

REVIEW

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Pleiotropic pharmacological activities and multiple-organ toxicities of triptolide: a programmed cell death perspective

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Abstract

Triptolide, a bioactive triepoxide diterpenoid extracted from *Tripterygium wilfordii* Hook. f., has demonstrated broad pharmacological activities and significant toxicities. Mechanistically, triptolide has exerted therapeutic effects by regulating programmed cell death (PCD) through multiple pathways; however, its toxic reactions have been closely associated with this process. This review systematically summarizes the molecular mechanisms by which triptolide regulated various forms of PCD and its application progress in disease treatment, including apoptosis, autophagy, pyroptosis, ferroptosis, cuproptosis, necroptosis, and PANoptosis. A plethora of extant studies have revealed that triptolide exerted a regulatory effect on the PCD networks by intervening in multiple important signaling pathways and their key signaling nodes. Nevertheless, due to its poor target specificity, triptolide has resulted in multi-organ toxicities, which has in turn limited its clinical translation. Nano-delivery systems have explored as a potential strategy to mitigate the toxicity and improve the efficacy of triptolide by enhancing its tissue targeting (Specific nanocarriers can increase LD₅₀ from 0.48 to 0.88 mg/kg). Furthermore, key pharmacodynamic evidences from triptolide's current clinical studies are limited, necessitating the elucidation of precise target sites and the advancement of standardized clinical trials. This review systematically integrates the pleiotropic pharmacological activities and multiple-organ toxicities of triptolide from a PCD perspective, providing novel insights and theoretical references for overcoming its clinical translation barriers.

Keywords Triptolide, Programmed cell death, Molecular mechanism, Pharmacological activities, Multi-organ toxicities, Nano-delivery system

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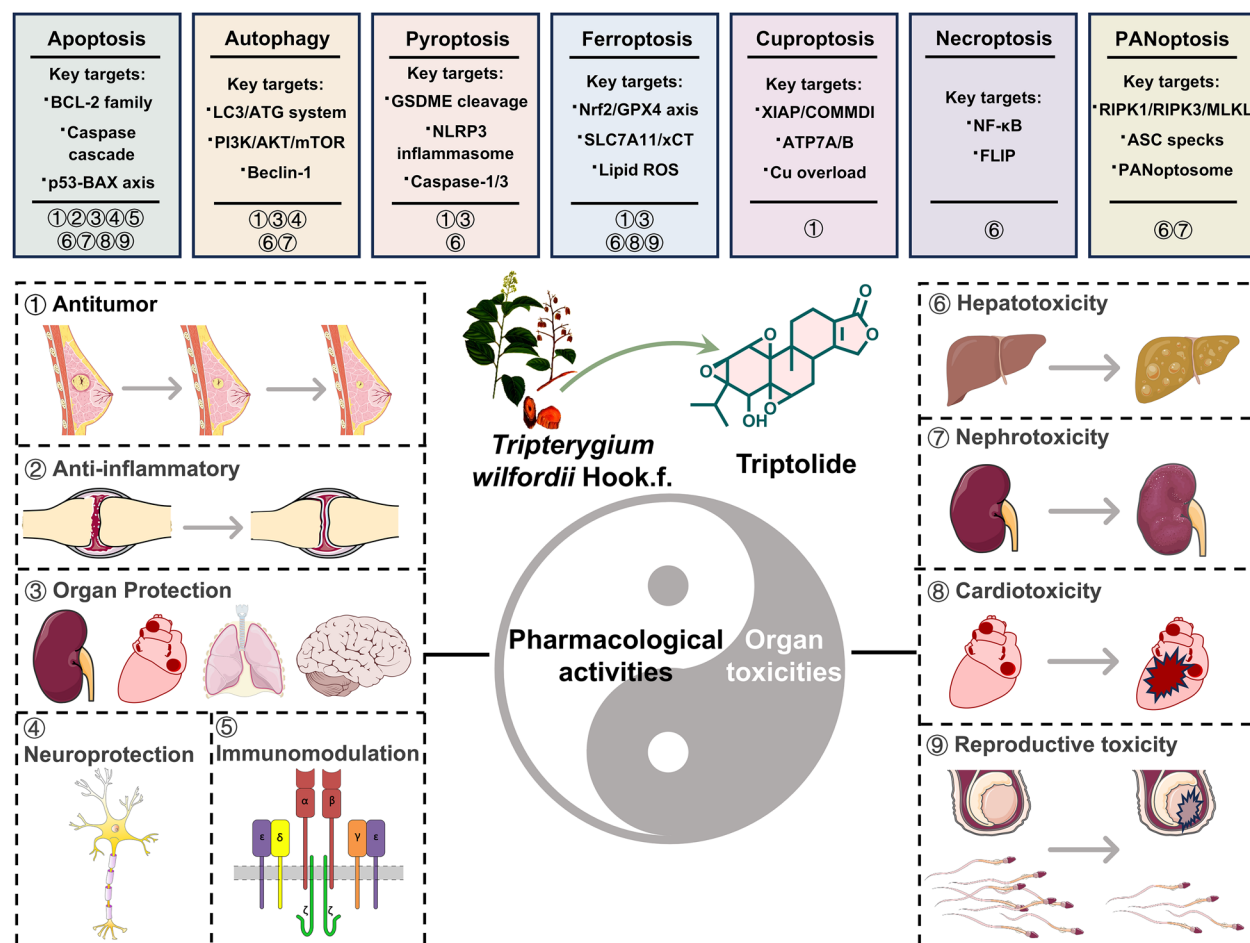
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Graphical Abstract

Triptolide Modulates Programmed Cell Death Pathways: Therapeutic Benefits vs. Multi-Organ Toxicities



Introduction

“To combat poison with poison” is special Traditional Chinese Medicine Theory, toxic herb *Tripterygium wilfordii* Hook.f. has long been regarded as a representative sample of this theory [1]. Triptolide is the principal bioactive constituent of three medicinal *Tripterygium* species (*T. wilfordii*, *T. regelii* Sprague & Takeda, and *T. hypoglaucom* (H.Lév.) Hutch.) [2, 3], and its multi-effect pharmacology highly aligned with “to combat poison with poison” principle of *T. wilfordii*, displaying potent anti-inflammatory, immunosuppressive and antitumor activities [4–9]. Valuably, triptolide has been listed by *Cell* as one of the most five promising natural lead compounds with potential for development of modern drug, due to its multifunctional pharmacological properties

at nanomolar concentrations [10]. However, the therapeutic window of triptolide substantially narrow (with a mouse LD₅₀ of 0.83 mg/kg) [11], especially triptolide has induced toxicities in the liver, kidneys, heart, and reproductive organs [12]. From a dialectical perspective, the toxicity of triptolide and *T. wilfordii* can manifest as cytotoxicity against tumor cells and inflammatory cells in pharmacology, and as damage to normal cells and organs in toxicology.

Mechanically, the modulation of various programmed cell death (PCD) pathways by triptolide may associated with for its dual attributes of therapy and toxicity, due to its unique epoxide structure and multi-target regulatory capacity [13]. The “to combat poison with poison” effect of triptolide may achieve through the potent induction

of various forms of PCD, including but not limited to apoptosis, autophagy, and pyroptosis [13]. Triptolide-mediated-PCD has enabled the specific elimination of pathological cells such as tumor cells and abnormally activated immune cells, representing a central mechanism underlying its pharmacological action [14]. Notably, triptolide has exhibited poor target specificity in regulating PCD. Although inducing death in pathological cells, triptolide may also trigger similar PCD processes in normal tissue cells, ultimately leading to dose-dependent multiple-organs damage, which has constituted the significant source of triptolide's toxicity [15, 16].

The efficacious-poison duality of *Tripterygium* herbs and triptolide may closely associated with bidirectional regulation of PCD. Dialectically, the relationship between efficacy and toxicity in *Tripterygium* herbs has been not a simple dichotomy, but rather a dynamic unity that has been interdependent and mutually transformative within the context of specific diseases. The patterns of transformation must be understood within the “person-medicine-disease” system. In clinical practice, only by adhering to “differentiated diagnosis-based medication, precise dosing, and rational drug combinations” can the “toxic properties” of *Tripterygium* herbs be transformed into “therapeutic efficacy,” ultimately achieving the health goal of “yin-yang balance” [12]. *Tripterygium* herbs and triptolide has served as an effective remedy through precise regulation of PCD, whereas disordered or excessive PCD has underlain their potential toxicity [14]. From this perspective, the principle of “to combat poison with poison” can be reinterpreted as a primitive form of targeted intervention against abnormal cell fate [13]. Therefore, exploring bidirectional regulation mechanism of PCD of triptolide will help bridge empirical traditional *Tripterygium* herb medicine and modern precision medicine, providing a rational mechanistic basis for the safe and effective application of *Tripterygium* herbs.

In this review, the molecular mechanisms underlying the pharmacological activities and multi-organ toxicities of triptolide by regulating various PCD were summarized, majorly including apoptosis, autophagy, pyroptosis, ferroptosis, cuproptosis, necroptosis, and PANoptosis, and provides an in-depth exploration of triptolide in signal pathway regulation, intervention of key targets, and determination of cellular fate. To overcome the key limitations of triptolide, such as severe off-target toxicities, poor delivery and tissue selectivity, advanced nano-delivery systems has represented a highly promising strategy, mitigating off-target toxicity and boosting therapeutic efficacy. Furthermore, the clinical tests and evidence of triptolide formulations or derivatives are limited, both elucidating triptolide's core target molecules and integrated signaling networks should be strengthened in

the future to establish a more robust foundation for the successful translation of triptolide derivative drugs. This review provides a valuable reference for guiding clinical trials and future clinical applications of triptolide.

Literature retrieval

A comprehensive literature search was conducted in multiple scientific databases, included Web of Science, PubMed, and Google Scholar, covering publications from May 2005 to May 2025 using the search term “triptolide”. A total of 153 relevant studies on triptolide's pleiotropic pharmacological activities and multi-organ toxicities were systematically collected, screened, and synthesized from the perspective of programmed cell death, adhering to predefined inclusion and exclusion criteria (Fig. 1).

Bidirectional apoptosis modulation by triptolide generates pharmacological effects and toxicities

Apoptosis plays a key role in maintaining tissue homeostasis and regulating disease progression and drug effects (activities and toxicities) [17]. Triptolide has displayed significant therapeutic potential by targeting multiple apoptotic molecules and pathways, showing efficacy in various pathological conditions, including cancer, ischemia/reperfusion injury, inflammatory diseases, and liver and kidney diseases [18–21]. However, it has also been reported to cause toxicities in hepatic, renal, cardiac and testicular tissues [22–24] (Fig. 2).

Apoptotic modulation in pharmacological activities of triptolide

Promoting apoptosis to exert antitumor effects

Triptolide has been demonstrated to promote tumor cell apoptosis via the mediation of endoplasmic reticulum stress in intrinsic apoptosis pathway, exhibiting significant cytotoxic effects in various cancers [19, 25–33]. 300 μ M triptolide elevated reactive oxygen species (ROS) levels and induced endoplasmic reticulum stress and apoptosis by targeting peroxiredoxin 2 in human gastric cancer cell lines AGS and IM95, providing a new insight into the potential mechanisms of triptolide for treating gastric cancer [34]. The combination of 1–15 ng/mL triptolide with cisplatin enhanced cisplatin-induced mitochondrial apoptosis in gastric cancer SC-M1 cells, as evidenced by the activation of Caspase-3, Caspase-9, and Poly(ADP-ribose) Polymerase (PARP) cleavage. This effect was further confirmed in a severe combined immunodeficiency mouse xenograft model, supporting the potential clinical application of triptolide-cisplatin combination therapy [35].

Targeting mitochondria, triptolide has promoted endogenous apoptosis by regulating the B-cell lymphoma 2 (BCL-2) protein family, demonstrating significant

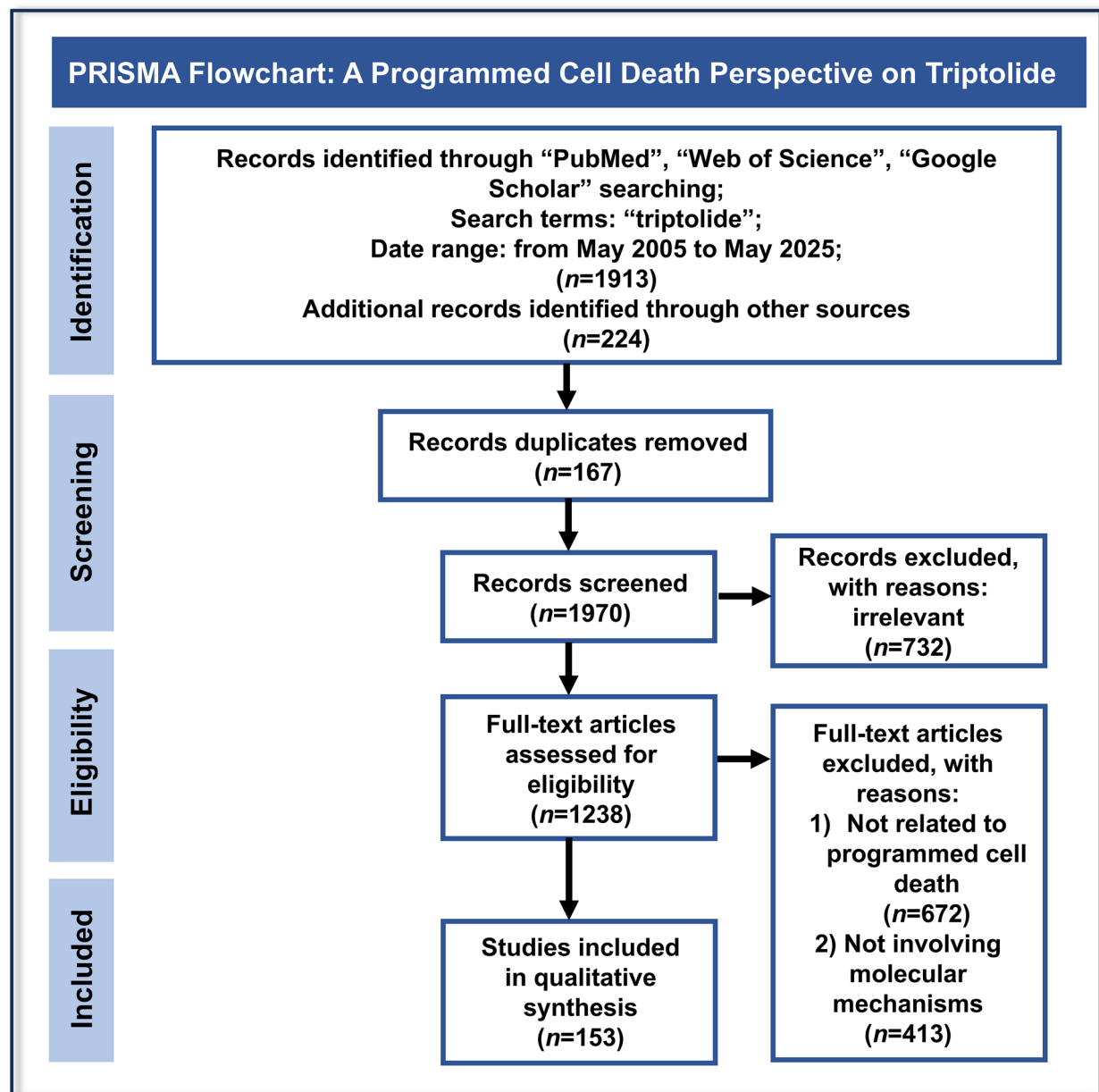


Fig. 1 PRISMA flow diagram for the systematic review on Pleiotropic pharmacological activities and multiple-organ toxicities of triptolide: a programmed cell death perspective

antitumor activity in various types of leukemia. In the context of acute myeloid leukemia (AML), the combination of triptolide with the BCL-2 inhibitor ABT-199 led to the downregulation of Myeloid cell leukemia 1 (MCL-1) and upregulation of pro-apoptotic BH3-only proteins, resulting in mitochondrial apoptosis pathway activation, effectively overcoming chemotherapy resistance and prolonging survival in xenograft animal models [36]. In the treatment of chronic myeloid leukemia (CML), triptolide was observed to effectively downregulate Bcr-Abl

mRNA and protein levels independently of the caspase or proteasome pathways and then induced mitochondrial-dependent apoptosis in primary CML cells with Bcr-Abl-T315I mutations and STI571 resistance, suggesting that triptolide represented a promising therapeutic agent for overcoming STI571 resistance in CML cells [37]. In the absence of p53 and with unaltered BCL2-Associated X Protein (BAX) levels, 20 nM triptolide still triggered caspase-mediated BCL-2 cleavage, cytochrome C release, and amplification of the caspase cascade in human

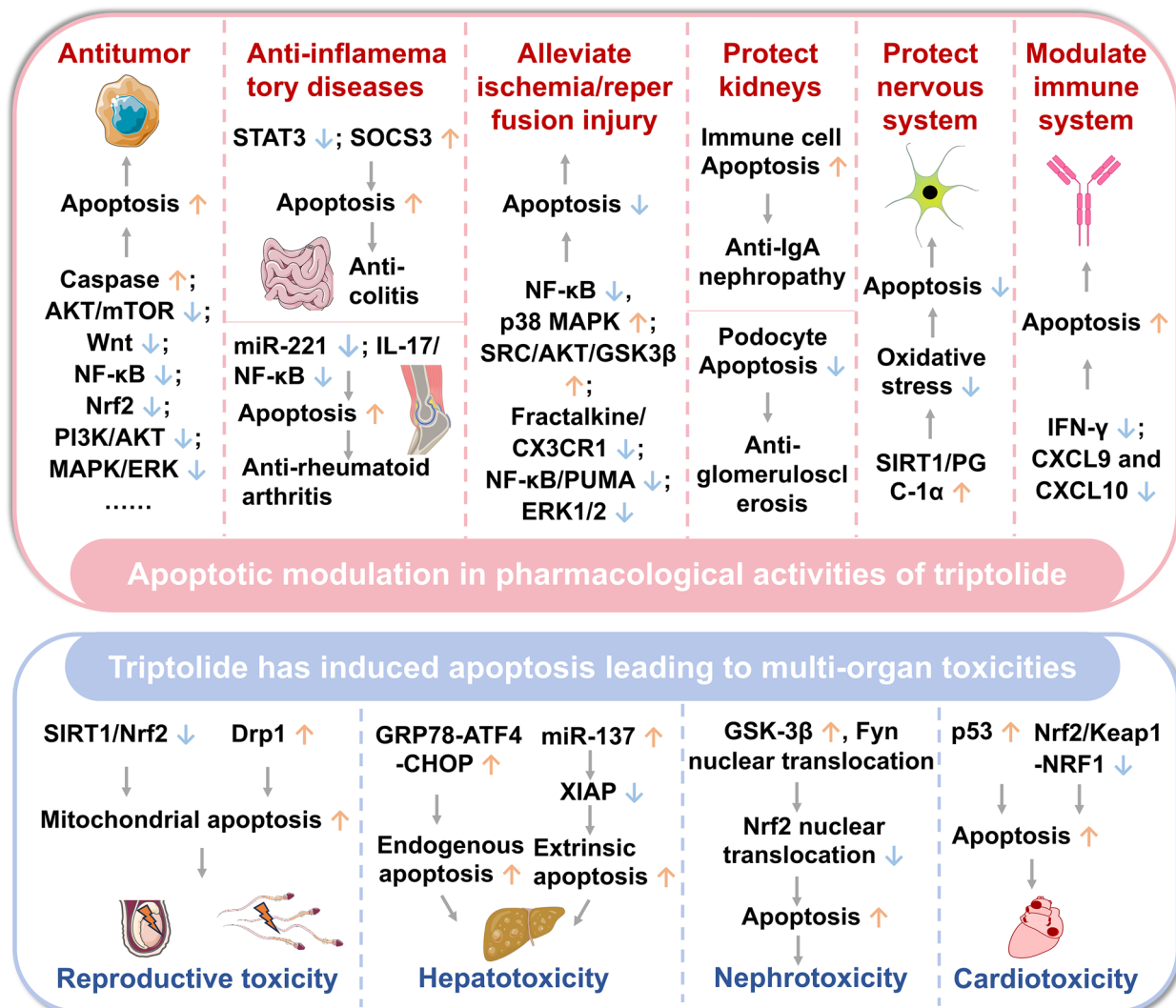


Fig. 2 Bidirectional apoptosis modulation by triptolide generates pharmacological effects and toxicities. ↑: Activation or Upregulation; ↓: Inhibition or Downregulation. Other gene and protein abbreviations appearing in this figure can be found in the Abbreviation List

promyelocytic leukemia HL-60 cell lines, leading to mitochondrial-dependent apoptosis and exerting a therapeutic effect on promyelocytic leukemia [38].

