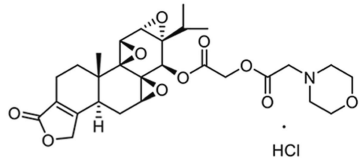
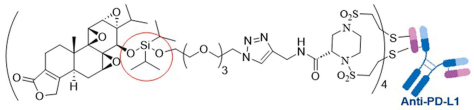
(TP-PEG-SS) assembled with ginsenoside Rg3 and lecithin to form nanovesicles		targeted mitochondria and M2 macrophage; selectively accumulated in the tumor; improved the immunosuppressive tumor microenvironment;	[74]
functionally-modified triptolide liposome (FA+TPP-TP-Lips)		accumulated in tumor tissues; improves their targeted delivery to mitochondria; reduce systemic toxicity	[75]
TP-P1		water-solubility and rapid release; inhibit acute myeloid leukemia in vivo; enhance the efficacy of FLT3 inhibitors	[76]
TPL@TFBF	Not available	Trigger systemic anti-tumor immune response; inducing ferroptosis and pyroptosis; synthetic effect combined with immune checkpoint blockade	[77]
A10 (one silyl ether-based linker conjugated with antibody drug)		targeted cytotoxicity for cells with high PD-L1 expression; bystander killing effect on cells with low PD-L1 expression; accumulated in tumor tissues	[78]
Na2GA&TP-BM	Not available	increase cytotoxicity to tumor cells; increase water-solubility; extend the blood circulation time with less system toxicity	[79]

* The molecular formula was adopted from corresponding reference.

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6. The Antitumor Mechanism and Preclinical Studies of TPL

6.1. XPB and RPB1 are the Major Targets of TPL

Multiple studies have shown that TPL inhibits de novo RNA synthesis, suggesting that RNA polymerases might be the target. However, the precise mechanisms were only elucidated recently (Figure 3). Titov et al. demonstrated that TPL covalently binds to XPB, a subunit of transcription factor TFIIH, thereby inhibiting its DNA-dependent ATPase activity[5]. In parallel, TPL induces rapid depletion of RPB1, the main subunit of RNA polymerase II, which is a hallmark of transcription elongation blockage. This is accompanied by Ser-5 hyperphosphorylation and increased ubiquitination within the RPB1 C-terminal domain[80, 81]. Together, these two mechanisms inhibit the transactivation of several transcription factors, such as NF-κB, AP-1, p53, and HSF-1, ultimately leading to apoptosis and cell death.

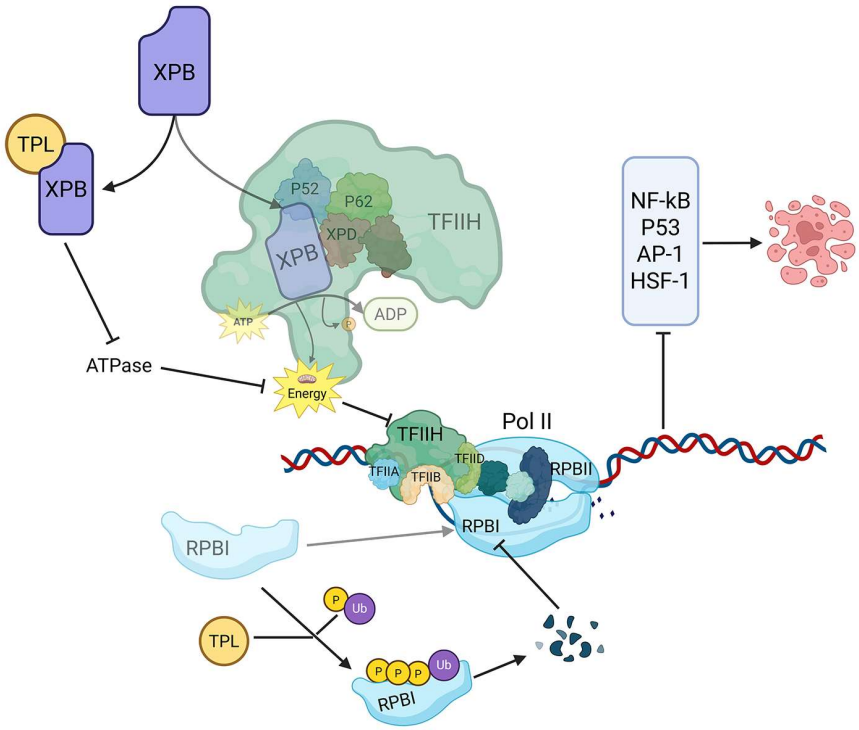

Figure 3. Mechanism of TPL inducing cell death. The two main mechanisms of TPL inducing cell death. First, TPL covalently binds to the XPB subunit and inhibits its ATPase activity, thereby impairing the function of the TFIIH complex; Second, TPL promotes the phosphorylation and ubiquitination of RPB1, leading to its depletion. Together, these mechanisms inhibit the activity of key transcription factors, resulting in suppressed cell proliferation and induction of apoptosis. (Created with BioRender.com)