In addition to regulating endogenous apoptosis, triptolide has been shown to exert anti-AML effects by activating the extrinsic apoptosis pathway and modulating CFLAR protein expression. Gene expression analysis in 60 European AML patients demonstrated that triptolide significantly upregulated apoptosis-related genes, including cellular FLICE-like inhibitory protein (*CFLAR*), peptidylprolyl isomerase like 3 (*PPIL3*), caspase 8 (*CASP8*), caspase 10 (*CASP10*), and signal transducer and activator of transcription 6 (*STAT6*). Mechanistically, *CFLAR* knockdown markedly enhanced sensitivity to triptolide in Human Acute Monocytic Leukemia cell line-1 AML

cells, implying *CFLAR* as a key target of triptolide's cytotoxic effects [39].

Triptolide has also exhibited multidimensional antitumor effects in non-small cell lung cancer. The mechanism by which it promoted apoptosis involved a reduction in 6-Phosphofructo-2-kinase/Fructose-2,6-bisphosphatase 2 (PFKFB2) expression, resulting in the inhibition of phosphatidylinositol 3-kinase (PI3K)/AKT serine/threonine kinase (AKT) pathway [40]; the blocking of interleukin-6 (IL-6)/signal transducer and activator of transcription 3 (STAT3) axis activation [41]; the interference with Wntless/Integrated (Wnt) pathway transmission [42]; the inhibition of AKT/mechanistic target of rapamycin (mTOR)/hexokinase II (HKII) network [43]; and the activation of calcium/

calmodulin-dependent protein kinase kinase beta (CaMKK β)-AMP-activated protein kinase (AMPK) pathway [44]. Furthermore, triptolide has been shown to selectively inhibit the activity of nucleotide excision repair, thus inducing apoptosis in lung cancer cells and enhancing the efficacy of cisplatin treatment in these cells [45].

Triptolide effectively modulated nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), and PI3K/AKT pathways, promoting tumor cell apoptosis and exhibiting significant antitumor activity across a range of cancer models (Table 1). This majorly included nasopharyngeal carcinoma [26], adrenocorticotrophic hormone-secreting pituitary adenoma [19], osteosarcoma [27], thyroid cancer [28, 29], breast cancer [46], glioma [47], Burkitt lymphoma [48], multiple myeloma [20, 49], cervical cancer [50], prostate cancer [51], esophageal squamous cell carcinoma [30, 31], bladder cancer [32, 33], and renal cell carcinoma [52].

Promoting apoptosis to treat inflammatory diseases

Triptolide has alleviated colitis symptoms by promoting apoptosis, offering a novel therapeutic strategy for the management of inflammatory bowel disease. Intraperitoneal injection of 0.07 mg/kg triptolide significantly upregulated suppressor of cytokine signaling 3 (SOCS3) protein expression in the lamina propria monocytes of interleukin-10 (IL-10)-deficient colitis mice, while concomitantly downregulating the anti-apoptotic genes *Bcl-2* and *Bcl-xl* by inhibiting STAT3 pathway. This mechanism was further validated in colonic explant experiments from Crohn's disease patients (treated with 20 ng/mL triptolide), confirming the therapeutic effect of triptolide through the regulation of IL-6/STAT3/SOCS3 pathway [53].

Moreover, triptolide has exhibited substantial therapeutic potential in rheumatoid arthritis models. 5–15 ng/mL triptolide to rheumatoid arthritis fibroblast-like synovial cells resulted in the downregulation of synovial cell exosome microRNA-221 (miR-221), the promotion of cartilage cell proliferation and secretory function, and the induction of apoptosis, thereby effectively treating rheumatoid arthritis [21]. The combination of triptolide with curcumin inhibited IL-17/NF- κ B pathway in rats with rheumatoid arthritis and in MH7A cells, induced apoptosis and enhanced anti-inflammatory effects, providing a novel therapeutic strategy for rheumatoid arthritis [54].

Inhibiting apoptosis to alleviate ischemia/reperfusion injury

Triptolide has displayed anti-apoptotic activity in normal cells and has conferred robust protection against neurological ischemia/reperfusion injury. 5–80 ng/mL triptolide alleviated oxygen–glucose deprivation and tumor necrosis factor-alpha (TNF- α)-induced apoptosis in SH-SY5Y cells in a concentration-dependent manner. Intraperitoneal injection of 1.0 mg/kg of this drug ameliorated cerebral ischemia/reperfusion injury in murine models of ischemic stroke by inhibiting NF- κ B and p38 MAPK activation [55]. Intraperitoneal injection of 20 μ g/kg triptolide alleviated white matter damage in mice with chronic cerebral hypoperfusion by inhibiting microglial activation and the release of pro-inflammatory factors, and inhibited apoptosis in oligodendrocytes following oxygen–glucose deprivation by activating Sarcoma proto-oncogene, non-receptor tyrosine kinase (SRC)/AKT/ Glycogen Synthase Kinase-3 Beta (GSK3 β) pathway, thus exerting concentration-dependent protective effects (0.001–0.1 nM) [56]. Furthermore, triptolide inhibited apoptosis by suppressing fractalkine/C-X3-C motif chemokine receptor 1 (CX3CR1) pathway in rats [57] or NF- κ B/p53 upregulated modulator of apoptosis (PUMA) pathway [58], thereby alleviating brain ischemia/reperfusion injury.

Similarly, triptolide inhibited cardiac myocyte apoptosis, effectively alleviating myocardial ischemia/reperfusion injury. Mechanistically, triptolide synergistically inhibited NF- κ B, ROS, and ERK1/2 pathways, induced anti-inflammatory, antioxidant, and anti-apoptotic activities, resulting in a substantial reduction in ischemia/reperfusion injury in rat hearts and H9C2 cells [59].

Regulating apoptosis to protect kidneys

Triptolide has demonstrated renal protective effects through differential regulating apoptosis, and its impact has varied depending on the cell type, promoting apoptosis in immune nephropathy while suppressing it in glomerulosclerosis [60, 61].

In tonsillar mononuclear cells derived from patients with Immunoglobulin A (IgA) nephropathy, 10–30 ng/mL triptolide downregulated the levels of anti-apoptotic proteins BCL-2 and BCL-XL in a dose-dependent manner, concomitantly upregulated the pro-apoptotic protein BAX, resulting in promoting apoptosis of immune cells under pathological conditions, providing a novel therapeutic option for the clinical treatment of IgA nephropathy [60].

In terms of podocyte protection, triptolide has been demonstrated to exhibit anti-apoptotic effects. 10 ng/mL triptolide downregulated the expression of apoptotic gene growth arrest and DNA-damage-inducible 45 beta

Table 1 Triptolide exerts antitumor activity by promoting apoptosis

Cancer types	Cell lines/models	Dosage	Molecular mechanisms	Refs.
NSCLC	Human lung cancer cell line PC-9	10–50 nM TP, in vitro	TP targeted miR-21, by ↑PTEN	[177]
NSCLC	A549 and H1299 cells	50–150 nM, in vitro	↓PFKFB2 led to ↑P13K/AKT	[40]
NSCLC	Mouse xenograft model	0.8 mg/kg TP, s.c	↓PFKFB2 expression led to ↑P13K/AKT	[40]
NSCLC	PC9 and A549 cells	30–120 nM TP, in vitro	↓IL-6/STAT3 axis	[41]
NSCLC	A549, H460, H358, and H1299 cell lines	1–10 nM TP, in vitro	↓Wnt signaling	[42]
NSCLC	Mouse xenograft model	1.5 mg/kg TP, s.c	↓Wnt signaling	[42]
NSCLC	H1299 and NC-H460 cell lines	50–150 nM TP, in vitro	↓AKT/mTOR HKII	[43]
Lung cancer	HTB182, A549, CRL5810, and CRL5922 lung cancer cells	5 or 10 ng/mL TP, in vitro	↓Nucleotide excision repair	[45]
Gastric cancer	Gastric cancer SC-M1 cells	1–15 ng/mL TP, in vitro	↑Caspase-3 and Caspase-9, and PARP was cleaved in SC-M1 cells	[35]
Gastric cancer	Severe combined immunodeficiency mouse xenograft	0.4 mg/kg TP + 3 mg/kg Cisplatin, s.c	↑Caspase-3 and Caspase-9, and PARP was cleaved in SC-M1 cells	[35]
Gastric cancer	Human gastric cancer cell lines AGS and IM95	300 μM TP, in vitro	↑ROS, resulting in endoplasmic reticulum stress	[34]
AML	MV4-11 and MOLM-13 cells	1.25–5 nM TP + ABT-199, in vitro	↓MCL-1, and ↑pro-apoptotic BH3 pure proteins	[36]
AML	Xenotransplantation model	0.5 mg/kg TP; i.p. + 50 mg/kg ABLT-199, i.g	↓MCL-1, and ↑pro-apoptotic BH3 pure proteins	[36]
AML	OCI-AML3, U937, and Jurkat cells	–	↓XIAP and ↑p53-mediated DR5	[25]
AML	60 European AML patients and THP1 AML cell line	–	↑Genes related to apoptosis (<i>CFLAR</i> , <i>PPI3</i> , <i>CASP-8</i> , <i>CASP-10</i> , and <i>STAT6</i>)	[39]
Promyelocytic leukemia	HL-60 and MCF-7 cell lines	20 nM TP, in vitro	↑BCL-2 cleavage, mitochondrial cytochrome C release, and Caspase	[38]
CML	CML cell lines and primary cells from CML patients clinically resistant to ST1571	5–50 nM TP, in vitro	↓Bcr-Abl transcription, and ↓survivin, MCL-1, and AKT	[37]
Bladder cancer	T24R2 cells	–	↑Caspase-3, 8, and 9, PARP, and cytochrome C	[32]
Bladder cancer	Bladder cancer cell lines EJ and UMUC3	72 nM TP + 1.9 μg/mL Gsithamine, or 50 nM TP + 0.25 μg/mL Gsithamine, in vitro	↑Caspase-8 and BCL-XL proteins, ↑ROS, and ↓AKT/GSK3β pathway	[33]
Nasopharyngeal carcinoma	Human nasopharyngeal carcinoma cells	2–8 Gy IR + 2–8 ng/mL TP, in vitro	↑BAX expression and ↓NF-κB p65 phosphorylation	[26]
Nasopharyngeal carcinoma	Nasopharyngeal carcinoma cell line HONE-1	5–50 nM TP, in vitro	↓Lnc-THOR-IGF2BP1 signaling	[178]
Adrenocorticotrophic hormone-secreting pituitary adenoma	AtT-20 cell line	25–400 nM TP, in vitro	↑Mitochondrial membrane depolarization, ↑Caspase-3, ↓BCL2/BAX ratio, and ↓phosphorylation of NF-κB p65 subunit and extracellular ERK	[19]
Adrenocorticotrophic hormone-secreting pituitary adenoma	Xenotransplantation in mice	0.15 mg/kg TP, i.p	↑Mitochondrial membrane depolarization, ↑Caspase-3, ↓BCL2/BAX ratio, and ↓phosphorylation of NF-κB p65 subunit and extracellular ERK	[19]
Osteosarcoma	Human osteosarcoma U2OS cells	100 nM TP + 30 μM AMD3100, in vitro	↓The phosphorylation levels of ERK1/2, AKT, STAT3, ↓the nuclear translocation and phosphorylation of NF-κB p65	[27]
Osteosarcoma	MG-63 cells	50–200 nM TP, in vitro	↑TRAIL-DR-5 pathway	[179]
Thyroid cancer	Human ATC cell line TA-K cells	–	↓NF-κB independently of p53	[28]

Table 1 (continued)

Cancer types	Cell lines/models	Dosage	Molecular mechanisms	Refs.
Thyroid cancer	Thyroid cancer cell line TPC-1	50–200 nM TP, in vitro	↑CDKN1A and protein levels of phosphorylated p53, but ↓protein levels of phosphorylated c-JUN and phosphorylated NF-κB p65	[29]
Breast cancer	Human breast cancer MDA-MB-231 cells	MCF-7 13–400 nM TP + 10 ng/mL TNF-α, in vitro	↓XAP and cIAP1/2, and downstream anti-apoptotic genes activated by NF-κB	[46]
Breast cancer	MDA-MB-231 breast cancer cells	0.31–40 ng/mL TP, in vitro	↑Oxidative stress and endoplasmic reticulum stress via PERK-eIF2α pathway	[180]
Glioma	U251 cells, mouse cardiomyocytes, and LN229 cells	5–320 nM TP, in vitro	↑ROS and ↓NF-κB pathway	[47]
Burkitt lymphoma	Raji, NAMALWA, and Daudi cells	20–80 nM TP, in vitro	↑SIRT3 and ↓SIRT3/GSK3β/BAX pathway	[48]
Multiple myeloma	Multiple myeloma cell line U266	40–160 nM TP, in vitro	↑G2/M cell cycle arrest and Caspase-dependent apoptosis	[49]
Multiple myeloma	Human multiple myeloma cell line U266	100 nM TP, in vitro	↓STAT3 signaling pathway	[20]
Liver cancer	HepG2 cells	10–50nM TP, in vitro	↑p53 tumor suppressor gene	[181]
Cervical cancer	Human cervical cancer cells	–	↓AKT phosphorylation and MCL-1	[50]
Pancreatic cancer and Cervical cancer	Pancreatic cancer PANC-1 and cervical adenocarcinoma HeLa cells	–	↑Caspase-3 and Caspase-8, PARP and Bid were cleaved, and ↓BCL-2	[182]
Pancreatic cancer	PANC-1 and MiaPaCa-2 cells	50–200 nM TP, in vitro	↓HSP70 mRNA and protein levels	[173]
Pancreatic cancer	In situ pancreatic tumors in nude mice	0.2 mg/kg TP, i.p	↓HSP70 mRNA and protein levels	[173]
Endometrial cancer	HEC-1B cells	10–320 nM TP, in vitro	↑Caspase-3/9 and ↓BCL-2 without altering BAX levels	[182]
Melanoma	SK-MEL5 and SK-MEL-28 cells, as well as HaCaT cells	10–40 nM TP, in vitro	↓SRC-ERK signaling	[183]
Melanoma	Xenograft mouse model	150 and 300 µg/kg TP, i.p	↓SRC-ERK signaling	[183]
Glioblastoma	U251 cells	50–200 nM TP, in vitro	↓PROX1	[184]
Colorectal cancer	HT29 cell line	25–100 nM TP, in vitro	↓Nrf2 signaling	[185]
Prostate cancer	Human prostate cancer cell line PC3	12.5–50 nM TP, in vitro	↓IRF3, and ↑IFN signaling	[51]
Ovarian cancer	Ovarian cancer cell lines A2780 and A2780/CP70	–	↓HK 2n and ↑Hsa-mir-6751	[186]
Epithelial ovarian cancer	COC1/DDP cells	1–100 ng/mL TP, in vitro	↓PI3K/AKT pathway	[187]
Epithelial ovarian cancer	In situ rat model of ovarian cancer	0.025–0.1 mg/kg TP, i.p	↓PI3K/AKT pathway	[187]
Esophageal squamous cell carcinoma	KYSE150 and KYSE180 cells	4–8 nM TP, in vitro	↑MAPK/ERK pathway	[30]
Esophageal squamous cell carcinoma	KYSE30 and TE1 cells	2 nM TP, in vitro	↓Glycolysis and ↑mitochondrial dysfunction	[31]
Esophageal squamous cell carcinoma	Xenograft model	0.45 mg/kg TP, i.p	↓Glycolysis and ↑mitochondrial dysfunction	[31]
Renal cell carcinoma	ACHN, A498, Caki-1, 769-P, and 786-O cell lines	TP + rTRAIL, in vitro	↑TRAIL-induced apoptosis and ↓HSP70	[52]

Other gene and protein abbreviations appearing in this table can be found in the Abbreviation List

TP: Triptolide; NSCLC: Non-small Cell Lung Cancer; AML: Acute Myeloid Leukemia; CML: Chronic Myeloid Leukemia; s.c.: subcutaneous injection; i.p.: intraperitoneal injection; i.g.: intragastric administration; ROS: Reactive Oxygen Species

↑ = Activation or Upregulation

↓ = Inhibition or Downregulation.

b in zebrafish podocytes, blocked NF- κ B/growth arrest and DNA-damage-inducible 45 beta b signaling, attenuated podocyte apoptosis, and significantly ameliorated proteinuria [61]. Furthermore, 160 mg/kg triptolide (intragastric administration) ameliorated focal segmental glomerulosclerosis in rats. Mechanistically, triptolide inhibited IL-4/STAT6 pathway, upregulated key podocyte molecules nephrin and podocin, and suppressed p53-mediated podocyte apoptosis, suggesting that it may be a potential therapeutic option for focal segmental glomerulosclerosis [62].

Inhibiting apoptosis to protect nervous system

Triptolide has produced neuroprotective effects through inhibiting apoptotic pathways and diminishing oxidative damage in nervous system [63]. In an amyloid- β protein fragment 25-35-induced differentiated PC12 cell model, 0.01–1 nM triptolide significantly reduced nerve cell apoptosis, with the mechanism involving upregulation of superoxide dismutase activity while inhibiting reactive oxygen species, H_2O_2 , and malondialdehyde, thereby counteracting amyloid- β toxicity [64]. Furthermore, intraperitoneal injection of 5 μ g/kg triptolide reduced oxidative stress levels in the hippocampus of rats with vascular dementia, decreased neuronal apoptosis, and improved learning and memory impairments by activating Sirtuin 1 (SIRT1)/peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α) pathway, providing a potential therapeutic strategy for neurodegenerative diseases [65].

Promoting apoptosis to modulate immune system

Triptolide has exhibited considerable immunosuppressive properties [66]. In aortic transplantation mice, subcutaneous injection of 0.5 mg/kg triptolide resulted in a significant alleviation of thickening of the endothelium in allograft vessels. In addition, it exhibited a dose-dependent inhibition of MOVAS-1 cell activity (5–80 ng/mL), reduced the proportion of interferon-gamma (IFN- γ)-positive T lymphocytes, decreased the secretion of IFN- γ and its inducible factors (C-X-C motif chemokine ligand 9 (CXCL9) and CXCL10, and inhibited vascular smooth muscle cell proliferation while inducing their apoptosis, offering a substantial scientific evidence for the development of novel anti-rejection strategies [67].

Triptolide induces apoptosis leading to multi-organ toxicities

Induction of apoptosis leading to reproductive toxicity

Triptolide has damaged spermatogenic cells or caused structural injury to testicular tissue through inducing oxidative stress and activating the mitochondrial apoptosis pathway, ultimately impairing male reproductive

function [68]. In male C57BL/6J mice, intraperitoneal administration of 0.2 mg/kg triptolide induced oxidative stress, triggered mitochondrial apoptosis in spermatogonia, and caused abnormalities in mitochondrial morphology and structure, leading to severe testicular damage. N-acetyl-L-cysteine mitigated triptolide-induced testicular damage and apoptosis by alleviating oxidative stress [69]. Mechanistically, triptolide suppressed SIRT1/nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, triggered oxidative stress, and altered mitochondrial morphology and membrane potential, disrupting rat testicular structure (100 μ g/kg, intraperitoneal injection) and inducing apoptosis in TM4 cells (40–640 nM); melatonin alleviated triptolide-induced damage to testicular supporting cells by modulating the crosstalk between SIRT1 and Nrf2 [70].

In rats and the Leydig cell line TM3, triptolide induced the expression of dynamin-related protein 1 (Drp1), disrupted mitochondrial dynamic stability, and activated the mitochondrial apoptosis pathway, ultimately inducing testicular interstitial cell apoptosis in vitro and in vivo, exhibiting significant reproductive toxicity. The selective Drp1 inhibitor Mdivi-1 attenuated reproductive toxicity of triptolide [23].

Induction of apoptosis leading to hepatotoxicity

The hepatotoxicity of triptolide has represented a significant barrier to its clinical application [71, 72]. The underlying mechanism of this process involved endoplasmic reticulum stress-mediated endogenous apoptosis [22], extrinsic apoptosis through the activation of death receptor pathways [73], and a synergistic effect of these two pathways [74].

Intragastric administration of 500 μ g/kg triptolide to female C57BL/6J mice induced ROS generation and activated glucose-regulated protein 78 (GRP78)-activating transcription factor 4 (ATF4)-C/EBP homologous protein (CHOP) axis through proteasome inhibition, which in turn enhanced endoplasmic reticulum stress-related apoptosis and caused hepatocyte damage. The ROS inhibitor N-acetylcysteine alleviated triptolide-induced hepatotoxicity by reducing the expression of endoplasmic reticulum stress-related apoptotic proteins and ROS levels [22].

In C57BL/6J mice, intragastric administration of 500 μ g/kg triptolide for 7 consecutive days inhibited X-linked inhibitor of apoptosis protein (XIAP) expression, enhanced hepatocyte sensitivity to Fas cell surface death receptor (Fas)/Fas ligand (FasL) pathway, and induced hepatocyte apoptosis mediated via death receptor pathway. Additionally, treatment of AML12 cells with 25–50 nM triptolide upregulated miR-137, inhibited XIAP protein expression, and rendered hepatocytes more

susceptible to apoptosis, ultimately leading to hepatotoxicity [73].