6.2. Glioma

Glioma is a common intracranial malignant tumor characterized by high incidence, rapid progression, frequent recurrence, and poor prognosis. Over the past two decades, TPL has demonstrated promising potential in preclinical glioma models in vitro[82]. Subsequent studies have shown that TPL induces glioma cell apoptosis by modulating the NF-κB signaling pathway and promoting ROS generation[83]. In IDH1-mutant supratentorial gliomas, TPL disrupts glutathione metabolism, establishing a synthetic lethality with ROS[84]. Furthermore, TPL counteracts the immunosuppressive tumor microenvironment by reversing glioma-mediated CD4+ T cell inhibition and promoting IFN-γ secretion, highlighting its immunomodulatory function[85].

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TPL also enhances the radiosensitivity of glioma cells in vitro, suggesting a potential role as a radiosensitizer for high-grade gliomas[86]. When injected, TPL-preloaded hydrogel applied in resected glioblastoma cavity achieved marked antitumor efficacy via ferroptosis and prolonged survival in an orthotopic relapse model[87]. Similarly, a dendrimer-TPL conjugate designed to target tumor-associated macrophages has also been actively reducing tumor burden with minimal systemic exposure[88]. MicroRNA let-7b-5p has been identified as an important mediator of TPL's anti-glioma activity[89].

6.3. Pancreatic Tumor

Pancreatic cancer, a highly aggressive malignancy, remains a paramount challenge in oncology. Current chemotherapeutic options are limited by their efficacy and selectivity. Recent efforts have been directed toward developing TPL-based prodrugs to improve TPL's therapeutic profile. Wang et al. developed antibody-drug conjugates incorporating TPL via silyl ether linkers, which enhanced tumor-targeted cytotoxicity and demonstrated potent bystander-killing effects[78]. In a multifaceted approach, TPL prodrug nanovesicles co-loaded with ginsenoside Rg3 were designed to simultaneously target tumor mitochondria and reprogram immunosuppressive M2 macrophages, thereby remodeling the tumor microenvironment and reducing tumor burden in vivo[74]. Similarly, Lycium barbarum polysaccharide-modified selenium nanoparticles encapsulating TPL were shown to reduce systemic toxicity and enhance solubility[90]. To improve water solubility and therapeutic efficacy, Su et al. conjugated TPL to octreotide using a linker derived from succinic anhydride[91]. Beyond delivery systems, a novel TPL analog was designed to inhibit the NF-κB pathway, increase oxidative phosphorylation, and induce mitochondrial-mediated apoptosis[71]. Moser et al. identified TPL as a covalent inhibitor of XPB, demonstrating that it disrupts the TFIIH complex and induces RPB1 degradation, while also synergizing with TRAIL to promote apoptosis[92]. TPL and its prodrug Minnelide exert anti-tumor effects by targeting the cell cycle, super-enhancers, the SP1 transcription factor, and the RAS signaling pathway in pancreatic in vivo models[93-96].

6.4. Leukemia

Leukemia comprises a heterogeneous group of hematological malignancies driven by genetic and epigenetic dysregulation. As leukemic cells are systemically distributed, the development of targeted delivery systems for TPL has received comparatively less attention than in solid tumors. Nevertheless, Kang et al. synthesized a series of water-soluble TPL prodrugs that exhibited faster and more complete release profiles than Minnelide and effectively suppressed leukemia growth in vivo[76]. Most research has centered on combination therapies and overcoming chemoresistance. TPL has been shown to potentiate the efficacy of various agents, including the BET inhibitor JQ1, the Bcl-2 inhibitor ABT-199, the XPO1 inhibitor selinexor, idarubicin, and Ara-C, through distinct synergistic pathways[4, 97-100]. Furthermore, TPL can reverse chemoresistance, notably to adriamycin, by promoting ROS generation and disrupting the DNA damage response[100-102]. Apoptosis is a major antitumor mechanism of TPL in leukemia. Multiple signaling pathways and mechanisms mediate the proapoptotic effect of TPL. TPL induced apoptosis in leukemia cells by activating ROCK1 and phosphorylating MLC and MYPT1. Minnelide has also been extensively investigated. It induces apoptosis and cell cycle arrest by targeting the Ars2/miR-190a-3p/Akt pathway and downregulating the transcriptional regulator c-Myc, thereby inhibiting the growth of patient-derived leukemia cells in both in vitro and in vivo models[103, 104].