In HepaRG cells, 100–400 nM triptolide elevated ROS levels, dissipated mitochondrial membrane potential, and shifted the apoptotic balance through upregulation of Fas, BAX, p53 and cleaved Caspase-3/8/9, coupled with BCL-2 downregulation, indicating that triptolide inhibited HepaRG cell proliferation and induced apoptosis through Fas death pathway and mitochondrial pathway, ultimately causing hepatotoxicity [74].

Induction of apoptosis leading to nephrotoxicity

Triptolide has been shown to exhibit potent anti-renal cell carcinoma activity by sensitizing Renca cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis and suppressing heat shock protein 70 (HSP70) expression [52]. However, it has simultaneously triggered apoptosis in renal cells by regulating oxidative stress-related pathways, exacerbating kidney injury [75].

Triptolide exhibited significant cytotoxicity towards renal tubular epithelial cell line NRK-52E, specifically manifested as 160 nM triptolide inhibited the nuclear translocation of the transcription factor Nrf2 through the activation of GSK3 β and the promotion of FYN proto-oncogene, Src family tyrosine kinase (Fyn) protein nuclear translocation, resulting in oxidative stress and renal tubular epithelial cell damage and ultimately contributing to nephrotoxicity [24]. In addition, triptolide increased ROS, lactate dehydrogenase, malondialdehyde (MDA) and glutathione (GSH) while reducing superoxide dismutase, inducing apoptosis in HK2 cells and renal cells of BALB/c mice, resulting in renal impairment. Triptolide counteracted triptolide-induced apoptosis in renal cells by suppressing oxidative stress [76].

Induction of apoptosis leading to cardiotoxicity

Triptolide has induced cardiotoxicity by triggering myocardial cell apoptosis through mitochondrial damage via the activation of p53-BAX axis or the suppression of Nrf2/Kelch-like ECH-associated protein 1 (Keap1)-nuclear respiratory factor 1 (NRF1) axis. Treating H9c2 cells and primary myocardial cells with 160 nM triptolide for 24 h significantly upregulated the expression of p53 protein and its downstream target genes, leading to increased mitochondrial outer membrane permeability and mitochondrial dysfunction. In p53 knockout mice, an intravenous injection of 1.2 mg/kg triptolide did not cause significant cardiac tissue damage, and both p53 and BAX antagonists mitigated triptolide-induced cardiotoxicity, further confirming that triptolide exerted cardiotoxicity through the activation of p53-BAX axis [77].

Furthermore, triptolide induced cardiotoxicity by enhancing Nrf2-Keap1 interaction and disrupting Nrf2-PGC-1 α binding which promoted Nrf2 ubiquitination and degradation [78], while simultaneously suppressing NRF1 expression, collectively leading to oxidative stress, mitochondrial dysfunction, and ultimately cardiomyocyte apoptosis; calycosin coordinately activated both Nrf2 and NRF1 pathways, representing a promising strategy to mitigate triptolide-induced cardiotoxicity [79].

Bidirectional autophagy modulation by triptolide generates pharmacological effects and toxicities

Triptolide, a potential bidirectional autophagy regulator, has been shown to exhibit dose-dependent effects. At low doses, it has activated survival autophagy through pathways such as ROS/c-Jun N-terminal kinase (JNK), demonstrating pleiotropic pharmacological benefits. In contrast, high doses have induced autophagic cell death, which has been associated with toxic side effects [80].

Triptolide has exhibited potent anti-tumor activity by finely modulating the cell death pathway network, inducing synergistic crosstalk between autophagy and apoptosis, with demonstrated efficacy against pancreatic cancer, leukemia, and triple-negative breast cancer [81–83]. Regarding organ protection, triptolide has restored autophagy function through multi-pathway regulation, mitigating diabetic nephropathy, IgA nephropathy, spinal cord injury, and salivary gland dysfunction [84–87]. Its neuroprotective effects have arisen from enhanced neuronal autophagy, promoting the clearance of pathogenic α -synuclein aggregates, suggesting therapeutic potential in Parkinson's disease [88]. Additionally, triptolide has exerted anti-fibrotic effects by inhibiting PI3K/AKT/mTOR pathway, thereby attenuating renal and surgery-induced epidural fibrosis [86, 89]. However, its therapeutic potential has been restricted by hepatotoxicity and nephrotoxicity, primarily driven by mitochondrial dysfunction and dysregulated autophagy pathways [90, 91] (Fig. 3).

Autophagic modulation by triptolide in pharmacological activities

Promoting autophagy to exert antitumor effects

Triptolide has regulated the autophagy pathway through multiple molecular mechanisms and has exhibited significant antitumor activity in cancer. Triptolide (20–120 nM) induced ROS accumulation, increased mitochondrial membrane potential, and activated Caspase-8, -9, and -3 in WEHI-3 cells. It also promoted autophagy by enhancing microtubule-associated protein 1 light chain 3 (LC3), autophagy related 5 (ATG5), ATG7, and ATG12 expression, suggesting that triptolide synergistically

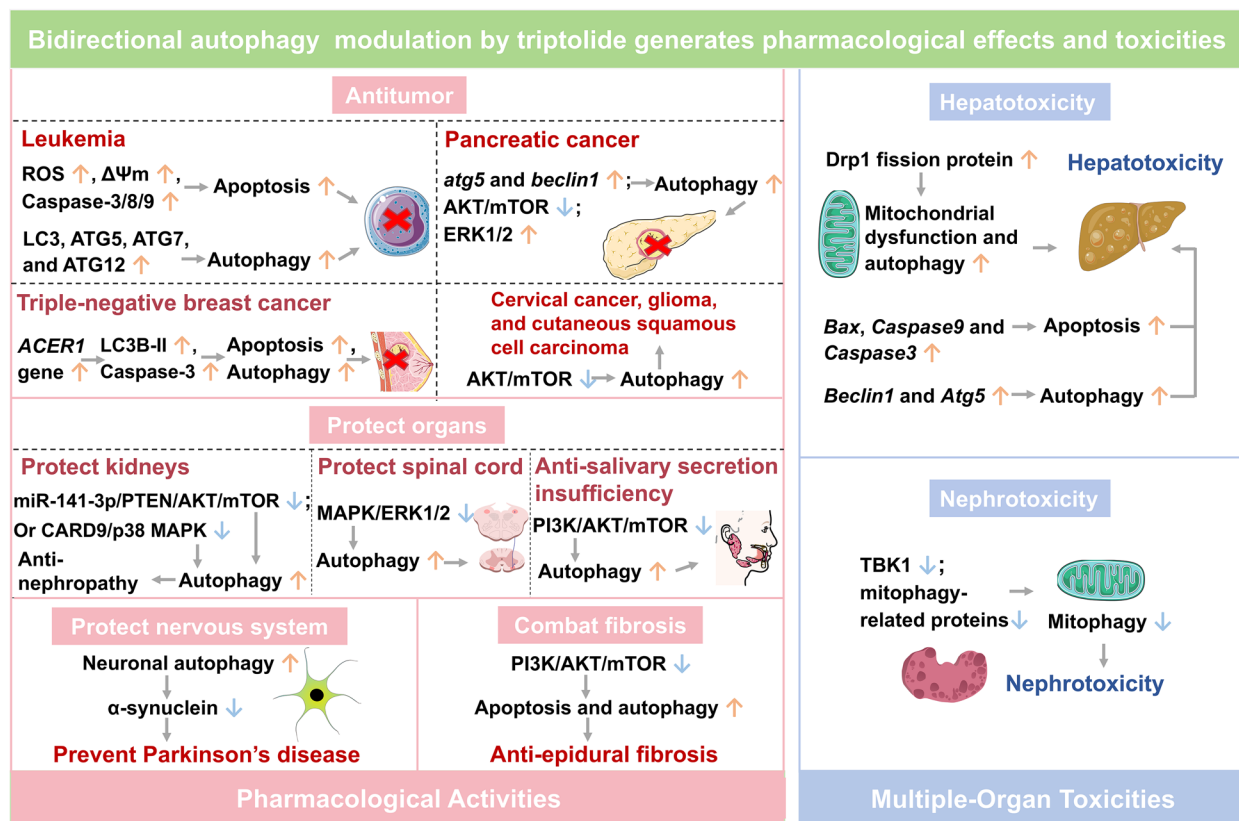


Fig. 3 Bidirectional autophagy modulation by triptolide generates pharmacological effects and toxicities. ↑: Activation or Upregulation; ↓: Inhibition or Downregulation. Other gene and protein abbreviations appearing in this figure can be found in the Abbreviation List

activated both apoptosis and autophagy pathways to exert anti-leukemic effects [92].

In pancreatic cancer, triptolide activated autophagy by downregulating PUM1 and enhancing tumor cell sensitivity to TRAIL [93]. It also induced both caspase-dependent and caspase-independent autophagic cell death in various cell lines, and this autophagy induction depended on the *atg5* and *beclin1* genes and was accompanied by the inhibition of AKT/mTOR pathway and the activation of ERK1/2 pathway, indicating that triptolide was an effective chemotherapeutic agent for treating pancreatic cancer [82].

In triple-negative breast cancer, 25 nM triptolide induced both autophagy and apoptosis in MDA-MB-231 cells by downregulating p62, upregulating the LC3B-II and activating Caspase-3 making it a potential anticancer lead compound for triple-negative breast cancer [94]. Further research revealed that alkaline ceramidase 1 (*ACER1*) gene overexpression enhanced triptolide-induced apoptosis in MDA-MB-231 cells, promoted autophagosome formation (LC3B-II upregulation and p62 downregulation) and inhibited cell migration and invasion, establishing *ACER1* as a potential target for

triptolide intervention in triple-negative breast cancer [95].

In addition, triptolide inhibited AKT/mTOR signaling and induced autophagy and apoptosis in cancer cells, exerting cytotoxicity in cervical cancer [96], glioma [83], and cutaneous squamous cell carcinoma [97], collectively highlighting its broad-spectrum antitumor properties.

Promoting autophagy to protect organs

Triptolide has restored cellular autophagy capacity and has exerted significant renal protective effects against various diseases. For instance, triptolide downregulated miR-141-3p expression, and upregulated phosphatase and tensin homolog deleted on chromosome 10 (PTEN) levels, then inhibited AKT/mTOR pathway to restore cellular autophagy and alleviate diabetic fibrosis [98]. Moreover, triptolide promoted autophagy by downregulating caspase recruitment domain-containing protein 9 (CARD9)/p38 MAPK pathway, which inhibited mesangial cell proliferation in both IgA nephropathy mice (300 µg/kg, intragastric administration) and IgA1-induced human mesangial cells (20 ng/mL), providing a novel therapeutic approach for IgA nephropathy [85].

In a spinal cord injury model, intraperitoneal injection of 0.2 mg/kg triptolide induced autophagy by inhibiting MAPK/ERK1/2 pathway, exerting a protective effect and reducing kidney damage [84].

Furthermore, 2.5 ng/mL triptolide promoted autophagy and M2 polarization in aged macrophages by inhibiting PI3K/AKT/mTOR pathway, and improved salivary gland structure and function, which potentially prevented age-related salivary secretion insufficiency [87].

Promoting autophagy to protect nervous system

Triptolide has been shown to effectively promote the clearance of α -synuclein by neuronal autophagy, facilitating the removal of damaged or senescent neurons [99]. 0.5–50 nM triptolide reduced the levels of α -synuclein in neuronal cells and primary cortical neurons via the activation of autophagy, underscoring its therapeutic potential for Parkinson's disease and other neurodegenerative disorders characterized by protein aggregation [88].

Promoting autophagy to combat organ fibrosis

In addition to mitigating diabetic renal fibrosis by restoring autophagy via miR-141-3p/PTEN/AKT/mTOR pathway [98], triptolide has also demonstrated significant efficacy against surgery-related epidural fibrosis. 2–8 μ g/mL triptolide significantly suppressed human fibroblast proliferation by inhibiting PI3K/AKT/mTOR pathway, while simultaneously promoting apoptosis and autophagy. In a rat model, local administration of 0.2 and 0.4 mg/mL triptolide effectively alleviated postoperative fibrosis, offering a potential therapeutic strategy for preventing surgery-related epidural fibrosis [89].

Triptolide has induced autophagy leading to multi-organ toxicities

Induction of autophagy leading to hepatotoxicity

Triptolide has induced hepatotoxicity by causing mitochondrial dysfunction and the activation of mitochondrial autophagy. For instance, triptolide increased the expression of Drp1 fission protein in LO2 cells, along with the colocalization of autophagosomes with mitochondria; the selective Drp1 inhibitor Mdivi-1 alleviated triptolide-induced hepatotoxicity. In rat liver tissue treated with 400 μ g/kg triptolide, mitochondrial fission was significantly activated, further indicating that targeting the mitochondrial fission and autophagy pathways represented a new therapeutic approach against triptolide-induced hepatotoxicity [90].

Triptolide has also induced hepatotoxicity by activating the pathways of autophagy and apoptosis [100]. In a zebrafish model, exposure to 0.2–0.8 μ M triptolide activated Fas-Caspase-8 apoptosis pathway, characterized by the upregulation of the pro-apoptotic genes *Bax*,

Caspase-9 and *Caspase-3*. Meanwhile, the expression of the autophagy-related genes *Beclin1*, *Atg5*, *Atg3* and *Lc3* was significantly increased, with the most prominent changes observed in *Beclin1* and *Atg5*, suggesting that death receptor *Fas* may be the primary target of triptolide-induced hepatotoxicity [101].

Inhibition of autophagy leading to nephrotoxicity

The mechanism of triptolide-induced nephrotoxicity has been linked to its disruption of mitochondrial function and suppression of mitophagy. In Sprague–Dawley rats, intragastric administration of 0.5–2.0 mg/kg triptolide downregulated TANK-binding kinase 1 (TBK1) and mitophagy-related proteins, reducing mitochondrial autophagosome formation and impairing renal function; TBK1 overexpression restored mitophagy and mitochondrial function, indicating that targeting the TBK1-mitophagy pathway could be a potential therapeutic strategy to mitigate triptolide-induced nephrotoxicity [91].

Bidirectional pyroptosis modulation by triptolide generates pharmacological effects and toxicities

Pyroptosis, also known as inflammatory necrosis, is primarily caused by the activation of inflammasomes, which activate Caspase-1 or Caspase-4/5, ultimately leading to cell membrane rupture, release of cellular contents, and a strong inflammatory response [102].

Triptolide has exhibited various pharmacological and toxic effects through pyroptosis regulation. In antitumor research, this compound has been shown to enhance immune responses and inhibit cancer cell growth via the activation of gasdermin E (GSDME)-mediated pyroptosis pathway [103]. For renal injury, triptolide has demonstrated the renal protection to alleviate podocyte damage through Nrf2/ROS/NOD-like receptor family, pyrin domain-containing 3 (NLRP3) axis [104]. However, triptolide has also been reported to induce Kupffer cell pyroptosis by activating the Caspase-3/GSDME pathway, resulting in hepatotoxicity [105] (Fig. 4).

Pyroptotic modulation by triptolide in pharmacological activities

Promoting pyroptosis to exert anti-tumor effects

Triptolide has demonstrated both antitumor immunity enhancement and cytotoxicity towards head and neck cancer cells through agitation of GSDME-mediated pyroptosis. Treating HK1, FaDu, and C666-1 cells with 50 nM triptolide significantly suppressed cellular myelocytomatosis viral oncogene homolog (c-Myc) and mitochondrial hexokinase II expression, activated the Bcl-2-associated death promoter (BAD)/BAX-Caspase 3 cascade, subsequently induced Caspase 3-mediated

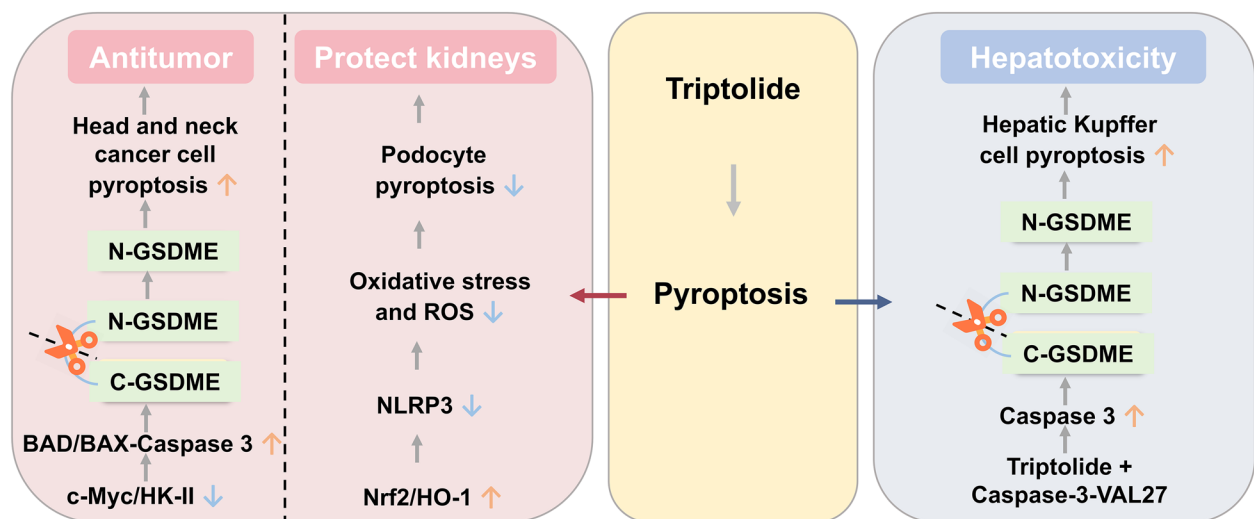


Fig. 4 Bidirectional pyroptosis modulation by triptolide generates pharmacological effects and toxicities. ↑: Activation or Upregulation; ↓: Inhibition or Downregulation. Other gene and protein abbreviations appearing in this figure can be found in the Abbreviation List

cleavage of GSDME, and triggered tumor cell pyroptosis, establishing a new paradigm for triptolide as a pyroptosis-inducing agent in cancer therapy [103].

Inhibiting pyroptosis to protect the kidneys

Triptolide has been shown to alleviate podocyte damage in diabetic nephropathy by regulating Nrf2/ROS/NLRP3 axis. Specifically, intragastric administration of triptolide (100 µg/kg/day) activated Nrf2/heme oxygenase 1 (HO-1) pathway while inhibiting NLRP3 inflammasome pathway, reduced oxidative stress and ROS levels, attenuated pyroptosis, and improved renal function and histopathological damage in diabetic nephropathy mice [104].

Triptolide induces pyroptosis leading to hepatotoxicity

Twenty–200 µM triptolide bound to the VAL27 site of hepatic Kupffer cells, induced the cleavage of GSDME to generate N-GSDME by promoting Caspase-3 maturation and activation, and ultimately triggered hepatic cell pyroptosis. Knocking out Caspase-3 or administration of Caspase-3 inhibitors counteracted triptolide-induced liver damage in mice, which further confirmed that triptolide exerted hepatotoxicity through the activation of GSDME/CASP3 axis [105].

Bidirectional ferroptosis modulation by triptolide generates pharmacological effects and toxicities

Ferroptosis is an iron-dependent cell death driven by the accumulation of lethal lipid peroxides [106]. Extensive investigations have characterized triptolide as a potent inducer of ferroptosis in various cancer cell lines, and a tumor suppressor or a drug sensitizer in standard

chemotherapy regimens [107–110]. Regarding organ protection, triptolide has significantly suppressed ferroptosis in lung and kidney tissues, exerting protective effects against acute lung injury and diabetic nephropathy [111, 112]. Nonetheless, triptolide has also been associated with ferroptosis-related toxicities, contributing to reproductive, cardiac, and hepatic damage [113–115] (Fig. 5).

Ferroptotic modulation by triptolide in pharmacological activities

Promoting ferroptosis to exert anti-tumor effects

Triptolide has induced ferroptosis in tumor cells by regulating Nrf2 and its downstream targets [glutathione peroxidase 4 (GPX4), solute carrier family 7 member 11 (SLC7A11)], exerting broad-spectrum antitumor effects [107, 108, 116]. 25–100 nM triptolide downregulated SLC7A11 and GPX4 expression via the inhibition of PI3K/AKT/Nrf2 pathway, promoting ferroptosis and producing cytotoxicity in colorectal cancer cells (HCT116 and LoVo). In transplanted tumor, intraperitoneal injection of triptolide (5 mg/kg) activated ferroptosis by suppressing SLC7A11/GPX4 axis and inhibited tumor growth in colorectal cancer [107]. Furthermore, triptolide-loaded hydrogels activated ferroptosis in glioblastoma cells by the suppression of Nrf2/SLC7A11/GPX4 pathway, significantly prolonging survival in mice with transplanted recurrent glioblastoma [108].