6.5. Lung Cancer

Non-small cell lung cancer (NSCLC), the most prevalent form of lung cancer, has been the subject of substantial research interest regarding the therapeutic potential of TPL. Initial investigations date back to 2002, when Lee et al. demonstrated that TPL sensitizes NSCLC cells to TRAIL-induced apoptosis by inhibiting NF-κB activation[105]. Subsequent studies have elucidated

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multiple molecular targets of TPL. It induced apoptosis and exerted antimetastatic effects by targeting the MAPK-ERK and MAPK-MKP pathways[106, 107]. Furthermore, TPL activates ERK1/2 to stabilize p53, which in turn inhibits IκBα phosphorylation and NF-κB nuclear translocation, thereby blocking NF-κB-mediated survival signaling in NSCLC cells[108]. This downregulation of NF-κB can reverse paclitaxel resistance, a key mechanism of treatment failure[109]. Mechanistically, TPL also inhibits the PI3K/AKT pathway by reducing the expression of PFKFB2, a critical glycolytic enzyme required for cell growth[110, 111]. Additionally, TPL directly binds to HNF1A, thereby attenuating the Sonic Hedgehog pathway and overcoming paclitaxel resistance[112]. From an immunotherapeutic perspective, TPL downregulates PD-L1 expression on NSCLC cells by suppressing the IFN-γ-JAK-STAT signaling axis, suggesting a potential role in modulating immune checkpoint inhibition[113]. It is noteworthy that, to the best of our knowledge, no studies have yet been published on the efficacy of TPL against small-cell lung cancer.

6.6. Other Cancers

TPL has demonstrated efficacy against a broad spectrum of other cancers in vitro and in vivo, often through shared pathways. For instance, a C60-modified self-microemulsifying drug delivery system for TPL exhibited reduced cytotoxicity against normal cells compared with liver and gastric cancer cells in vitro[114]. Similarly, various TPL-loaded nanoplatforms have been developed for esophageal, hepatocellular, breast, and gastric cancers, demonstrating improved biosafety and enhanced on-target efficacy[115-118]. Mechanistically, TPL induces gastric cancer cell apoptosis by covalently binding to PRDX2 and subsequently elevating intracellular ROS levels[119]. In the context of cancer immunotherapy, TPL downregulates PD-L1 expression and suppresses the IFN-γ-mediated JAK2-STAT1 pathway in oral cancer[120]. Furthermore, TPL modulates different forms of cell death and stress responses. It induces cuproptosis, a novel copper-dependent cell death linked to metabolism, in cervical cancer by regulating the XIAP/COMMD1/ATP7A/B axis[121].

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Table 3. The clinical trials associated with TPL in oncology.

ID	Title	Tumor type	Phase	Intervention	Status	Conclusion	Reference
NCT04896073	Superenhancer Inhibitor Minnelide in Advanced Refractory Adenosquamous Carcinoma of the Pancreas	Advanced Refractory Adenosquamous Carcinoma of the Pancreas	II	Minnelide	Completed	Platform data without publication. 16 patients enrolled and 12 patients completed the trial. The investigator provided baseline characteristics including age, sex, ethnicity, race, region. In term of side effect, 8.7%-25% patients showed Grade 4 side effect mainly related to blood cell (anemia, platelet and white blood cell) count decrease, and without grade 5 side effect. However, the most important part, neither patient showed complete response nor partial response, overall survival is 4.91 (1.96-7.85) months.	[122]
NCT03117920	A Phase II, International Open Label Trial of Minnelide in Patients with Refractory Pancreatic Cancer	Refractory Pancreatic Cancer	II	Minnelide	Completed	No results posted on the platform or publication	https://clinicaltrials.gov/
NCT05566834	Minnelide Capsules Alone and in Combination with Paclitaxel in Advanced Gastric Cancer (AGC)	Advanced Gastric Cancer	I	Minnelide	Completed	Minnelide alone at a dose of 1.25 mg was tolerable for AGC patients and the combination of Minnelide and paclitaxel exhibited meaningful clinical efficacy alongside a manageable safety profile.	[123]
NCT01927965	Study of Minnelide in Patients with Advanced GI Tumors	Advanced gastrointestinal carcinoma	I	Minnelide	Completed	The trial identified a dose and schedule of Minnelide in patients with refractory GI cancers and observed efficacy of Minnelide treatment. Grade ≥ 3 toxicities occurred in 69% of patients, most common neutropenia (38%).	[124]
NCT05166616	Minnelide and Osimertinib for the Treatment of Advanced EGFR Mutated Non-Small Cell Lung Cancer	Advanced EGFR Mutated NSCLC	Ib	Minnelide+osimertinib	Recruiting		https://clinicaltrials.gov/
NCT03129139	A Phase 1, Multi-Center, Open-Label, Dose-Escalation, Safety, Pharmacokinetic, and Pharmacodynamic Study of Minnelide Capsules Given Alone or in Combination with Protein-Bound Paclitaxel in Patients With Advanced Solid Tumors	Advanced Solid Tumors	I	Minnelide	Recruiting		https://clinicaltrials.gov/
NCT05557851	Minnelide Along with Abraxane Plus Gemcitabine in Patients With Metastatic Adenocarcinoma of the Pancreas	Metastatic Adenocarcinoma of the Pancreas	Ib	Minnelide+Abraxane+gemcitabine	Recruiting		https://clinicaltrials.gov/

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NCT03760523	Dose Escalation Study of Minnelide in Relapsed or Refractory Acute Myeloid Leukemia	Relapsed or Refractory Acute Myeloid Leukemia	I	Minnelide	Terminated	Two Dose Limiting Toxicity events occurred	https://clinicaltrials.gov/
NCT03347994	Minnelide in Adult Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML)	Relapsed or Refractory AML	I	Minnelide	Withdrawn	Discordance in contractual language and terms.	https://clinicaltrials.gov/

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7. Clinical Trial

A systematic search of clinical trial registries, including the NIH clinical trial (https://clinicaltrials.gov), the European clinical trial (https://euclinicaltrials.eu/), and the Chinese clinical trial registry (https://www.chictr.org.cn/index.html), identified nine registered clinical trials investigating TPL (specifically its prodrug, Minnelide) for oncological indications, all listed on the NIH platform (Table 3). Among these, four trials have been completed, half of which were Phase I studies. Two Phase I trials conducted by the same research group demonstrated the safety and preliminary efficacy of Minnelide in patients with advanced gastrointestinal cancers[123, 124]. One Phase II trial (NCT03117920) focusing on refractory pancreatic cancer was completed in 2023, but no results have been reported in the registry or in peer-reviewed publications. Another Phase II trial (NCT04896073) reported its outcomes: of the 16 enrolled patients, 12 completed the study. Grade 4 adverse events, primarily hematological (e.g., anemia, thrombocytopenia, leukopenia), occurred in 8.7%-25% of patients, with no Grade 5 events reported. Critically, no objective responses (complete or partial) were observed, and the median overall survival was 4.91 months (95% CI: 1.96-7.85). Currently, three Phase I trials for advanced NSCLC, pancreatic cancer, and solid tumors are recruiting, while one trial for acute myeloid leukemia was terminated due to dose-limiting toxicities (NCT03760523). Although preclinical studies continue to support Minnelide's potential in other malignancies[2, 68, 104], its clinical translation requires further optimization. Notably, a growing body of literature on novel TPL conjugates and delivery systems has shown superior preclinical profiles (Table 2), suggesting promising alternatives for future clinical development.

8. Conclusion

Despite its broad biological activities, including antitumor, anti-inflammatory, immunosuppressive, and neuroprotective effects, the clinical application of TPL is significantly limited by its systemic toxicity[125-127]. To overcome this challenge, numerous derivatives and drug delivery systems have been developed to mitigate toxicity and enhance on-target efficacy. Among them, Minnelide, a water-soluble prodrug derivative formed by adding a phosphate group to TPL, has emerged as one of the most promising candidates and has been widely evaluated in clinical trials owing to its reduced toxicity[68]. According to major clinical trial registries, Minnelide has been involved in nine trials across several malignancies, including leukemia, pancreatic, gastric, and lung cancers. Importantly, Minnelide has demonstrated an acceptable safety profile in patients, with the main adverse event being reversible acute cerebellar toxicity. However, since Minnelide is reconverted to TPL by phosphatases in vivo, it does not fully resolve neither the compound's inherent toxicity nor on-target effect[68]. Consequently, alternative delivery strategies using novel materials, including MOF, PLGA nanoparticles, and cancer cell-platelet hybrid membranes, have been explored[55-57]. Nevertheless, their clinical translation remains hampered by challenges related to production cost, quality control, biocompatibility, and potential long-term toxicity.

Alternatively, combination therapy is a viable strategy to reduce the required doses of individual drugs, target multiple mechanisms, delay resistance development, and improve therapeutic efficacy[128]. Due to the systemic toxicity in DMG preclinical models, alternative combination therapies remain a promising approach to enhance the clinical profile of TPL. Such prospective combinations may provide the opportunity to reduce TPL toxicity by using a lower dose of the drug.

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Abbreviations

The following abbreviations are used in this manuscript:

TPL	Triptolide
ROS	Reactive oxygen species
GPX4	Glutathione peroxidase 4
PK	Pharmacokinetic
DMG	Diffuse midline glioma
Cmax	Maximum concentration
Tmax	Time to maximum concentration
TwHF	Tripterygium wilfordii Hook. f.
HCC	Hepatocellular carcinoma
MOFs	Metal-organic frameworks
NSCLC	Non-small cell lung cancer
PLGA	Poly (lactic-co-glycolic acid)
TF	Transcription factor
AGC	Advanced gastric cancer
AML	Acute myeloid leukemia

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