Triptolide (10–50 nM) promoted peroxidized lipid accumulation by inhibiting Nrf2/GPX4/SLC7A11 axis, then induced ferroptosis in HeLa and SiHa cervical cancer cells; and 10–20 mg/kg triptolide significantly inhibited cervical cancer xenograft growth, supporting its

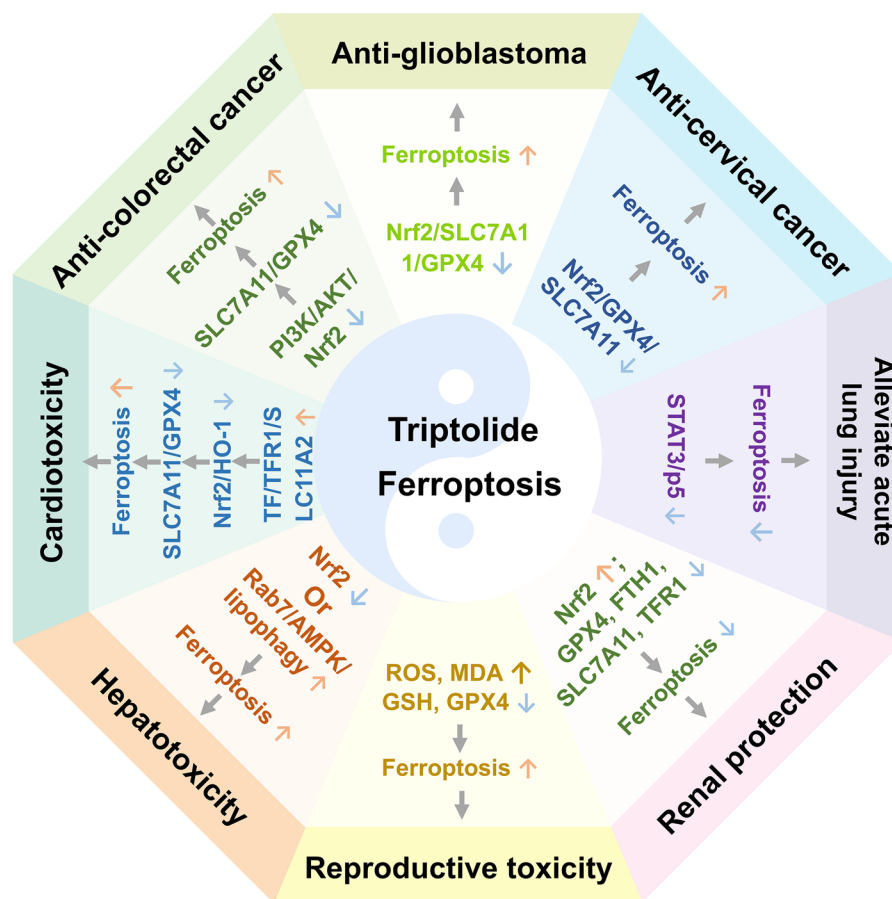


Fig. 5 Bidirectional ferroptosis modulation by triptolide generates pharmacological effects and toxicities. ↑: Activation or Upregulation; ↓: Inhibition or Downregulation. Other gene and protein abbreviations appearing in this figure can be found in the Abbreviation List

potential as a therapeutic candidate for cervical cancer treatment [109]. Interestingly, 40 nM triptolide reversed doxorubicin resistance in leukaemia cells through Nrf2 suppression and restored chemotherapy sensitivity, indicating that triptolide-doxorubicin combination therapy improved leukemia treatment efficacy [110].

Inhibiting ferroptosis to protect organs

Triptolide could inhibit ferroptosis mediated by STAT3/p53 pathway and reduce inflammation, alleviating acute lung injury. Intraperitoneal administration of triptolide (50 µg/kg/d, 7 days) significantly decreased STAT3 and p53 phosphorylation levels in lung tissue. Mechanistically, triptolide (1–1000 nM) suppressed lipopolysaccharide-induced ferroptosis in human bronchial epithelial cells (BEAS-2B) through inhibition of STAT3/p53 pathway, suggesting its therapeutic potential for acute lung injury [111].

Triptolide has also demonstrated significant renal protection in diabetic nephropathy by inhibiting ferroptosis-mediated oxidative stress. In db/db mice, triptolide

significantly upregulated Nrf2 expression while down-regulating GPX4, ferritin heavy chain 1 (FTH1), and SLC7A11 levels in renal tissue, suppressed transferrin receptor 1 (TFR1) production, and effectively inhibited the ferroptosis cascade. These effects collectively stabilized the glomerular podocyte cytoskeleton, reduced oxidative stress, and improved mitochondrial dysfunction, consequently ameliorating diabetic nephropathy-associated proteinuria [112].

Triptolide induces ferroptosis leading to multi-organ toxicities

Induction of ferroptosis leading to reproductive toxicity

Through induction of ferroptosis in spermatogonia, triptolide has caused testicular damage and has impaired spermatogenic function. In a mouse model, triptolide significantly increased ROS and MDA levels while reducing GSH content and GPX4 expression. Mechanistically, triptolide triggered Lysine 63 (K63)-linked polyubiquitination-mediated GPX4 degradation, activated ferroptosis pathway and consequently induced testicular

tissue damage and spermatogenic abnormalities (reduced sperm concentration and morphological defects), while this male reproductive toxicity was attenuated by the ferroptosis inhibitor ferrostatin-1 [113].

Induction of ferroptosis leading to hepatotoxicity

Triptolide has demonstrated bidirectional regulation of Nrf2 pathway, producing opposite biological effects in different tissues. In renal tissue, triptolide attenuated ferroptosis by upregulating Nrf2, thereby maintaining renal tight junction integrity in diabetic nephropathy [112]. Conversely, hepatic exposure to triptolide promoted Nrf2 degradation, triggering ferroptosis-mediated liver injury. 70 nM triptolide inhibited Nrf2 signaling in LO2 and AML12 hepatocytes, potentiating ferroptosis. Nrf2-knockout mice administered 1.2 mg/kg triptolide via intraperitoneal injection exhibited exacerbated lipid metabolic disorders and hepatotoxicity, which were ameliorated by exogenous Nrf2 overexpression [114].

Triptolide has activated RAS-associated protein RAB-7 (Rab7)-mediated lipophagy and induced hepatocyte ferroptosis, resulting in hepatotoxicity. 25–100 nM triptolide upregulated Rab7 expression by activating AMPK pathway, promoting lipid droplet degradation and free fatty acid release, which subsequently induced mitochondrial dysfunction and oxidative stress, leading to ferroptosis in the human normal liver cell line HL7702; intraperitoneal injection of 0.4–0.8 mg/kg triptolide in male C57BL/6J mice impaired liver function, activated lipophagy, and elevated ferroptosis markers, while the inhibition of lipophagy effectively alleviated triptolide-induced ferroptosis and hepatotoxicity, further confirming that triptolide triggered ferroptosis through Rab7/AMPK/lipophagy axis [117].

Induction of ferroptosis leading to cardiotoxicity

Through modulation of SLC7A11/GPX4 axis, triptolide has exhibited dual pharmacological effects: inducing ferroptosis to exert both antitumor activity [107, 108] and organ protection [112], while paradoxically mediating potential cardiotoxicity via the same pathway. 20–640 nM triptolide inhibited Nrf2/HO-1 antioxidant pathway by upregulating transferrin (TF)/TFR1/SLC11A2 axis, leading to iron overload, Fenton reaction-mediated ROS generation, and the accumulation of lethal lipid peroxides. Additionally, triptolide directly bound to SLC7A11, subsequently suppressed SLC7A11/GPX4 axis and induced ferroptosis in the human cardiomyocyte line AC16, ultimately causing cardiac damage. The ferroptosis inhibitor Ferrostatin-1 alleviated the cardiotoxicity, further confirming triptolide-mediated ferroptosis cardiotoxicity [115].

Triptolide triggers cuproptosis to exert pharmacological activities

Cuproptosis is a copper-dependent cell death pathway initiated by the binding of copper to lipoylated tricarboxylic acid cycle proteins, resulting in protein aggregation, proteotoxic stress, and cell death [118]. Triptolide has induced cuproptosis in cervical cancer cells through XIAP/copper metabolism domain containing 1 (COMMD1)/ATPase copper transporting alpha (ATP7A) and beta (ATP7B)-mediated copper dysregulation, holding great promise for anticancer therapy. Targeting XIAP and modulating COMMD1, triptolide (20–160 nM) induced cuproptosis in HeLa and SiHa cells, characterized by downregulated expression of copper export proteins ATP7A/B but unaltered expression of copper import protein copper transporter 1. Moreover, administration of 0.2–0.6 mg/kg triptolide markedly suppressed tumor growth in nude mice bearing cervical cancer xenografts, supporting the therapeutic potential of triptolide-induced cuproptosis in cervical cancer treatment [119].

Triptolide triggers necroptosis leading to hepatotoxicity

Necroptosis, a form of PCD mediated by receptor-interacting protein kinase 1 (RIPK1) and RIPK3 kinases, is triggered by pro-inflammatory extracellular stimuli and involves necrosome formation and mixed lineage kinase domain-like (MLKL) activation, representing a highly relevant process in liver pathophysiology [120, 121].

Triptolide induced hepatic hypersensitivity, leading to hepatocyte apoptosis and necroptosis. Mechanistically, triptolide inhibited NF- κ B-dependent transcriptional activity and suppressed FLICE-like inhibitory protein (FLIP) expression, sensitizing mice and human hepatic cell line LO2 to lipopolysaccharide and TNF- α , which subsequently triggered hepatocyte apoptosis and necroptosis. Etanercept (a TNF- α inhibitor) or exogenous FLIP overexpression effectively blocked necroptosis-related proteins, including RIPK1, MLKL, and P-MLKL, and markedly reduced triptolide-induced hepatotoxicity, underscoring the pivotal role of NF- κ B/FLIP axis in mediating triptolide-associated hepatotoxicity [16]. While necroptosis has been implicated in triptolide-induced hepatotoxicity in the studied model [16], whether it contributes to toxicity in other organs remains to be fully elucidated.

Triptolide triggers PANoptosis leading to multi-organ toxicities

Currently, only the hepatotoxicity and nephrotoxicity of triptolide induced by PANoptosis have been experimentally confirmed. Whether PANoptosis elicits other pharmacological or toxic effects of triptolide in different tissues or under other pathological conditions remains to be investigated. Triptolide has been shown to simultaneously activate pyroptosis, apoptosis, and necroptosis, forming PANoptosome complexes and inducing PANoptosis [122], ultimately leading to hepatotoxicity and nephrotoxicity in vivo and in vitro. Mechanistically, in mouse macrophages (J774A.1) and human primary macrophages, 6.25–200 nM triptolide triggered ASC speck formation (pyroptosis induction), Caspase-8 activation (apoptosis induction), and RIPK3 aggregation (necroptosis induction), while promoting colocalization of ASC with RIPK3 or Caspase-8. In C57BL/6J mice, intraperitoneal injection of 1–2 mg/kg triptolide induced cleaved CASP3 (apoptosis), GSDME-NT, CASP1p10, GSDMD-NT (pyroptosis), and p-MLKL (necroptosis) in liver tissue, confirming PANoptosis-mediated organ toxicities and suggesting its inhibition as a potential therapeutic strategy [123].

Based on the PCD regulatory characteristics and multi-organ toxicities limitations of triptolide (Table 2), nano-delivery systems have become a potential strategy to break through the bottleneck of clinical translation.

Nanostrategies for attenuating organ toxicity and potentiating therapeutic effects of triptolide

By enhancing targeted delivery to disease sites [124, 125], promoting cellular uptake [126, 127], and selective accumulation in pathological tissues [128, 129], nanotechnology-based approaches have effectively reduced multi-organ toxicities of triptolide. Furthermore, nano-delivery systems have significantly enhanced the therapeutic efficacy of triptolide through combination therapy [130, 131], microenvironment-responsive release [132, 133], and optimized pharmacokinetic behavior [134–137], offering a promising pathway toward its clinical application (Table 2).

However, all current triptolide nano-delivery formulations remain at the preclinical research stage, which fully exposes the severity of its industrialization prospects. Specifically, (1) Existing formulations have generally suffered from low drug loading (TLP-HA has exhibited only 2.17% [127] and TP-FPNPs only 1.11% [126]) and burst release phenomena (DT/Pep1 has released explosively at pH 7.4 [138], and TPL-NPs has shown sudden release after 12 h [139]). (2) Numerous intelligent formulations have performed well in controlled laboratory

environments, factors such as temperature gradients, pH fluctuations, and uneven illumination in industrial-scale production reactors have led to the loss of predictability of their response behavior [132, 140]. (3) The long-term safety and in vivo metabolic characteristics of TP-TPBC-PEG as well as the long-term stability of TF-TP@LIP all require costly and time-consuming research verification [124, 141] (Table 3).

Nanotechnology-based strategies to mitigate toxicity of triptolide

The clinical application of triptolide has been primarily limited by its severe systemic toxicity. Conventional formulations have led to rapid biodistribution, resulting in widespread tissue damage [14, 15]. Fortunately, nanotechnology has offered promising strategies to mitigate these challenges. By enabling targeted delivery, enhancing cellular uptake, and improving site-specific accumulation, nanoscale formulations have significantly reduced the off-target toxicity of triptolide while maintaining therapeutic efficacy [126, 128, 142, 143].

Stimuli-responsive nanoplateforms for triptolide delivery

Triptolide-based smart delivery systems have demonstrated significant potential in improving drug safety by responding to specific microenvironments [144]. For glioblastoma treatment, dendrimer-triptolide conjugates selectively targeted tumor-associated macrophages, induced intracellular drug release and reprogrammed macrophages from a pro-tumor to an anti-tumor phenotype, thereby enhancing therapeutic effects while markedly reducing hepatotoxicity and cardiotoxicity [143].

TP-TPBC-PEG nanospheres enabled controlled triptolide release through dual pH- and near-infrared-responsive mechanisms, activating Hippo pathway to induce tumor cell death. Notably, the nanospheres exhibited no organ toxicity in mice, suggesting promise for both primary osteosarcoma treatment and lung metastasis prevention [124]. For rheumatoid arthritis, pH-sensitive TP@NPs selectively accumulated in the acidic synovial microenvironment to deliver potent anti-inflammatory and chondroprotective effects at ultra-low doses, effectively minimizing systemic exposure and overcoming the toxicity limitations of free triptolide for safer therapeutic outcomes [125].

Targeted delivery strategies for enhanced triptolide nanomedicine accumulation

Targeted optimization of triptolide nanomedicines has significantly enhanced tumor-specific drug accumulation while reducing off-target distribution, thereby lowering systemic toxicity [128]. Sulfated dextran and arginine-glycine-aspartate peptide co-modified

Table 2 Programmed cell death-mediated multi-organ toxicities induced by triptolide

Toxicities	Cell lines/models	Dosage	Molecular mechanisms	Refs.
Hepatotoxicity	C57BL/6 mice	500 µg/kg TP, i.g	↓XIAP protein, ↑the sensitivity of hepatocytes to Fas/FasL pathway, ↑apoptosis	[73]
	AML12 cell line	25 and 50 nM TP, in vitro	↓XIAP protein, ↑the sensitivity of hepatocytes to Fas/FasL pathway, ↑apoptosis	[73]
	HepaRG cells	100–400 nM TP, in vitro	↑Fas death pathway and mitochondrial apoptosis	[74]
	C57BL/6J female mice	500 µg/kg TP, i.g	↓Proteasome and ↑ROS production via ATF4, thereby ↑ERS-related apoptosis	[22]
	LO2 cells	–	↑Drp1-related mitochondrial dysfunction and mitochondrial autophagy	[90]
	Zebrafish	0.2–0.8 µM TP, <i>waterborne administration</i>	↑Autophagy-related genes <i>Beclin1, Atg5, Atg3</i> and <i>Lc3</i>	[101]
	Zebrafish	300 nM TP, <i>waterborne administration</i>	↑Oxidative stress, lipid metabolism, autophagy, and apoptosis	[100]
	Kupffer cells	20–200 µM TP, in vitro	↑Caspase-3-GSDME pyroptosis	[105]
	C57BL/6 mice and Caspase-3 knockout mice	1000 µg/kg TP, i.g	↑Caspase-3-GSDME pyroptosis	[105]
	LO2 cells and AML12 cells	70 nM TP, in vitro	↓Nrf2 pathway, ↑ferroptosis	[114]
	Nrf2—/—mice and C57BL/6J mice	1.2 mg/kg TP, i.p	↓Nrf2 pathway, ↑ferroptosis	[114]
	Male Wistar rats	2 mg/kg TP, i.p	↑Proapoptotic proteins cytochrome C, cleaved Caspase-3 and BCL-2-associated X	[188]
	Female C57BL/6J mice	0.1 mg/kg TP, i.p	↑Hepatocyte apoptosis via mitochondrial dysfunction	[189]
	AML12 cells	50 nM TP, in vitro	↑JNK pathway, ↓hepatocyte apoptosis	[189]
	LO2 cells	50 nM TP, in vitro	↑Hepatotoxicity-associated proteins PKCα and FIS1, ↑mitochondrial apoptosis	[190]
	Female BALB/c mice	500 µg/kg TP, i.p	↑Hepatotoxicity-associated proteins PKCα and FIS1, ↑mitochondrial apoptosis	[190]
	Human normal liver cell line HL7702	25–100 nM TP, in vitro	↑Rab7-mediated lipophagy, ↑hepatic cells ferroptosis	[117]
	Male C57BL/6J mice	0.4–0.8 mg/kg TP, i.p	↑Rab7-mediated lipophagy, ↑hepatic cells ferroptosis	[117]
	Mice	500 µg/kg TP, i.g. + 0.1 mg/kg LPS, i.p	↓NF-κB and FLIP, ↑hepatocytes apoptosis and necroptosis	[16]
	Human hepatic cell line LO2	25 nM TP + 50 ng/mL TNF-α, in vitro	↓NF-κB and FLIP, ↑hepatocytes apoptosis and necroptosis	[16]
Nephrotoxicity	NRK-52E cells	80–320 nM TP, in vitro	↑Apoptosis by promoting Nrf2 degradation through ubiquitination via GSK3β/Fyn pathway	[24]
	HK2 cell	5–640 nM TP, in vitro	↑Oxidative stress, ↑nephrocyte apoptosis	[76]
	BALB/c mice	1 mg/kg TP, i.g	↑Oxidative stress and ↑renal function parameters, ↑renal injury	[76]
Hepatotoxicity and Nephrotoxicity	Sprague–Dawley rats	0.5–2.0 mg/kg/d TP, i.g	↓TBK1 and mitophagy-related proteins	[91]
	J774A.1 mouse macrophage cell line and primary macrophages	6.25–200 nM TP, in vitro	PANoptosome assembly	[123]
	C57BL/6J mice	1 and 2 mg/kg TP, i.p	CASP3, GSDME-NT, and p-MLKL cleavage, PANoptosome assembly	[123]

Table 2 (continued)

Toxicities	Cell lines/models	Dosage	Molecular mechanisms	Refs.
Cardiotoxicity	H9c2 cells and rat primary cardiomyocytes	160 nM TP, in vitro	↑BAX-induced mitochondrial-mediated apoptosis	[77]
	p53 ^{−/−} mice and C57BL/6J mice	1.2 mg/kg TP, i.v	↑BAX-induced mitochondrial-mediated apoptosis	[77]
	Male Balb/c mice	1.5 mg/kg TP, i.p	↓Nrf2/Keap1-NRF1 axis, ↑cardiomyocyte apoptosis	[79]
	H9C2 cardiomyocytes	200 nM TP, in vitro	↓Nrf2/Keap1-NRF1 axis, ↑cardiomyocyte apoptosis	[79]
	AC16 Human cardiac muscle cell line	20–640 nM TP, in vitro	↑SLC7A11/GPX4 inactivation-mediated ferroptosis	[115]
Reproductive toxicity	C57BL/6J male mice	0.2 mg/kg TP, i.p	↑Mitochondrial apoptosis pathway	[69]
	Sprague–Dawley male rats	100 µg/kg, i.p	↓SIRT1/Nrf2 pathway, ↑apoptosis	[70]
	TM4 cells	40–640 nM, in vitro	↓SIRT1/Nrf2 pathway, ↑apoptosis	[70]
	Adult male Sprague–Dawley rats	400 µg/kg TP, i.g	↑Drp1, ↑mitochondrial apoptosis pathway	[23]
	Testicular interstitial cell line TM3	–	↑Leydig cell apoptosis by disrupting mitochondrial dynamics in rats	[23]
	Male mice	100 µg/kg TP, i.p	↑K63-linked polyubiquitination of GPX4 in spermatogonia, ↑ferroptosis	[113]
	GC-2spd cell line	0.2 µM TP, in vitro	↑K63-linked polyubiquitination of GPX4 in spermatogonia, ↑ferroptosis	[113]

Other gene and protein abbreviations appearing in this figure can be found in the Abbreviation List

TP: Triptolide; i.v.: intravenous; i.p.: intraperitoneal injection; i.g.: intragastric administration; Drp1: Dynamin-related protein 1; LPS: Lipopolysaccharide

↑ = Activation or Upregulation

↓ = Inhibition or Downregulation

TP-SP@NPs demonstrated efficient tumor accumulation and potent anti-pancreatic cancer activity by reducing pro-tumor M2 macrophage infiltration, with significantly lower systemic toxicity than free triptolide, showing strong clinical translation potential [129]. Furthermore, mitochondrial-targeted triptolide liposomes FA + TPP–TP–Lips specifically localized to liver cancer cell mitochondria, disrupted membrane potential and elevated intracellular ROS levels, significantly increased tumor cell apoptosis while reducing hepatotoxicity and systemic side effects, establishing a promising targeted strategy for hepatocellular carcinoma therapy with enhanced efficacy and reduced toxicity [145].

For rheumatoid arthritis treatment, FA-TP@VA nanoparticles achieved targeted delivery and efficient accumulation in inflamed joints through folate receptor-mediated uptake by M1 macrophages, significantly enhancing therapeutic efficacy while reducing triptolide-induced hepatic oxidative stress and systemic toxicity [146]. Similarly, PAT nanocarriers selectively accumulated in affected joints, showing comparable therapeutic efficacy to free triptolide while exhibiting markedly reduced toxicity, thus offering a safer treatment option for rheumatoid arthritis [147].

Cellular-uptake boosted triptolide nanomedicine

The cellular uptake efficiency of triptolide nanomedicines has been significantly enhanced by ligand modification. For instance, folate-functionalized Pluronic F127/P123 nanoparticles encapsulating triptolide facilitated folate receptor-mediated endocytosis, improving drug delivery for renal ischemia–reperfusion injury while reducing renal, hepatic, and reproductive toxicity, thereby demonstrating superior therapeutic safety [126]. Similarly, hyaluronic acid-coated triptolide nanomedicines promoted targeted accumulation in breast cancer tissue, enhancing antitumor efficacy and minimizing systemic toxicity [127].

Nanotechnology-based strategies to enhance efficacy of triptolide

The nanodelivery system for triptolide has employed multidimensional strategies, including targeted drug delivery, combination therapy, tumor microenvironment modulation, and pharmacokinetic optimization, to significantly enhance drug accumulation and therapeutic efficacy at disease sites [148]. These innovations have substantially improved the clinical potential of triptolide

Table 3 Summary of disease applications, advantages, and limitations of triptolide nanoformulations

Nanoformulations	Diseases	Advantages	Limitations	Refs.
TP-LHSP	Bladder cancer	TP-LHSP outperformed the free TP by suppressing tumor volume to 0.173 cm ³ in mice	Release rate required further optimization	[156]
TP-LP-HA	Breast cancer	Increased LD ₅₀ by 2.36-fold (to 3.07 mg/kg) vs. free TP (1.30 mg/kg), achieved 51.6% tumor inhibition, and alleviated hepatorenal toxicity	Relatively low drug loading capacity (only 2.17%)	[127]
DT/Pep1	Breast cancer	DT/Pep1 achieved a high tumor suppression rate of 68.4%	Drug burst release occurred at pH 7.4	[138]
TP-L@nano-gel	Breast cancer	TP-L@nano-gel significantly prolonged median survival in tumor-bearing mice to > 36 days (vs. 22 days with free TP), without significant weight loss	Drug loading efficiency = 4.52%	[149]
Cel + TP/RB-CM@R8-Lip	Breast cancer and liver cancer	Effective immune evasion and tumor enrichment	Nanoparticle hydrated size increased to ~99.6 nm	[153]
TP-L-GNR@MSN-3P	Cancer	TP-L-GNR@MSN-3P accumulated at the tumor site within 6 h	Drug release was triggered only upon concurrent high intracellular GSH and external laser irradiation	[140]
TP-L-NPs	Chronic dermatitis	Transdermal permeation was significantly enhanced	Sudden release occurred after 12 h	[139]
D-Trip	Glioblastoma	D-Trip reduced tumor burden to 12% (from 35%) and cut liver toxicity fivefold in a glioblastoma model	Only approximately 30% TP was released within 24 h	[143]
(SFN + TP-L)@CPLCNPs	Hepatocellular carcinoma	69.4% apoptosis in Huh-7 cells, superior in vivo tumor suppression, prolonged circulation without aggregation	Initial rapid release phenomenon	[131]
FA + TPP-TP-Lips	Hepatocellular carcinoma	79.37% tumor inhibition rate in tumor-bearing mice	In vivo AST elevation implied hepatotoxic risk	[145]
NF-Trip	Hepatocellular carcinoma	NF-Trip increased survival to 80% with reduced toxicity in mice, compared to 30% in controls	Drug release depended on folate receptor expression and an acidic environment	[128]
TP/GLLNPs	Hepatocellular carcinoma	Effective tumor inhibition (87.2%) with low hemolysis (< 5%) and minimal systemic toxicity at therapeutic doses	Slow drug release and liver accumulation	[151]
TF-TP@LIP	Hepatocellular carcinoma	Potent tumor-targeted activity (IC ₅₀ = 42.3 nM)	Long-term stability required further validation	[141]
TP-L@mPLGA	Hepatocellular carcinoma	The tumor growth inhibition rate reached as high as 69.25%	Slow release hindered rapid drug action at the tumor	[150]
PSSP@TP	Hepatocellular carcinoma	PSSP@TP significantly enhanced the therapeutic index of TP by boosting antitumor efficacy while reducing hepatotoxicity in LO2 cells	Low encapsulation efficiency	[133]
TP-L@TFBF	Melanoma	TP-L@TFBF achieved a 65.6% anti-tumor rate with a hemolysis rate below 2%, indicating high safety	Drug efficacy depended on an acidic microenvironment	[152]
TP-L@PLGA@F127	Myocardial infarction	Cardiac function was effectively improved while reducing toxicity	Burst release and poor myocardial retention	[142]
TP-TPBC-PEG	Osteosarcoma	Mortality from 60% (free TP) to 0% (nanomedicine); severe multi-organ damage prevented	Long-term safety and in vivo metabolic profile required further validation	[124]
PVGLIG-MTX-D/T-NMs	Ovarian cancer	PVGLIG-MTX-D/T-NMs achieved a tumor suppression rate exceeding 50%	Particle size stability was below the ideal level	[160]
TP-SP@NPs	Pancreatic cancer	Targeting both pancreatic cancer cells (IC ₅₀ 14.62 ng/mL) and M2 macrophages (IC ₅₀ 7.55 ng/mL)	Stability in certain biological media was limited	[129]
TP-L-Lip	Pancreatic cancer	The survival period of tumor-bearing mice was extended from 28 to 45 days	The prodrug (TP-L-LA) was metabolized slowly in blood plasma, with 32.68% converted after 24 h	[191]
NVs	Pancreatic cancer	A 10.6-fold increase in tumor accumulation, M2-to-M1 macrophage repolarization, and 56% tumor cell apoptosis with low systemic toxicity	The blood half-life of NVs was 17.75 h, and risks elevated liver and spleen accumulation	[154]

Table 3 (continued)

Nanoformulations	Diseases	Advantages	Limitations	Refs.
Sequential delivery (CRE-NP (α-M) + CRP-MC (Tripl))	Pancreatic ductal adenocarcinoma	Median survival was significantly extended to 50 days (vs. 28 days in controls)	The complexity of the delivery system posed challenges for clinical translation and large-scale production	[158]
T10-AHNAK-MBs	Parkinson's disease	T10-AHNAK-MBs enhanced brain drug delivery via ultrasound, reducing neuron loss to 21.4%, restoring dopamine to 414.1 ng/mL, and improving motor function in Parkinson's mice	This microbubble system required focused ultrasound to open the blood-brain barrier	[99]
TP/BIBF-bHDL	Renal fibrosis	TP/BIBF-bHDL markedly improved kidney injury targeting while reducing systemic toxicity, with LD ₅₀ increased from 0.48 to 0.88 mg/kg	Long-term distribution within the body was influenced by hepatic uptake	[157]
TP-FPNPs	Renal ischemia-reperfusion injury	A 3.2-fold higher drug accumulation in the kidneys, a 2.9-fold lower acute tubular injury score, and alleviated off-target toxicity	Relatively low loading capacity (1.11%)	[126]
TP@NPs	Rheumatoid arthritis	Substantially lower toxicity than free TP	Off-target risk persists due to premature drug release (~21% within 36 h)	[125]
FA-TP@VA NPs	Rheumatoid arthritis	FA-TP@VA NPs showed approximately 3 times higher cellular uptake than unmodified nanoparticles	Notable off-target accumulation in the liver and spleen	[146]
PAT	Rheumatoid arthritis	High drug loading (48.6%) and sustained release (29 h half-time), combined with reduced toxicity of free TP	In vitro, the toxicity of PAT converged with that of the free TP over a 72-h exposure period	[147]
TP-LCNPS-GEL	Rheumatoid arthritis	TP-LCNPS-GEL effectively reduced organ toxicities caused by oral administration	Its phase transition occurred at approximately 32°C, near body temperature	[135]
TP/PNPs	Rheumatoid arthritis	TP/PNPs targeted macrophages via cluster of differentiation 44, alleviating arthritis symptoms in rats with reduced systemic toxicity	Drug release was slow in a neutral environment	[153]
TP-LNLC	Rheumatoid arthritis	TP-LNLC significantly alleviated knee joint swelling and lowered inflammatory cytokine levels in rheumatoid arthritis rats	Once-daily dosing for 14 consecutive days to maintain therapeutic efficacy	[134]
GDR-TPT	Rheumatoid arthritis	GDR-TPT effectively targeted and accumulated in inflamed joints	Less than 20% drug was released after 48 h in a pH 7.4 environment	[144]
HTC@ZIF8	Triple-negative breast cancer	HTC@ZIF8 enhanced tumor platinum delivery by twofold and increased normal cell IC ₅₀ by over 1700 times, improving both efficacy and safety	HTC@ZIF8' large hydrated size (~261 nm) hindered deep tumor penetration and uniform distribution	[159]
(TP + A)@TKPEG NPs	Triple-negative breast cancer	(TP + A)@TKPEG achieved light-triggered drug release (90.9%), extending survival to 60 days in 40% of mice, surpassing the fully lethal control	Therapeutic efficacy was highly dependent on external light activation	[132]

TP: Triptolide; GSH: Glutathione

in treating cancers, rheumatoid arthritis, and chronic kidney disease [148, 149].

Active-targeting nanodelivery system for site-specific triptolide accumulation

In tumor therapy, innovative nanocarrier systems have demonstrated remarkable targeting precision and therapeutic potential. Transferrin-modified triptolide liposomes TF-TP@LIP exploited transferrin receptor-mediated endocytosis to enhance drug accumulation in hepatocellular carcinoma tissues, significantly improving antitumor efficacy [141]. Biomimetic TPL@mPLGA nanoparticles, functionalized with Huh-7 cell membranes, achieved homologous tumor targeting, promoting active drug deposition and demonstrating potent anti-hepatocellular carcinoma activity in both in vitro and in vivo models [150]. Additionally, glycyrrhizic acid-based lipid nanoparticles TP/GLLNP not only enhanced triptolide uptake, cytotoxicity, and apoptosis in HepG2 cells but also exhibited superior tumor retention in H22 xenografts, offering a novel strategy for synergistic hepatocellular carcinoma therapy [151].

Similarly, DT/Pep1 system achieved targeted co-delivery of doxorubicin and triptolide to breast cancer through peptide-mediated recognition, and exploited nanoparticle morphology transitions to prolong tumor retention, significantly enhancing intracellular drug accumulation and apoptotic induction, representing an effective and safe therapeutic approach for breast cancer [138]. TPL@TFBF employed fatty acid-mediated cellular uptake to co-deliver triptolide, Fe^{3+} , and tannic acid into tumor cells, where it triggered a cascade of therapeutic effects including Fenton reaction-driven ROS generation, Nrf2 pathway inhibition, dual induction of ferroptosis (via GPX4 inactivation) and pyroptosis (through Caspase-3/GSDME activation), while concurrently activating dendritic cell-mediated antitumor immunity, establishing a novel multimodal immunogenic cell death strategy for melanoma therapy [152].

In the treatment of inflammatory diseases, cluster of differentiation 44 receptor-targeted polymeric nanoparticles TP/PNPs leveraged the “ELVIS” effect and macrophage-selective uptake mechanisms to achieve efficient triptolide delivery to arthritic lesions, while their pH-responsive design facilitated lysosomal escape to further enhance inflammatory site-specific drug accumulation, ultimately providing effective symptomatic relief in rheumatoid arthritis [153].

Co-encapsulated triptolide nanomedicines for combination therapy

Triptolide-based nanocarriers have provided an ideal platform for combination therapy by co-delivering

multiple drugs with complementary mechanisms of action. This strategy has enhanced synergistic effects, reduced drug resistance, and lowered individual drug doses [154]. PTPP was a tumor-targeting nanomedicine co-delivering paclitaxel and triptolide, exhibiting excellent solubility and synergistic therapeutic effects. By modulating NF- κ B pathway, it induced ROS generation and enhanced ferroptosis, overcame chemotherapy resistance effectively, providing a promising approach for treating non-small cell lung cancer [130]. The bio-inspired nanomedicine system (SFN + TPL)@CPLCNPs, which simultaneously delivered sorafenib and triptolide for tumor-targeted therapy, not only inhibited liver tumor growth and promoted apoptosis but also exhibited strong synergistic effects with reduced toxicity, presenting a clinically viable solution for hepatocellular carcinoma treatment [131].

In breast cancer treatment, triptolide-based nanocarriers have exhibited synergistic therapeutic effects through multimodal mechanisms. The red blood cell membrane-coated, R8-modified biomimetic liposomes Cel + TP/RBCm@R8-Lip evaded reticuloendothelial clearance and achieved tumor-specific delivery via R8-mediated endocytosis, where the released triptolide and celastrol simultaneously induced apoptosis, suppressed metastasis/invasion, and disrupted autophagy in breast and liver cancers, offering an efficient combination therapy [155]. Additionally, triptolide-naringin conjugate nanoparticles enabled EGFR-targeted delivery while concurrently inhibiting both EGFR and PI3K/AKT pathways, presenting a novel natural product-based targeted therapy for breast cancer [156].

Triptolide nanocarriers have also delivered effective treatment for non-tumor diseases through synergistic drug combinations. Biomimetic high-density lipoprotein nanoparticles co-encapsulating triptolide and nintedanib actively remodeled fibrotic microenvironments by concurrently suppressing inflammatory cytokines, blocking immune cell infiltration, and preventing myofibroblast activation, achieving significant reduction in renal fibrosis and opening new therapeutic avenues for chronic kidney disease [157].

Exploiting aberrant tumor microenvironment features for smart triptolide nanodelivery

The pathological features of the tumor microenvironment, including hypoxia, acidic pH, elevated GSH levels, and immune suppression, create both therapeutic barriers and opportunities for smart drug delivery system design [148]. Emerging microenvironment-responsive nanosystems have significantly advanced antitumor potential of triptolide [158]. The (TP + A)@TkPEG system, which integrated a photosensitizer, an aggregation-induced

emission material, and autophagy-regulator triptolide within ROS-responsive nanoparticles, amplified ROS and controlled triptolide release in 4T1 cells, concurrently inducing apoptosis and suppressing Beclin-1-mediated autophagy, establishing a novel therapeutic paradigm for triple-negative breast cancer [132].

GSH-sensitive triptolide-loaded nanoparticles have achieved sustained drug delivery through a GSH-triggered mechanism, significantly enhancing tumor-specific drug accumulation and antitumor efficacy [133]. The temperature- and redox-responsive nanocarrier TPL-GNR@MSN-3P enabled precise triptolide release under high intratumoral GSH levels and localized near-infrared-induced heating, effectively counteracting the heat shock response from photothermal therapy to reduce cancer cell thermal tolerance [140]. Similarly, the acid- and GSH-responsive nanoplateform HTC@ZIF8 depleted GSH and inhibited GPX4 activity in the tumor microenvironment, thereby synergizing with cisplatin while releasing triptolide, which further suppressed GSH synthesis via Nrf2 regulation to induce dual apoptosis and ferroptosis in breast cancer cells, offering a promising clinical translation strategy for breast cancer therapy [159].

Additionally, PVGLIG-MTX-D/T-NMs released docetaxel and triptolide in response to high levels of matrix metalloproteinase-2 in the tumor microenvironment, which enhanced tumor cell uptake of the drugs and inhibited tumor angiogenesis and metastasis by regulating the expression of proteins related to epithelial-mesenchymal transition, presenting a new approach for targeted ovarian cancer therapy [160].

Triptolide-loaded nanocarriers with optimized pharmacokinetic profiles

Delivery systems including nanolipid carriers, cubic and hexagonal liquid crystals, and C16-N nanofibers have significantly improved the transdermal penetration and sustained release of triptolide, demonstrating strong potential for treating rheumatoid arthritis and hepatocellular carcinoma [134–137].

Triptolide-loaded nanostructured lipid carriers TPL-NLCs demonstrated excellent drug permeability and sustained-release properties, effectively enhancing transdermal drug absorption while maintaining high local drug concentrations, thereby offering a promising delivery platform for transdermal rheumatoid arthritis therapy [134].

Triptolide-loaded cubic and hexagonal liquid crystals significantly improved transdermal drug delivery by enhancing the 48 h cumulative skin penetration,

achieving higher drug concentrations in the skin than in the bloodstream, thereby markedly increasing bioavailability. These systems exerted anti-inflammatory effects by reducing TNF- α and IL-1 β levels, effectively alleviating foot swelling in arthritic rats and suppressing inflammatory responses, which confirmed the therapeutic potential of triptolide for rheumatoid arthritis treatment [135, 136].

Furthermore, the triptolide-loaded C16-N nanofibers achieved sustained drug release for 14 days, showing remarkable therapeutic effects against hepatocellular carcinoma. After intraperitoneal injection of the C16-N/T hydrogel, the drug preferentially accumulated and persisted in mouse liver tissue for 13 days, significantly suppressing *in situ* tumor growth and extending the median survival time of tumor-bearing mice by twofold, underscoring the potential of triptolide for hepatocellular carcinoma chemotherapy and combination therapies [137].

Future perspectives and translational potential

Considerable studies have explored and confirmed that triptolide exerted pleiotropic pharmacological activities, such as antitumor, anti-inflammatory, and immunomodulatory effects, by regulating multiple types of programmed cell death [161, 162]. However, its clinical application has remained encumbered by challenges, including potential severe hepatotoxicity, nephrotoxicity, cardiotoxicity, and reproductive toxicity [163–165]. Future research should concentrate on increasing organ targeting, alleviating toxicities, identifying precise molecular targets of triptolide, and developing innovative delivery systems based on nanocarriers [139, 159, 166, 167].

Among the various delivery strategies for triptolide, engineered systems that can “sense” pathological cues, “navigate” to target tissues, and “activate” at disease sites while orchestrating multiple mechanisms to address complex disorders have been a focal point of contemporary research [143, 144]. These approaches have demonstrated promising efficacy and favorable biosafety across a range of preclinical models [168]. Such advances are expected to markedly enhance the targeting efficiency of triptolide, minimize systemic toxicity, and improve therapeutic outcomes, thereby offering crucial support for its clinical safety and efficacy [125, 139, 143].

Elucidating the molecular targets of triptolide

The reported direct targets of triptolide majorly include Xeroderma Pigmentosum group B, TGF-beta activated kinase 1 binding protein 1 (TAB1), XIAP, and HSP70, among others [119, 169–173]. Specifically, triptolide have covalently modified the Cys342 residue of Xeroderma

Pigmentum group B [169], subsequently inducing degradation of the RNA polymerase II core subunit Rpb1 [170], thus exerting anticancer and immunosuppressive effects [171]; triptolide has bound to TAB1 and interfering with TAK1-TAB1 complex formation, resulting in inhibition of TAK1 kinase activity and anti-inflammatory effects [172]; triptolide has directly targeted XIAP to modulate the XIAP/COMMD1/ATP7A/B signaling axis, disrupting intracellular copper homeostasis and inducing cuproptosis in cervical cancer cells [119]; and triptolide has inhibited HSP70 activity, affecting cellular stress responses and protein folding processes, supporting anti-tumor and immunomodulatory functions [173].

Beyond the validated targets discussed, a number of potential targets currently remain at the stage of *in silico* prediction or functional correlation, necessitating further validation through affinity techniques. Song et al. [174] combined network pharmacology with molecular docking to predict six potential target proteins (MCL-1, MAPK8, CXCL8, and STAT1) for triptolide in rheumatoid arthritis treatment, providing direction for subsequent mechanism studies. Liang et al. [5] utilized colorectal cancer mice, organoids, cell lines, and clinical samples to ascertain that triptolide inhibited RNA polymerase III transcription by blocking the TBP/TFIIB-related factor 1 interaction, thereby reduced TFIIB formation on tRNA and 5S rRNA promoters, offering a novel mechanism for treating colorectal cancer.

Conducting scientifically rigorous clinical trials

Triptolide has been observed to exert activities and toxicities on the liver, kidneys, and heart, demonstrating a protective organ effect at low doses but inducing organ toxicities at high doses [12]. Hepatotoxicity is the most prevalent and clinically significant risk associated with the use of triptolide preparations, characterized by complex mechanisms and insidious development [14]. In clinical practice, regular monitoring of serum markers, including alanine aminotransferase, aspartate aminotransferase, and total bilirubin, is essential. Based on the observed adverse events and laboratory results, appropriate dose adjustments should be implemented to manage potential toxicity of triptolide and triptolide preparations [175].

Moreover, the tested concentration ranges in bioassay applied in current *in vitro* studies have varied widely, such as from 0.01 to 1 nM [41, 43], which may prevent experimental results from accurately reflecting the true biological effects of triptolide, thereby undermining clinical translational value. Consequently, these limitations have underscored the necessity for further validation of triptolide's efficacy, safety, and pharmacokinetic profile

in humans through rigorously designed clinical trials. To date, this review has collected 13 registered clinical trials involving triptolide (and its formulations and derivatives) via searches of the International Clinical Trials Registry Platform, ClinicalTrials.gov, Chinese Clinical Trial Registry, and the Drug Clinical Trial Registration and Information Disclosure Platform with details summarized in Table 4. Notably, two of these trials have reported key outcomes. A Phase 2 study of (5R)-5-hydroxytriptolide (LLDT-8) with long-term suppressed but immunologically non-responsive HIV/AIDS has indicated that oral administration of LLDT-8 (0.5 mg or 1 mg once daily for 48 weeks) effectively promoted CD4⁺ T-cell recovery and reduced inflammation [176]. Additionally, a Phase 3 trial of a triptolide-containing formulation with autosomal dominant polycystic kidney disease has demonstrated that oral administration (1 mg/kg per day, dynamically adjusted over 6 months) significantly reduced proteinuria from 2645 ± 1408 mg/d to 702 ± 418 mg/d post-treatment [175].

In the future, well-designed, large-scale, multicenter randomized controlled trials are needed to systematically evaluate triptolide's efficacy and safety across different indications, clarify its specific plasma concentrations corresponding to the therapeutic and toxic windows, dose/concentration-effect relationship, and potential adverse reactions from long-term use. Such studies would provide more robust evidence-based medical support for the clinical application of triptolide.

Concluding remarks

Triptolide has been demonstrated to regulate a variety of programmed cell death processes, including apoptosis, autophagy, pyroptosis, ferroptosis, cuproptosis, necroptosis, and PANoptosis, through a complex and precise network of signaling pathways. It has shown considerable potential in the treatment of cancer, immune and inflammatory diseases, and neurodegenerative diseases, but its clinical translation has been severely limited by hepatotoxicity, nephrotoxicity, cardiotoxicity, and reproductive toxicity. To overcome these limitations, advanced nanodelivery systems offer a promising strategy to enhance the targeted delivery and controlled release of triptolide, thereby reducing its toxicity while improving therapeutic efficacy. In the future, clarifying triptolide's precise target mechanisms and conducting internationally compliant clinical trials are anticipated to overcome the clinical application limitations of triptolide and promote it as a highly effective and low-toxicity candidate drug for clinical use. This review provides theoretical references for the clinical translation of triptolide.

Table 4 Clinical progress of triptolide formulations/derivatives

Derivatives/formulations	Indication	Phases	Intervention	Key outcomes	TrialID
(5R)-5-hydroxytriptolide (LLDT-8)	HIV/AIDS	Phase 2 (Completed)	Oral LLDT-8 0.5 mg or 1 mg daily for 48 weeks	LLDT-8 demonstrated potential as a therapeutic option by enhancing CD4 recovery and reducing inflammation in long-term suppressed immunological non-responders	NCT04084444
Glucosidorum Tripterygii Totorum	Autosomal dominant polycystic kidney disease	Post-market (Not Recruiting)	Glucosidorum Tripterygii Totorum + losartan potassium	Unknown	ChiCTR-TRC-11001282
Minnelide Capsules	Advanced solid tumors	Phase 1 (Recruiting)	Minnelide Capsules administered orally once daily for 21 days followed by a 7-day break, with or without combination intravenous protein-bound paclitaxel on days 1, 8, and 15 in pancreas and breast cancer patients, in 28-day cycles	Unknown	NCT03129139
Minnelide	Non-small cell lung cancer	Phase 1b (Recruiting)	Minnelide administered orally once daily on days 1-21 and osimertinib orally once daily on days 1-28. Cycles repeat every 28 days for 6 months	Unknown	NCT05166616
Minnelide	Adenosquamous carcinoma of the pancreas	Phase 2 (Completed)	Minnelide administered orally (2 mg) once daily for 21 days of 28-day cycles for 12 cycles	Unknown	NCT04896073
Tripterygium glycosides	Crohn's disease	Phase 2/Phase 3 (Unknown)	Mesalazine 4 g/day and Tripterygium glycosides 2 mg/kg/day for 12 weeks	Unknown	NCT02044952
Tripterygium wilfordii granules	Psoriasis	N/A (Recruiting)	Tripterygium wilfordii granules	Unknown	ChiCTR2000036398
Triptolide Woldifii	HIV	Phase 1/Phase 2 (Recruiting)	Triptolide 2 tablets three times daily orally (20 mg per dose) for 12 months, in combination with cART	Unknown	NCT01817283
Triptolide Woldifii	HIV /AIDS	Phase 3 (Completed)	Triptolide Wilfordii 20 mg three times daily orally combined with ART for 12 months	Unknown	NCT03403569
Triptolide Woldifii	Polycystic Kidney	N/A (Terminated)	Triptolide Woldifii 60 mg/day	Unknown	NCT00801268
Triptolide Woldifion	HIV /AIDS	Phase 3 (Recruiting)	Triptolide 2 tablets three times daily orally for 12 months after initial 6 months of cART	Unknown	NCT02219672
Triptolide-Containing Formulation	Autosomal dominant polycystic kidney disease	Phase 3 (Recruiting)	Triptolide-Containing Formulation 1 mg/kg/day orally in three divided doses, with dose adjustment based on adverse events monitoring, for a core treatment period of 6 months	After 6 months of Tripterygium therapy, a reduction of proteinuria from 2,645 ± 1,408 mg/d to 702 ± 418 mg/d	NCT02115659

Table 4 (continued)

Derivatives/formulations	Indication	Phases	Intervention	Key outcomes	TrialID
Tripterygium Wilfordii Hook F extract	HIV	N/A (Completed)	Tripterygium Wilfordii Hook F extract 10 mg three times daily orally plus current cART	Unknown	NCT02002286

LLDT-8: (5R)-5-hydroxytriptolide; HIV: Human Immunodeficiency Virus; AIDS: Acquired Immunodeficiency Syndrome; cART: combination Antiretroviral Therapy; ART: Antiretroviral Therapy; N/A: Not Applicable

Abbreviations

ACER1	Alkaline ceramidase 1
AIDS	Acquired immunodeficiency syndrome
AKT	AKT serine/threonine kinase
AML	Acute Myeloid Leukemia
AMPK	AMP-activated protein kinase
ART	Antiretroviral therapy
ATF4	Activating transcription factor 4
ATG5	Autophagy related 5
ATP7A	ATPase copper transporting alpha
BAD	Bcl-2-associated death promoter
BAX	BCL2-associated X protein
BCL-2	B-cell lymphoma 2
CARD9	Caspase recruitment domain-containing protein 9
cART	Combination antiretroviral therapy
CASP10	Caspase-10
CASP8	Caspase-8
CFLAR	Cellular FLICE-like inhibitory protein
CHOP	C/EBP homologous protein
CML	Chronic Myeloid Leukaemia
c-Myc	Cellular myelocytomatosis viral oncogene homolog
COMMD1	Copper metabolism domain containing 1
CX3CR1	C-X3-C motif chemokine receptor 1
CXCL	C-X-C motif chemokine ligand
Drp1	Dynamin-related protein 1
ERK	Extracellular signal-regulated kinase
Fas	Fas cell surface death receptor
FLIP	FLICE-like inhibitory protein
FTH1	Ferritin heavy chain 1
Fyn	FYN proto-oncogene, Src family tyrosine kinase
GPX4	Glutathione peroxidase 4
GRP78	Glucose-regulated protein 78
GSDME	Gasdermin E
GSH	Glutathione
GSK3β	Glycogen synthase kinase-3 beta
HIV	Human Immunodeficiency Virus
HKII	Hexokinase II
HO-1	Heme oxygenase 1
HSP70	Heat shock protein 70
i.g.	Intragastric administration
i.p.	Intraperitoneal injection
IFN-γ	Interferon-gamma
IgA	Immunoglobulin A
IL	Interleukin
NK	C-jun N-terminal kinase
Keap1	Kelch-like ECH-associated protein 1
K63	Lysine 63
LC3	Microtubule-associated protein 1 light chain 3
LLDT-8	(5R)-5-hydroxytriptolide
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
MCL-1	Myeloid cell leukemia 1
MDA	Malondialdehyde
miR-221	MicroRNA-221
MLKL	Mixed lineage kinase domain-like
mTOR	Mechanistic target of rapamycin
N/A	Not applicable
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
NLRP3	NOD-like receptor family, pyrin domain-containing 3
NRF1	Nuclear respiratory factor 1
Nrf2	Nuclear factor erythroid 2-related factor 2
NSCLS	Non-small cell lung cancer
PARP	Poly(ADP-ribose) polymerase
PCD	Programmed cell death
PFKFB2	Phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2
PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PI3K	Phosphatidylinositol 3-kinase
PPIL3	Peptidylprolyl isomerase like 3
PTEN	Phosphatase and Tensin homolog deleted on chromosome 10
PUMA	P53 upregulated modulator of apoptosis

Rab7	RAS-associated protein RAB-7
RIPK	Receptor-interacting protein kinase
ROS	Reactive oxygen species
s.c.	Subcutaneous injection
SIRT1	Sirtuin 1
SLC7A11	Solute carrier family 7 member 11
SRC	Sarcoma proto-oncogene, non-receptor tyrosine kinase
STAT	Signal transducer and activator of transcription3
TAB1	TGF-beta activated kinase 1 binding protein 1
TBK1	TANK-binding kinase 1
TF	Transferrin
TFR1	Transferrin receptor 1
TNF-α	Tumor necrosis factor-alpha
TP	Triptolide
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand
Wnt	Wingless/integrated
XIAP	X-linked inhibitor of apoptosis protein

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Data availability

No datasets were generated or analysed during the current study.

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Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

- Liu Q. Triptolide and its expanding multiple pharmacological functions. *Int Immunopharmacol*. 2011;11(3):377–83. <https://doi.org/10.1016/j.intimp.2011.01.012>.
- Wang Y, Dai Z, Yan J, Wu X, Ma S. Comprehensive evaluation of the quality of Tripterygium Glycosides Tablets based on multi-component quantification combined with an in vitro biological assay. *Molecules*. 2022;27(16):5102.
- Huang Q, Tan C, Zheng C, Meng H, Wang Z, et al. DCTPP1, a reliable Q-biomarker for comprehensive evaluation of the quality of tripterygium glycoside tablets based on chemical references. *Phytomedicine*. 2023;119:154972. <https://doi.org/10.1016/j.phymed.2023.154972>.

4. Yu D, Liu Y, Zhou Y, Ruiz-Rodado V, Larion M, et al. Triptolide suppresses IDH1-mutated malignancy via Nrf2-driven glutathione metabolism. *Proc Natl Acad Sci USA*. 2020;117(18):9964–72.
5. Liang X, Xie R, Su J, Ye B, Wei S, et al. Inhibition of RNA polymerase III transcription by Triptolide attenuates colorectal tumorigenesis. *J Exp Clin Cancer Res*. 2019;38(1):217.
6. Burki S, Noda K, Philips B, Sanchez PG, Kumar A, et al. Triptolide attenuates graft inflammation during ex vivo lung perfusion. *J Heart Lung Transpl*. 2019;38(4):S15.
7. Tang B, Zhu J, Zhang B, Wu F, Wang Y, et al. Therapeutic potential of Triptolide as an anti-inflammatory agent in Dextran Sulfate Sodium-induced murine experimental colitis. *Front Immunol*. 2020;11:592084.
8. He H, Takahashi A, Yamamoto Y, Hori A, Miharuru Y, et al. The immunomodulatory effect of triptolide on mesenchymal stem cells in vitro. *Blood*. 2019;134:5011–5011.
9. Gao J, Zhang Y, Liu X, Wu X, Huang L, et al. Triptolide: pharmacological spectrum, biosynthesis, chemical synthesis and derivatives. *Theranostics*. 2021;11(15):7199–221.
10. Corson TW, Crews CM. Molecular understanding and modern application of traditional medicines: triumphs and trials. *Cell*. 2007;130(5):769–74.
11. Xu L, Qiu Y, Xu H, Ao W, Lam W, et al. Acute and subacute toxicity studies on Triptolide and Triptolide-loaded polymeric micelles following intravenous administration in rodents. *Food Chem Toxicol*. 2013;57:371–9. <https://doi.org/10.1016/j.fct.2013.03.044>.
12. Jiang S, Wan F, Lian H, Lu Z, Li X, et al. Friend or foe? The dual role of Triptolide in the liver, kidney, and heart. *Biomed Pharmacother*. 2023;161:114470. <https://doi.org/10.1016/j.biopha.2023.114470>.
13. AbdulHussein AH, Al-Taei MM, Radih ZA, Aljuboory DS, Mohammed ZQ, et al. Mechanisms of cancer cell death induction by triptolide. *BioFactors*. 2023;49(4):718–35. <https://doi.org/10.1002/biof.1944>.
14. Cui D, Xu D, Yue S, Yan C, Liu W, et al. Recent advances in the pharmacological applications and liver toxicity of triptolide. *Chem Biol Interact*. 2023;382:110651. <https://doi.org/10.1016/j.cbi.2023.110651>.
15. Xi C, Peng S, Wu Z, Zhou Q, Zhou J. Toxicity of triptolide and the molecular mechanisms involved. *Biomed Pharmacother*. 2017;90:531–41. <https://doi.org/10.1016/j.biopha.2017.04.003>.
16. Yuan Z, Yuan Z, Hasnat M, Zhang H, Liang P, et al. A new perspective of triptolide-associated hepatotoxicity: the relevance of NF- κ B and NF- κ B-mediated cellular FLICE-inhibitory protein. *Acta Pharm Sin B*. 2020;10(5):861–77. <https://doi.org/10.1016/j.apsb.2020.02.009>.
17. He R, Liu Y, Fu W, He X, Liu S, et al. Mechanisms and cross-talk of regulated cell death and their epigenetic modifications in tumor progression. *Mol Cancer*. 2024;23(1):267.
18. Park SW, Kim YI. Triptolide induces apoptosis of PMA-treated THP-1 cells through activation of caspases, inhibition of NF- κ B and activation of MAPKs. *Int J Oncol*. 2013;43(4):1169–75.
19. Li R, Zhang Z, Wang J, Huang Y, Sun W, et al. Triptolide suppresses growth and hormone secretion in murine pituitary corticotroph tumor cells via NF- κ B signaling pathway. *Biomed Pharmacother*. 2017;95:771–9. <https://doi.org/10.1016/j.biopha.2017.08.127>.
20. Kim JH, Park B. Triptolide blocks the STAT3 signaling pathway through induction of protein tyrosine phosphatase SHP-1 in multiple myeloma cells. *Int J Mol Med*. 2017;40(5):1566–72.
21. Li N, Chen Z, Feng W, Gong Z, Lin C, et al. Triptolide improves chondrocyte proliferation and secretion via down-regulation of miR-221 in synovial cell exosomes. *Phytomedicine*. 2022;107:154479. <https://doi.org/10.1016/j.phymed.2022.154479>.
22. Cheng R, Jiang Y, Zhang Y, Ismail M, Zhang L, et al. Proteasome activity inhibition mediates endoplasmic reticulum stress-apoptosis in triptolide/lipopolysaccharide-induced hepatotoxicity. *Cell Biol Toxicol*. 2024;40(1):60.
23. Lv L, Chang Y, Li Y, Chen H, Yao J, et al. Triptolide induces Leydig cell apoptosis by disrupting mitochondrial dynamics in rats. *Front Pharmacol*. 2021;12:616803.
24. Pan J, Shen F, Tian K, Wang M, Xi Y, et al. Triptolide induces oxidative damage in NRK-52E cells through facilitating Nrf2 degradation by ubiquitination via the GSK-3 β /Fyn pathway. *Toxicol In Vitro*. 2019;58:187–94. <https://doi.org/10.1016/j.tiv.2019.03.032>.
25. Carter BZ, Mak DH, Schober WD, Dietrich M, Pinilla C, et al. Triptolide sensitizes leukemic cells to TRAIL induced apoptosis via decrease of XIAP and p53-mediated increase of DR5. *Blood*. 2006;108(11):528–528.
26. Zhang W, Kang M, Zhang T, Li B, Liao X, et al. Triptolide combined with radiotherapy for the treatment of nasopharyngeal carcinoma via NF- κ B-related mechanism. *Int J Mol Sci*. 2016;17(12):2139.
27. Jiang C, Fang X, Zhang H, Wang X, Li MJ, et al. AMD3100 combined with triptolide inhibit proliferation, invasion and metastasis and induce apoptosis of human U2OS osteosarcoma cells. *Biomed Pharmacother*. 2017;86:677–85. <https://doi.org/10.1016/j.biopha.2016.12.055>.
28. Zhu W, Hu H, Qiu P, Yan G. Triptolide induces apoptosis in human anaplastic thyroid carcinoma cells by a p53-independent but NF- κ B-related mechanism. *Oncol Rep*. 2009;22(6):1397–401.
29. Wang F, An SJ, Yin Y, Li JJ, Sun CH, et al. Triptolide is a promising therapeutic approach in treating thyroid cancer based on in silico and in vitro experiment. *Drug Des Devel Ther*. 2021;15:4275–87.
30. Yanchun M, Yi W, Lu W, Yu Q, Jian Y, et al. Triptolide prevents proliferation and migration of esophageal squamous cell cancer via MAPK/ERK signaling pathway. *Eur J Pharmacol*. 2019;851:43–51. <https://doi.org/10.1016/j.ejphar.2019.02.030>.
31. Liu K, Liu J, Meng T, Wu N, Liu J, et al. Triptolide reverses cis-diamminedichloroplatinum resistance in esophageal squamous cell carcinoma by suppressing glycolysis and causing mitochondrial malfunction. *Mol Med Rep*. 2025;31(3):74.
32. Ho JN, Byun SS, Lee S, Oh JJ, Hong SK, et al. Synergistic antitumor effect of triptolide and cisplatin in cisplatin resistant human bladder cancer cells. *J Urol*. 2015;193(3):1016–22.
33. Yang Y, Zhang LJ, Bai XG, Xu HJ, Jin ZL, et al. Synergistic antitumor effects of triptolide plus gemcitabine in bladder cancer. *Biomed Pharmacother*. 2018;106:1307–16. <https://doi.org/10.1016/j.biopha.2018.07.083>.
34. Chen P, Zhong X, Song Y, Zhong W, Wang S, et al. Triptolide induces apoptosis and cytoprotective autophagy by ROS accumulation via directly targeting peroxiredoxin 2 in gastric cancer cells. *Cancer Lett*. 2024;587:216622. <https://doi.org/10.1016/j.canlet.2024.216622>.
35. Li CJ, Chu CY, Huang LH, Wang MH, Sheu LF, et al. Synergistic anticancer activity of triptolide combined with cisplatin enhances apoptosis in gastric cancer in vitro and in vivo. *Cancer Lett*. 2012;319(2):203–13. <https://doi.org/10.1016/j.canlet.2012.01.006>.
36. Shi YF, Liu L, He LL, Ye J, Lin ZJ, et al. Combining triptolide with ABT-199 is effective against acute myeloid leukemia through reciprocal regulation of Bcl-2 family proteins and activation of the intrinsic apoptotic pathway. *Cell Death Dis*. 2020;11(7):555.
37. Shi X, Jin Y, Cheng C, Zhang H, Zou W, et al. Triptolide inhibits Bcr-Abl transcription and induces apoptosis in ST1571-resistant chronic myelogenous leukemia cells harboring T315I mutation. *Clin Cancer Res*. 2009;15(5):1686–97.
38. Wan CK, Wang C, Cheung HY, Yang M, Fong WF. Triptolide induces Bcl-2 cleavage and mitochondria dependent apoptosis in p53-deficient HL-60 cells. *Cancer Lett*. 2006;241(1):31–41. <https://doi.org/10.1016/j.canlet.2005.10.001>.
39. Chauhan L, Fridley B, Tanya F, Ghosh TM, Bhise N, et al. Cflar genetic variant resulting in alternate splicing determines isoform specific production of H-Cflar protein and is predictive of cellular Cytotoxicity of triptolide in Hapmap lymphoblast and AML cell lines. *Blood*. 2013;122(21):1287–1287.
40. Ren J, Zhao S, Lai J. Triptolide restrains the growth, invasion, stemness, and glycolysis of non-small cell lung cancer cells by PFKFB2-mediated PI3K/AKT pathway. *Chem Biol Drug Des*. 2024;103(1):e14450. <https://doi.org/10.1111/cbdd.14450>.
41. Huang Y, Chen Z, Wang Y, Ba X, Huang Y, et al. Triptolide exerts an anti-tumor effect on non-small cell lung cancer cells by inhibiting activation of the IL-6/STAT3 axis. *Int J Mol Med*. 2019;44(1):291–300.
42. Nardi I, Reno T, Yun X, Sztain T, Wang J, et al. Triptolide inhibits Wnt signaling in NSCLC through upregulation of multiple Wnt inhibitory factors via epigenetic modifications to histone H3. *Int J Cancer*. 2018;143(10):2470–8. <https://doi.org/10.1002/ijc.31756>.
43. Hamdi AM, Jiang Z-Z, Guerram M, Yousef BA, Hassan HM, et al. Biochemical and computational evaluation of triptolide-induced cytotoxicity against NSCLC. *Biomed Pharmacother*. 2018;103:1557–66. <https://doi.org/10.1016/j.biopha.2018.04.198>.

44. Ren T, Tang YJ, Wang MF, Wang HS, Liu Y, et al. Triptolide induces apoptosis through the calcium/calmodulin-dependent protein kinase kinase β /AMP-activated protein kinase signaling pathway in non-small cell lung cancer cells. *Oncol Rep*. 2020;44(5):2288–96.
45. Wang G, Wang X, Xu X. Triptolide potentiates lung cancer cells to cisplatin-induced apoptosis by selectively inhibiting the NER activity. *Biomarker Res*. 2015;3(1):17.
46. Cheng X, Shi W, Zhao C, Zhang D, Liang P, et al. Triptolide sensitizes human breast cancer cells to tumor necrosis factor- α -induced apoptosis by inhibiting activation of the nuclear factor- κ B pathway. *Mol Med Rep*. 2016;13(4):3257–64.
47. Li X, Shan Y, Wang S, Wang J, Heng X. Triptolide induces apoptosis of glioma cells by inhibiting NF- κ B activation during oxidative stress. *Sci Rep*. 2024;14(1):29740.
48. Kong J, Wang L, Ren L, Yan Y, Cheng Y, et al. Triptolide induces mitochondria-mediated apoptosis of Burkitt's lymphoma cell via deacetylation of GSK-3 β by increased SIRT3 expression. *Toxicol Appl Pharmacol*. 2018;342:1–13. <https://doi.org/10.1016/j.taap.2018.01.011>.
49. Zhao F, Chen Y, Zeng L, Li R, Zeng R, et al. Role of triptolide in cell proliferation, cell cycle arrest, apoptosis and histone methylation in multiple myeloma U266 cells. *Eur J Pharmacol*. 2010;646(1):1–11. <https://doi.org/10.1016/j.ejphar.2010.05.034>.
50. Kim MJ, Lee TH, Kim SH, Choi Y-J, Heo J, et al. Triptolide inactivates Akt and induces caspase-dependent death in cervical cancer cells via the mitochondrial pathway. *Int J Oncol*. 2010;37(5):1177–85.
51. Ben Yebdri F, Van Grevenynghe J, Tang VA, Goulet M-L, Wu JH, et al. Triptolide-mediated inhibition of interferon signaling enhances Vesicular Stomatitis Virus-based oncolysis. *Mol Ther*. 2013;21(11):2043–53. <https://doi.org/10.1038/mt.2013.187>.
52. Brincks EL, Kucaba TA, James BR, Murphy KA, Schwertfeger KL, et al. Triptolide enhances the tumoricidal activity of TRAIL against renal cell carcinoma. *FEBS J*. 2015;282(24):4747–65. <https://doi.org/10.1111/febs.13532>.
53. Li Y, Tian Y, Zhu W, Gong J, Zhang W, et al. Triptolide induces suppressor of cytokine signaling-3 expression and promotes lamina propria mononuclear cells apoptosis in Crohn's colitis. *Int Immunopharmacol*. 2013;16(2):268–74. <https://doi.org/10.1016/j.intimp.2013.04.018>.
54. Zhang C, Weng Y, Wang H, Zhan S, Li C, et al. A synergistic effect of triptolide and curcumin on rheumatoid arthritis by improving cell proliferation and inducing cell apoptosis via inhibition of the IL-17/NF- κ B signaling pathway. *Int Immunopharmacol*. 2024;142:112953. <https://doi.org/10.1016/j.intimp.2024.112953>.
55. Hao M, Li X, Feng J, Pan N. Triptolide protects against ischemic stroke in rats. *Inflammation*. 2015;38(4):1617–23.
56. Wan YS, You Y, Ding QY, Xu YX, Chen H, et al. Triptolide protects against white matter injury induced by chronic cerebral hypoperfusion in mice. *Acta Pharmacol Sin*. 2022;43(1):15–25.
57. Zhou J, Ye W, Chen L, Li J, Zhou Y, et al. Triptolide alleviates cerebral ischemia/reperfusion injury via regulating the Fractalkine/CX3CR1 signaling pathway. *Brain Res Bull*. 2024;211:110939. <https://doi.org/10.1016/j.brainresbull.2024.110939>.
58. Zhang B, Song C, Feng B, Fan W. Neuroprotection by triptolide against cerebral ischemia/reperfusion injury through the inhibition of NF- κ B/PUMA signal in rats. *Ther Clin Risk Manag*. 2016;12:817–24.
59. Yang B, Yan P, Yang GZ, Cao HL, Wang F, et al. Triptolide reduces ischemia/reperfusion injury in rats and H9C2 cells via inhibition of NF- κ B, ROS and the ERK1/2 pathway. *Int J Mol Med*. 2018;41(6):3127–36.
60. Yan W, Youming P, Chan L, Muyao Y, Xian C, et al. Efficacy of triptolide on the apoptosis of tonsillar mononuclear cells from patients with IgA nephropathy. *Ren Fail*. 2016;38(1):109–16.
61. Wang L, Zhang L, Hou Q, Zhu X, Chen Z, et al. Triptolide attenuates proteinuria and podocyte apoptosis via inhibition of NF- κ B/GADD45B. *Sci Rep*. 2018;8(1):10843.
62. Li Y, Jiang X, Song L, Yang M, Pan J. Anti-apoptosis mechanism of triptolide based on network pharmacology in focal segmental glomerulosclerosis rats. *Biosci Rep*. 2020;40(9):BSR-20192920.
63. Zhang T, Gong X, Hu G, Wang X. EP2-PKA signaling is suppressed by triptolide in lipopolysaccharide-induced microglia activation. *J Neuroinflammation*. 2015;12(1):50.
64. Xu P, Wang H, Li Z, Yang Z. Triptolide attenuated injury via inhibiting oxidative stress in Amyloid-Beta25–35-treated differentiated PC12 cells. *Life Sci*. 2016;145:19–26. <https://doi.org/10.1016/j.lfs.2015.12.018>.
65. Yao P, Li Y, Yang Y, Yu S, Chen Y. Triptolide improves cognitive dysfunction in rats with vascular dementia by activating the SIRT1/PGC-1 α signaling pathway. *Neurochem Res*. 2019;44(8):1977–85.
66. Zhao D, Li S, Liao T, Wei Y, Liu M, et al. Triptolide inhibits donor-specific antibody production and attenuates mixed antibody-mediated renal allograft injury. *Am J Transplant*. 2018;18(5):1083–95. <https://doi.org/10.1111/ajt.14602>.
67. Luo Z, Liao T, Zhang Y, Zheng H, Sun Q, et al. Triptolide attenuates transplant vasculopathy through multiple pathways. *Front Immunol*. 2020;11:612.
68. Zhang X, Peng Z, Zheng H, Zhang C, Lin H, et al. The potential protective effect and possible mechanism of peptides from oyster (*Crassostrea hongkongensis*) hydrolysate on Triptolide-induced testis injury in male mice. *Mar Drugs*. 2021;19(10):566.
69. Zhao J, Cao M, Yi H, He G, Chen T, et al. Triptolide causes spermatogenic disorders by inducing apoptosis in the mitochondrial pathway of mouse testicular spermatocytes. *Toxics*. 2024;12(12):896.
70. Qin Z, Song J, Huang J, Jiang S, Zhang G, et al. Mitigation of Triptolide-induced testicular Sertoli cell damage by melatonin via regulating the crosstalk between SIRT1 and NRF2. *Phytomedicine*. 2023;118:154945. <https://doi.org/10.1016/j.phymed.2023.154945>.
71. Li Q, Huang J, Zhao Q, Li F. FXR as a pivotal role linking JNK and G0s2 mitigates Triptolide-induced hepatotoxicity through the regulation of metabolic disorder of liver. *Pharmacol Res*. 2025;216:107738. <https://doi.org/10.1016/j.phrs.2025.107738>.
72. Zhou Y, Xia L, Yao W, Han J, Wang G. Arctiin antagonizes Triptolide-induced hepatotoxicity via activation of Nrf2 pathway. *Biomed Res Int*. 2020;2020(1):2508952. <https://doi.org/10.1155/2020/2508952>.
73. Fan X, Zhu Y, Peng S, Miao Y, Lu Q, et al. TP induces hepatic intolerance to FasL-mediated hepatocyte apoptosis by inhibiting XIAP. *Toxicol Lett*. 2023;390:25–32. <https://doi.org/10.1016/j.toxlet.2023.11.001>.
74. You L, Dong X, Ni B, Fu J, Yang C, et al. Triptolide induces apoptosis through Fas death and mitochondrial pathways in HepaRG cell line. *Front Pharmacol*. 2018;9:813.
75. Yang F, Ren L, Zhuo L, Ananda S, Liu L. Involvement of oxidative stress in the mechanism of triptolide-induced acute nephrotoxicity in rats. *Exp Toxicol Pathol*. 2012;64(7):905–11. <https://doi.org/10.1016/j.etp.2011.03.013>.
76. Wang XW, Tian RM, Yang YQ, Lu ZY, Han XD, et al. Triptolide antagonizes triptolide-induced nephrocyte apoptosis via inhibiting oxidative stress in vitro and in vivo. *Biomed Pharmacother*. 2019;118:109232. <https://doi.org/10.1016/j.biopha.2019.109232>.
77. Xi Y, Wang W, Wang L, Pan J, Cheng Y, et al. Triptolide induces p53-dependent cardiotoxicity through mitochondrial membrane permeabilization in cardiomyocytes. *Toxicol Appl Pharmacol*. 2018;355:269–85. <https://doi.org/10.1016/j.taap.2018.07.011>.
78. Qi XM, Qiao YB, Zhang YL, Wang AC, Ren JH, et al. PGC-1 α /NRF1-dependent cardiac mitochondrial biogenesis: a druggable pathway of calyculin against triptolide cardiotoxicity. *Food Chem Toxicol*. 2023;171:113513. <https://doi.org/10.1016/j.fct.2022.113513>.
79. Qi XM, Zhang WZ, Zuo YQ, Qiao YB, Zhang YL, et al. Nrf2/NRF1 signaling activation and crosstalk amplify mitochondrial biogenesis in the treatment of triptolide-induced cardiotoxicity using calyculin. *Cell Biol Toxicol*. 2024;41(1):2.
80. Wei YM, Wang YH, Xue HQ, Luan ZH, Liu BW, et al. Triptolide, A potential autophagy modulator. *Chin J Integr Med*. 2019;25(3):233–40.
81. Li M, Li J, Tang Q, Zhu Y. Potential antitumor activity of triptolide and its derivatives: focused on gynecological and breast cancers. *Biomed Pharmacother*. 2024;180:117581. <https://doi.org/10.1016/j.biopha.2024.117581>.
82. Mujumdar N, Mackenzie TN, Dudeja V, Chugh R, Antonoff MB, et al. Triptolide induces cell death in pancreatic cancer cells by apoptotic and autophagic pathways. *Gastroenterology*. 2010;139(2):598–608.
83. Liu X, Zhao P, Wang X, Wang L, Zhu Y, et al. Triptolide induces glioma cell autophagy and apoptosis via upregulating the ROS/JNK and down-regulating the Akt/mTOR signaling pathways. *Front Oncol*. 2019;9:387.

84. Zhu N, Ruan J, Yang X, Huang Y, Jiang Y, et al. Triptolide improves spinal cord injury by promoting autophagy and inhibiting apoptosis. *Cell Biol Int*. 2020;44(3):785–94. <https://doi.org/10.1002/cbin.11273>.
85. Zhao L, Lan Z, Peng L, Wan L, Liu D, et al. Triptolide promotes autophagy to inhibit mesangial cell proliferation in IgA nephropathy via the CARD9/p38 MAPK pathway. *Cell Prolif*. 2022;55(9):e13278. <https://doi.org/10.1111/cpr.13278>.
86. Li XY, Wang SS, Han Z, Han F, Chang YP, et al. Triptolide restores autophagy to alleviate diabetic renal fibrosis through the miR-141-3p/PTEN/Akt/mTOR pathway. *Mol Ther Nucleic Acids*. 2017;9:48–56. <https://doi.org/10.1016/j.omtn.2017.08.011>.
87. Xin Z, Xu R, Dong Y, Jin S, Ge X, et al. Impaired autophagy-mediated macrophage polarization contributes to age-related hyposalivation. *Cell Prolif*. 2024;57(12):e13714. <https://doi.org/10.1111/cpr.13714>.
88. Hu G, Gong X, Wang L, Liu M, Liu Y, et al. Triptolide promotes the clearance of α -Synuclein by enhancing autophagy in neuronal cells. *Mol Neurobiol*. 2017;54(3):2361–72.
89. Dai J, Sun Y, Chen D, Zhang Y, Yan L, et al. Negative regulation of PI3K/AKT/mTOR axis regulates fibroblast proliferation, apoptosis and autophagy play a vital role in triptolide-induced epidural fibrosis reduction. *Eur J Pharmacol*. 2019;864:172724. <https://doi.org/10.1016/j.ejphar.2019.172724>.
90. Hasnat M, Yuan Z, Naveed M, Khan A, Raza F, et al. Drp1-associated mitochondrial dysfunction and mitochondrial autophagy: a novel mechanism in triptolide-induced hepatotoxicity. *Cell Biol Toxicol*. 2019;35(3):267–80.
91. Lu X, Huang Q, He Z, Zhou H, Chen Z, et al. TBK1 alleviates triptolide-induced nephrotoxic injury by up-regulating mitophagy in HK2 cells. *Biol Chem*. 2025;406(8–9):391–406.
92. Chan SF, Chen YY, Lin JJ, Liao CL, Ko YC, et al. Triptolide induced cell death through apoptosis and autophagy in murine leukemia WEHI-3 cells in vitro and promoting immune responses in WEHI-3 generated leukemia mice in vivo. *Environ Toxicol*. 2017;32(2):550–68. <https://doi.org/10.1002/tox.22259>.
93. Dai H, Jiang Y, Luo Y, Bie P, Chen Z. Triptolide enhances TRAIL sensitivity of pancreatic cancer cells by activating autophagy via downregulation of PUM1. *Phytomedicine*. 2019;62:152953. <https://doi.org/10.1016/j.phymed.2019.152953>.
94. Varghese E, Samuel SM, Varghese S, Cheema S, Mamtani R, et al. Triptolide decreases cell proliferation and induces cell death in triple negative MDA-MB-231 breast cancer cells. *Biomolecules*. 2018;8(4):163.
95. Huang L, Xue R, Zhu M, Xu S, Luo Y, et al. Triptolide's impact on ACER1 signaling: inducing autophagy for triple-negative breast cancer suppression. *Pathol Res Pract*. 2025;266:155823. <https://doi.org/10.1016/j.prp.2025.155823>.
96. Qin G, Li P, Xue Z. Triptolide induces protective autophagy and apoptosis in human cervical cancer cells by downregulating Akt/mTOR activation. *Oncol Lett*. 2018;16(3):3929–34. <https://doi.org/10.3892/ol.2018.9074>.
97. Zheng Z, Yan G, Xi N, Xu X, Zeng Q, et al. Triptolide induces apoptosis and autophagy in cutaneous squamous cell carcinoma via Akt/mTOR pathway. *Anticancer Agents Med Chem*. 2023;23(13):1596–604.
98. Li XY, Wang SS, Han Z, Han F, Chang YP, et al. Triptolide restores autophagy to alleviate diabetic renal fibrosis through the miR-141-3p/PTEN/Akt/mTOR pathway. *Mol Ther-Nucl Acids*. 2017;9:48–56.
99. Feng Y, An R, Zhang Y, Chen M, Wang L, et al. AHNK-modified microbubbles for the intracranial delivery of triptolide: in-vitro and in-vivo investigations. *Int J Pharm*. 2022;629:122351. <https://doi.org/10.1016/j.ijpharm.2022.122351>.
100. Li C, Zhang C, Zhu C, Zhang J, Xia Q, et al. Inflammation aggravated the hepatotoxicity of triptolide by oxidative stress, lipid metabolism disorder, autophagy, and apoptosis in zebrafish. *Front Pharmacol*. 2022;13:949312.
101. Huo J, Yu Q, Zhang Y, Liu K, Hsiao CD, Jiang Z, et al. Triptolide-induced hepatotoxicity via apoptosis and autophagy in zebrafish. *J Appl Toxicol*. 2019;39(11):1532–40. <https://doi.org/10.1002/jat.3837>.
102. Yu P, Zhang X, Liu N, Tang L, Peng C, et al. Pyroptosis: mechanisms and diseases. *Signal Transduct Target Ther*. 2021;6(1):128.
103. Cai J, Yi M, Tan Y, Li X, Li G, et al. Natural product triptolide induces GSDME-mediated pyroptosis in head and neck cancer through suppressing mitochondrial hexokinase-II. *J Exp Clin Cancer Res*. 2021;40(1):190.
104. Lv C, Cheng T, Zhang B, Sun K, Lu K. Triptolide protects against podocyte injury in diabetic nephropathy by activating the Nrf2/HO-1 pathway and inhibiting the NLRP3 inflammasome pathway. *Ren Fail*. 2023;45(1):2165103.
105. Han C, Pei H, Sheng Y, Wang J, Zhou X, et al. Toxicological mechanism of triptolide-induced liver injury: Caspase3-GSDME-mediated pyroptosis of Kupffer cell. *Ecotoxicol Environ Saf*. 2023;258:114963. <https://doi.org/10.1016/j.ecoenv.2023.114963>.
106. Yan HF, Zou T, Tuo QZ, Xu S, Li H, et al. Ferroptosis: Mechanisms and links with diseases. *Signal Transduct Target Ther*. 2021;6(1):49.
107. Wang W, Zhao X, Zhou J, Li H. A novel antitumor mechanism of Triptolide in colorectal cancer: Inducing ferroptosis via the SLC7A11/GPX4 axis. *Funct Integr Genomic*. 2024;24(4):126.
108. Wu H, Cao P, Wang H, Wang W, Yu H, et al. Postoperative injection of a Triptolide-preloaded hydrogel prevents the recurrence of glioblastoma by dual-pathway activation of ferroptosis. *Small*. 2024;20(50):2406036. <https://doi.org/10.1002/sml.202406036>.
109. Feng M, Wu H, Zhu L, Gao J, Deng G. Triptolide promotes ferroptosis in cervical cancer cell via NRF2/xCT/GPX4. *Phytother Res*. 2025;39(2):875–87. <https://doi.org/10.1002/ptr.8398>.
110. Wu X, Chen S, Huang K, Lin G. Triptolide promotes ferroptosis by suppressing Nrf2 to overcome leukemia cell resistance to doxorubicin. *Mol Med Rep*. 2023;27(1):17.
111. Zhou J, Li S, Yang Y, Zhou C, Wang C, et al. Triptolide alleviates acute lung injury by reducing mitochondrial dysfunction mediated ferroptosis through the STAT3/p53 pathway. *Free Radic Biol Med*. 2025;230:79–94. <https://doi.org/10.1016/j.freeradbiomed.2025.02.001>.
112. Wang HQ, Wu HX, Shi WQ, Yang Y, Lin M, et al. Triptolide attenuates renal slit diagram to tight junction transition in diabetic kidney disease by regulating Nrf2–ferroptosis pathway. *Am J Chinese Med*. 2024;52(07):2161–85.
113. Li J, Chen D, Suo J, Li J, Zhang Y, et al. Triptolide induced spermatogenesis dysfunction via ferroptosis activation by promoting K63-linked GPX4 polyubiquitination in spermatocytes. *Chem Biol Interact*. 2024;399:111130. <https://doi.org/10.1016/j.cbi.2024.111130>.
114. Guo L, Yang Y, Ma J, Xiao M, Cao R, et al. Triptolide induces hepatotoxicity by promoting ferroptosis through Nrf2 degradation. *Cell Biol Toxicol*. 2024;40(1):94.
115. Liu X, Chen C, Han D, Zhou W, Cui Y, et al. SLC7A11/GPX4 inactivation-mediated ferroptosis contributes to the pathogenesis of Triptolide-induced cardiotoxicity. *Oxid Med Cell Longev*. 2022;2022(1):3192607. <https://doi.org/10.1155/2022/3192607>.
116. Liu W, Wu G, Wang J, Wu S, Chen Z. Co-treatment with triptolide and RSL3 induces hepatocellular carcinoma cell apoptosis and ferroptosis. *Mol Med Rep*. 2025;32(1):202.
117. Liu S, Su Y, Han B, Yin L, Li H, et al. Activation of Rab7-mediated lipophagy is required for triptolide to induce ferroptosis in hepatic cells. *Food Chem Toxicol*. 2025;203:115568. <https://doi.org/10.1016/j.fct.2025.115568>.
118. Chen L, Min J, Wang F. Copper homeostasis and cuproptosis in health and disease. *Signal Transduct Target Ther*. 2022;7(1):378.
119. Xiao Y, Yin J, Liu P, Zhang X, Lin Y, et al. Triptolide-induced cuproptosis is a novel antitumor strategy for the treatment of cervical cancer. *Cell Mol Biol Lett*. 2024;29(1):113.
120. Weinlich R, Oberst A, Beere HM, Green DR. Necroptosis in development, inflammation and disease. *Nat Rev Mol Cell Biol*. 2017;18(2):127–36.
121. Schwabe RF, Luedde T. Apoptosis and necroptosis in the liver: a matter of life and death. *Nat Rev Gastroenterol Hepatol*. 2018;15(12):738–52.
122. Zhang X, Tang B, Luo J, Yang Y, Weng Q, et al. Cuproptosis, ferroptosis and PANoptosis in tumor immune microenvironment remodeling and immunotherapy: culprits or new hope. *Mol Cancer*. 2024;23(1):255.
123. Zhang HR, Li YP, Shi ZJ, Liang QQ, Chen SY, et al. Triptolide induces PANoptosis in macrophages and causes organ injury in mice. *Apoptosis*. 2023;28(11):1646–65.
124. Chang J, Wang W, Zhao F, Sun X, Guo S, et al. Photodynamic-therapy and chemotherapy of TPBC-PEG nanoplateform encapsulated triptolide synergistically inhibit primary osteosarcoma growth and pulmonary metastasis by activating HIPPO signaling. *Mater Des*. 2024;248:113482. <https://doi.org/10.1016/j.matdes.2024.113482>.

125. Liu Y, Jin J, Xu H, Wang C, Yang Y, et al. Construction of a pH-responsive, ultralow-dose triptolide nanomedicine for safe rheumatoid arthritis therapy. *Acta Biomater.* 2021;121:541–53. <https://doi.org/10.1016/j.actbio.2020.11.027>.
126. Huang C, Zeng T, Li J, Tan L, Deng X, et al. Folate Receptor-Mediated Renal-Targeting Nanoplatfor for the Specific Delivery of Triptolide to Treat Renal Ischemia/Reperfusion Injury. *ACS Biomater Sci Eng.* 2019;5(6):2877–86.
127. Zheng W, Wang C, Ding R, Huang Y, Li Y, et al. Triptolide-loaded nanoparticles targeting breast cancer in vivo with reduced toxicity. *Int J Pharm.* 2019;572:118721. <https://doi.org/10.1016/j.jipharm.2019.118721>.
128. Ling D, Xia H, Park W, Hackett MJ, Song C, et al. pH-sensitive nanoformulated triptolide as a targeted therapeutic strategy for hepatocellular carcinoma. *ACS Nano.* 2014;8(8):8027–39.
129. Ge Y, Zhu X, Zhang Z, Zhu H, Wang T, et al. RGD peptide/dextran sulfate-based nanocarriers loaded with triptolide for double-targeted apoptosis of both tumor cells and M2-like TAMs in pancreatic cancer therapy. *Int J Biol Macromol.* 2025;311:144032. <https://doi.org/10.1016/j.jbiomac.2025.144032>.
130. Wen Y, Li K, Ni M, Jiang H, Wu H, et al. Dendritic Polylysine with Paclitaxel and Triptolide Codelivery for Enhanced Cancer Ferroptosis through the Accumulation of ROS. *ACS ACS Appl Mater Interfac.* 2024;16(16):20143–56.
131. Li Z, Yang G, Han L, Wang R, Gong C, et al. Sorafenib and triptolide loaded cancer cell-platelet hybrid membrane-camouflaged liquid crystalline lipid nanoparticles for the treatment of hepatocellular carcinoma. *J Nanobiotechnol.* 2021;19(1):360.
132. Zhang X, Gao H, Wei D, Pei X, Zhang Y, et al. ROS responsive nanoparticles encapsulated with natural medicine remodel autophagy homeostasis in breast cancer. *Appl Mater Interfac.* 2023;15(25):29827–40.
133. He M, Yu L, Yang Y, Zou B, Ma W, et al. Delivery of triptolide with reduction-sensitive polymer nanoparticles for liver cancer therapy on patient-derived xenografts models. *Chin Chem Lett.* 2020;31(12):3178–82. <https://doi.org/10.1016/j.ccllet.2020.05.034>.
134. Gu Y, Tang X, Yang M, Yang D, Liu J. Transdermal drug delivery of triptolide-loaded nanostructured lipid carriers: preparation, pharmacokinetic, and evaluation for rheumatoid arthritis. *Int J Pharm.* 2019;554:235–44. <https://doi.org/10.1016/j.jipharm.2018.11.024>.
135. Pei WJ, Wu YZ, Wang YS, Ding Q, Guo XL, et al. Gel based on cubic liquid crystals nanoparticles enhance anti-inflammation and bone protection effects of triptolide. *J Drug Deliv Sci Technol.* 2022;72:103387. <https://doi.org/10.1016/j.jddst.2022.103387>.
136. Shan QQ, Jiang XJ, Wang FY, Shu ZX, Gui SY. Cubic and hexagonal liquid crystals as drug carriers for the transdermal delivery of triptolide. *Drug Deliv.* 2019;26(1):490–8.
137. Zhao X, Liu X, Zhang P, Liu Y, Ran W, et al. Injectable peptide hydrogel as intraperitoneal triptolide depot for the treatment of orthotopic hepatocellular carcinoma. *Acta Pharm Sin B.* 2019;9(5):1050–60. <https://doi.org/10.1016/j.apsb.2019.06.001>.
138. Wang K, Zhu K, Zhu Z, Shao F, Qian R, et al. Triptolide with hepatotoxicity and nephrotoxicity used in local delivery treatment of myocardial infarction by thermosensitive hydrogel. *J Nanobiotechnol.* 2023;21(1):227.
139. Liaw K, Sharma R, Sharma A, Salazar S, Appiani La Rosa S, et al. Systemic dendrimer delivery of triptolide to tumor-associated macrophages improves anti-tumor efficacy and reduces systemic toxicity in glioblastoma. *J Control Release.* 2021;329:434–44. <https://doi.org/10.1016/j.jconrel.2020.12.003>.
140. Li P, Yang X, Yang Y, He H, Chou CK, et al. Synergistic effect of all-trans-retinal and triptolide encapsulated in an inflammation-targeted nanoparticle on collagen-induced arthritis in mice. *J Control Release.* 2020;319:87–103. <https://doi.org/10.1016/j.jconrel.2019.12.025>.
141. Zhou L, Du Y, Shang Y, Xiang D, Xia X. A novel triptolide nano-liposome with mitochondrial targeting for treatment of hepatocellular carcinoma. *Int J Nanomedicine.* 2024;19:12975–98.
142. Zhu H, Wang Z, Cui J, Ge Y, Yan M, et al. PEGylated retinoate prodrug self-assembled nanomicelles loaded with triptolide for targeting treatment of rheumatoid arthritis and side effect attenuation. *Colloids Surf B Biointerfaces.* 2025;251:114618. <https://doi.org/10.1016/j.colsurfb.2025.114618>.
143. Zhang L, Chang J, Zhao Y, Xu H, Wang T, et al. Fabrication of a triptolide-loaded and poly- γ -glutamic acid-based amphiphilic nanoparticle for the treatment of rheumatoid arthritis. *Int J Nanomedicine.* 2018;13:2051–64.
144. Chao Y, Liu Z. Biomaterials tools to modulate the tumour microenvironment in immunotherapy. *Nat Rev Bioeng.* 2023;1(2):125–38.
145. Luo Y, Li J, Hu Y, Gao F, Pak-Heng Leung G, et al. Injectable thermo-responsive nano-hydrogel loading triptolide for the anti-breast cancer enhancement via localized treatment based on “two strikes” effects. *Acta Pharm Sin B.* 2020;10(11):2227–45. <https://doi.org/10.1016/j.apsb.2020.05.011>.
146. Zhao X, Yang Y, Su X, Xie Y, Liang Y, et al. Transferrin-modified triptolide liposome targeting enhances anti-hepatocellular carcinoma effects. *Biomedicine.* 2023;11(10):2869.
147. Li Z, Lan J, Wu Y, Ding Y, Zhang T. Homotypic cell membrane-camouflaged biomimetic PLGA nanoparticle loading triptolide for the treatment of hepatocellular carcinoma. *Drug Deliv.* 2024;31(1):2354687.
148. Xu Z, Huang Y, Wu Y, Chen J, Seto SW, et al. Glycyrrhizic acid-lipid framework nanovehicle loading triptolide for combined immunotherapy. *ACS Appl Mater Interfac.* 2023;15(35):41337–50.
149. Li H, Zhang P, Yuan X, Peng S, Yang X, et al. Targeted drug-loaded peptides induce tumor cell apoptosis and immunomodulation to increase antitumor efficacy. *Biomater Adv.* 2024;160:213852. <https://doi.org/10.1016/j.bioadv.2024.213852>.
150. Wang S, Guo Q, Xu R, Lin P, Deng G, et al. Combination of ferroptosis and pyroptosis dual induction by triptolide nano-MOFs for immunotherapy of Melanoma. *J Nanobiotechnol.* 2023;21(1):383.
151. Xin Li J, Jiao Zhang M, Feng Shi J, Peng Wang S, Mei Zhong X, et al. pH-sensitive nano-polyelectrolyte complexes with arthritic macrophage-targeting delivery of triptolide. *Int J Pharm.* 2023;632:122572. <https://doi.org/10.1016/j.jipharm.2022.122572>.
152. Wang J, Cui J, Chen Y, Zhou H, Li X, et al. Self-assembled triptolide produg nanovesicles loading with ginsenoside Rg3 for double-targeted therapy of pancreatic cancer. *Mater Today Bio.* 2025;33:102004. <https://doi.org/10.1016/j.mtbio.2025.102004>.
153. Cheng Q, Zhong X, Deng L, He X, Luo M, et al. RBC membrane-camouflaged nanosystem-mediated synergistic drug combination for enhanced anti-tumor therapy. *Adv Healthc Mater.* 2025;14(26):e2500446. <https://doi.org/10.1002/adhm.202500446>.
154. Li G, Song Z, Ru Y, Zhang J, Luo L, et al. Small-molecule nanoprodug with high drug loading and EGFR, PI3K/AKT dual-inhibiting properties for bladder cancer treatment. *Exploration.* 2023;3(5):20220141. <https://doi.org/10.1002/EXP.20220141>.
155. He S, Li X, He Y, Guo L, Dong Y, et al. High-density lipoprotein nanoparticles spontaneously target to damaged renal tubules and alleviate renal fibrosis by remodeling the fibrotic niches. *Nat Commun.* 2025;16(1):1061.
156. Feng J, Xu M, Wang J, Zhou S, Liu Y, et al. Sequential delivery of nanoformulated α -mangostin and triptolide overcomes permeation obstacles and improves therapeutic effects in pancreatic cancer. *Biomaterials.* 2020;241:119907. <https://doi.org/10.1016/j.biomaterials.2020.119907>.
157. Liu HJ, Wang M, Hu X, Shi S, Xu P. Enhanced photothermal therapy through the in situ activation of a temperature and redox dual-sensitive nanoreservoir of Triptolide. *Small Weinb.* 2020;16(38):2003398. <https://doi.org/10.1002/sml.202003398>.
158. Fang K, Sun Y, Yang J, Hu X, Chen M, et al. A dual stimuli-responsive nanoplatfor loaded PtIV-Triptolide produg for achieving synergistic therapy toward breast cancer. *Adv Healthc Mater.* 2023;12(28):2301328. <https://doi.org/10.1002/adhm.202301328>.
159. Liu Y, Kong L, Yu Y, Zang J, Zhang L, et al. Tumor microenvironment responsive key nanomicelles for effective against invasion and metastasis in ovarian cancer using mice model. *Int J Nanomed.* 2025;20:215–38.
160. Zhou ZL, Yang YX, Ding J, Li YC, Miao ZH. Triptolide: structural modifications, structure-activity relationships, bioactivities, clinical development and mechanisms. *Nat Prod Rep.* 2012;29(4):457–75.
161. Bao S, Yi M, Xiang B, Chen P. Antitumor mechanisms and future clinical applications of the natural product Triptolide. *Cancer Cell Int.* 2024;24(1):150.
162. Lu J, Zhang Y, Dong H, Sun J, Zhu L, et al. New mechanism of nephrotoxicity of Triptolide: oxidative stress promotes cGAS-STING signaling

- pathway. *Free Radic Biol Med*. 2022;188:26–34. <https://doi.org/10.1016/j.freeradbiomed.2022.06.009>.
163. Yang X, He L, Li X, Wang L, Bu T, et al. Triptolide exposure triggers testicular vacuolization injury by disrupting the Sertoli cell junction and cytoskeletal organization via the AKT/mTOR signaling pathway. *Ecotoxicol Environ Saf*. 2024;279:116502. <https://doi.org/10.1016/j.ecoenv.2024.116502>.
 164. Lee B, Park Y, Lee Y, Kwon S, Shim J. Triptolide, a cancer cell proliferation inhibitor, causes zebrafish muscle defects by regulating Notch and STAT3 signaling pathways. *Int J Mol Sci*. 2024;25(9):4675.
 165. Rodriguez-Blanco J, Salvador AD, Suter RK, Swiderska-Syn M, Palomo-Caturia I, et al. Triptolide and its prodrug Minnelide target high-risk MYC-amplified medulloblastoma in preclinical models. *J Clin Invest*. 2024;134:15.
 166. He QL, Minn I, Wang Q, Xu P, Head SA, et al. Targeted delivery and sustained antitumor activity of Triptolide through glucose conjugation. *Angew Chem Int Ed Engl*. 2016;55(39):12035–9. <https://doi.org/10.1002/anie.201606121>.
 167. Yang M, Gu Y, Yang D, Tang X, Liu J. Development of Triptolide-nanoemulsion gels for percutaneous administration: physicochemical, transport, pharmacokinetic and pharmacodynamic characteristics. *J Nanobiotechnol*. 2017;15(1):88.
 168. Li A, Gu Y, He M, Zeng Y, Wang X, et al. Engineered ginseng-derived nanovesicles with MCSP targeting and mitochondria-directed prodrug delivery for synergistic immunotherapy of metastatic melanoma. *Adv Funct Mater*. 2025. <https://doi.org/10.1002/adfm.202527351>.
 169. He QL, Titov DV, Li J, Tan M, Ye Z, et al. Covalent modification of a cysteine residue in the XPB subunit of the general transcription factor TFIIH through single epoxide cleavage of the transcription inhibitor triptolide. *Angew Chem Int Ed*. 2015;54(6):1859–63. <https://doi.org/10.1002/anie.201408817>.
 170. Manzo SG, Zhou ZL, Wang YQ, Marinello J, He JX, et al. Natural product triptolide mediates cancer cell death by triggering CDK7-dependent degradation of RNA polymerase II. *Cancer Res*. 2012;72(20):5363–73.
 171. Leuenroth SJ, Crews CM. Triptolide-induced transcriptional arrest is associated with changes in nuclear substructure. *Cancer Res*. 2008;68(13):5257–66.
 172. Lu Y, Zhang Y, Li L, Feng X, Ding S, et al. TAB1: a target of Triptolide in macrophages. *Chem Biol*. 2014;21(2):246–56. <https://doi.org/10.1016/j.chembiol.2013.12.009>.
 173. Phillips PA, Dudeja V, McCarroll JA, Borja-Cacho D, Dawra RK, et al. Triptolide induces pancreatic cancer cell death via inhibition of heat shock protein 70. *Cancer Res*. 2007;67(19):9407–16.
 174. Song X, Zhang Y, Dai E, Wang L, Du H. Prediction of Triptolide targets in rheumatoid arthritis using network pharmacology and molecular docking. *Int Immunopharmacol*. 2020;80:106179. <https://doi.org/10.1016/j.intimp.2019.106179>.
 175. Chen D, Ma Y, Wang X, Yu S, Li L, et al. Triptolide-containing formulation in patients with autosomal dominant polycystic kidney disease and proteinuria: an uncontrolled trial. *Am J Kidney Dis*. 2014;63(6):1070–2. <https://doi.org/10.1053/j.ajkd.2014.01.418>.
 176. Cao W, Liu X, Han Y, Song X, Lu L, et al. (5R)-5-hydroxytriptolide for HIV immunological non-responders receiving ART: a randomized, double-blinded, placebo-controlled phase II study. *Lancet Regional Health*. 2023;34:100724.
 177. Li X, Zang A, Jia Y, Zhang J, Fan W, et al. Triptolide reduces proliferation and enhances apoptosis of human non-small cell lung cancer cells through PTEN by targeting miR-21. *Mol Med Rep*. 2016;13(3):2763–8.
 178. Wang SS, Lv Y, Xu XC, Zuo Y, Song Y, et al. Triptonide inhibits human nasopharyngeal carcinoma cell growth via disrupting Lnc-RNA THOR-IGF2BP1 signaling. *Cancer Lett*. 2019;443:13–24. <https://doi.org/10.1016/j.canlet.2018.11.028>.
 179. Zhao X, Zhang Q, Chen L. Triptolide induces the cell apoptosis of osteosarcoma cells through the TRAIL pathway. *Oncol Rep*. 2016;36(3):1499–505.
 180. Tan BJ, Chiu GNC. Role of oxidative stress, endoplasmic reticulum stress and ERK activation in triptolide-induced apoptosis. *Int J Oncol*. 2013;42(5):1605–12.
 181. Sun YY, Xiao L, Wang D, Ji YC, Yang YP, et al. Triptolide inhibits viability and induces apoptosis in liver cancer cells through activation of the tumor suppressor gene p53. *Int J Oncol*. 2017;50(3):847–52.
 182. Wang XF, Zhao YB, Wu Q, Sun ZH, Li HJ. Triptolide induces apoptosis in endometrial cancer via a p53-independent mitochondrial pathway. *Mol Med Rep*. 2014;9(1):39–44.
 183. Zhang H, Zhang Z, Jiang M, Wang S, Wang J, et al. Triptolide suppresses melanoma cell growth in vitro and in vivo through the Src-ERK signaling pathway. *J Cancer*. 2024;15(19):6345–54.
 184. Yuan C, Liao Y, Liao S, Huang M, Li D, et al. Triptolide inhibits the progression of Glioblastoma U251 cells via targeting PROX1. *Front Oncol*. 2023;13:1077640.
 185. Wang HF, Zhao ZL. Triptolide inhibits proliferation and invasion of colorectal cancer cells by blocking Nrf2 expression. *Chem Biol Drug Des*. 2024;103(1):e14410. <https://doi.org/10.1111/cbdd.14410>.
 186. Wang R, Xiaoping M, Shan S, Liu Y. Triptolide antagonized the Cisplatin resistance in human ovarian cancer cell line A2780/CP70 via hsa-mir-6751. *Future Med Chem*. 2018;10(16):1947–55.
 187. Hu H, Luo L, Liu F, Zou D, Zhu S, et al. Anti-cancer and sensitization effect of Triptolide on human epithelial ovarian cancer. *J Cancer*. 2016;7(14):2093–9.
 188. Wang L, Huang QH, Li YX, Huang YF, Xie JH, et al. Protective effects of silymarin on triptolide-induced acute hepatotoxicity in rats. *Mol Med Rep*. 2018;17(1):789–800.
 189. Zhou S, Cheng R, Zhang Y, Jiang Y, Zhang L, et al. CHIR-98014, a GSK 3 β inhibitor, protects against triptolide/lipopolysaccharide-induced hepatotoxicity by mitochondria-dependent apoptosis inhibition. *Chem Res Toxicol*. 2024;37(2):407–18.
 190. Cao Z, Liu B, Yan L, Shu H, Wang L, et al. Glycyrrhizic acid rebalances mitochondrial dynamics to mitigate hepatotoxicity induced by triptolide. *J Funct Foods*. 2024;113:106006. <https://doi.org/10.1016/j.jff.2024.106006>.
 191. Chen H, Wang X, Liu M, Yang J, Kuang Y, et al. Synergism and attenuation of triptolide through prodrug engineering combined with liposomal scaffold strategy to enhance inhibition in pancreatic cancer. *Int J Pharm*. 2023;648:123623. <https://doi.org/10.1016/j.ijpharm.2023.123623>.

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