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Pharmacological activity and clinical progress of Triptolide and its derivatives LLDT-8, PG490-88Na, and Minnelide: a narrative review

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Abstract. – Triptolide, a compound isolated from a Chinese medicinal herb, has potent anti-tumor, immunosuppressive, and anti-inflammatory properties. Due to its interesting structural features and diverse pharmacological activities, it has attracted great interest by the Society of Organic Chemistry and Pharmaceutical Chemistry. However, its clinical potential is greatly hampered by limited aqueous solubility and oral bioavailability, and multi-organ toxicity. In recent years, various derivatives of Triptolide have made varying degrees of progress in the treatment of inflammatory diseases, autoimmune diseases, and cancer. The most researched and potentially clinically valuable of them were (5R)-5-hydroxytriptolide (LLDT-8), PG490-88Na (F6008), and Minnelide. In this review, we provide an overview of the advancements made in triptolide and several of its derivatives' biological activity, mechanisms of action, and clinical development. We also summarized some prospects for the future development of triptolide and its derivatives. It is hoped to contribute to a better understanding of the progress in this field, make constructive suggestions for further studies of Triptolide, and provide a theoretical reference for the rational development of new drugs.

Key Words:
Triptolide, LLDT-8, PG490-88Na, Minnelide, Pharmacological activity, Clinical progress.

Introduction

Triptolide is a natural diterpenoid compound derived from the traditional Chinese herb *Tripterygium wilfordii*[1]. It has many pharmacological effects, including anti-rheumatic, anti-bacterial, anti-inflammatory, immunomodulatory, and anti-tumor effects[2-6]. However, Triptolide has multiple organ toxicity, such as hepatotoxicity, nephrotoxicity, cardiotoxicity, and reproductive system toxicity[7-10]. The content of triptolide in medicinal plants is extremely low[11]; meanwhile, it also has a relatively narrow therapeutic window and poor water solubility. These drawbacks greatly limit the clinical application of triptolide. To reduce the toxicity of triptolide, researchers have adopted strategies that rely on chemical structure modification, novel drug delivery systems, and combination drug therapy. Among them, chemical structure modification has the advantages of a short development cycle, low cost, and low market risk. The C-14 β- Hydroxyl group and lactone ring of triptolide are essential for its effectiveness and cytotoxicity so that it can serve as one of the bases for chemical structural modification[12].

The most important functional groups of triptolide have been studied in detail and structurally modified to obtain many critical structure-activity relationships (SARs) information, leading to the synthesis of a series of well-water-soluble and less toxic derivatives (Figure 1). Many triptolide derivatives have so far advanced in clinical trials, based on the development of triptolide's structural modification. Despite the fact that many derivatives have been created, the majority of them have been lost because of poor distribution or absorption. Only a few derivatives of triptolide (such as LLDT-8 and Minnelide) have entered phase I/II clinical trials, while some clinical trials of derivatives, such as PG490-88Na (F6008), have been terminated due to serious side effects or even fatal events[13]. LLDT-8 exhibits superior drug formation, higher solubility, and lesser toxicity when compared to

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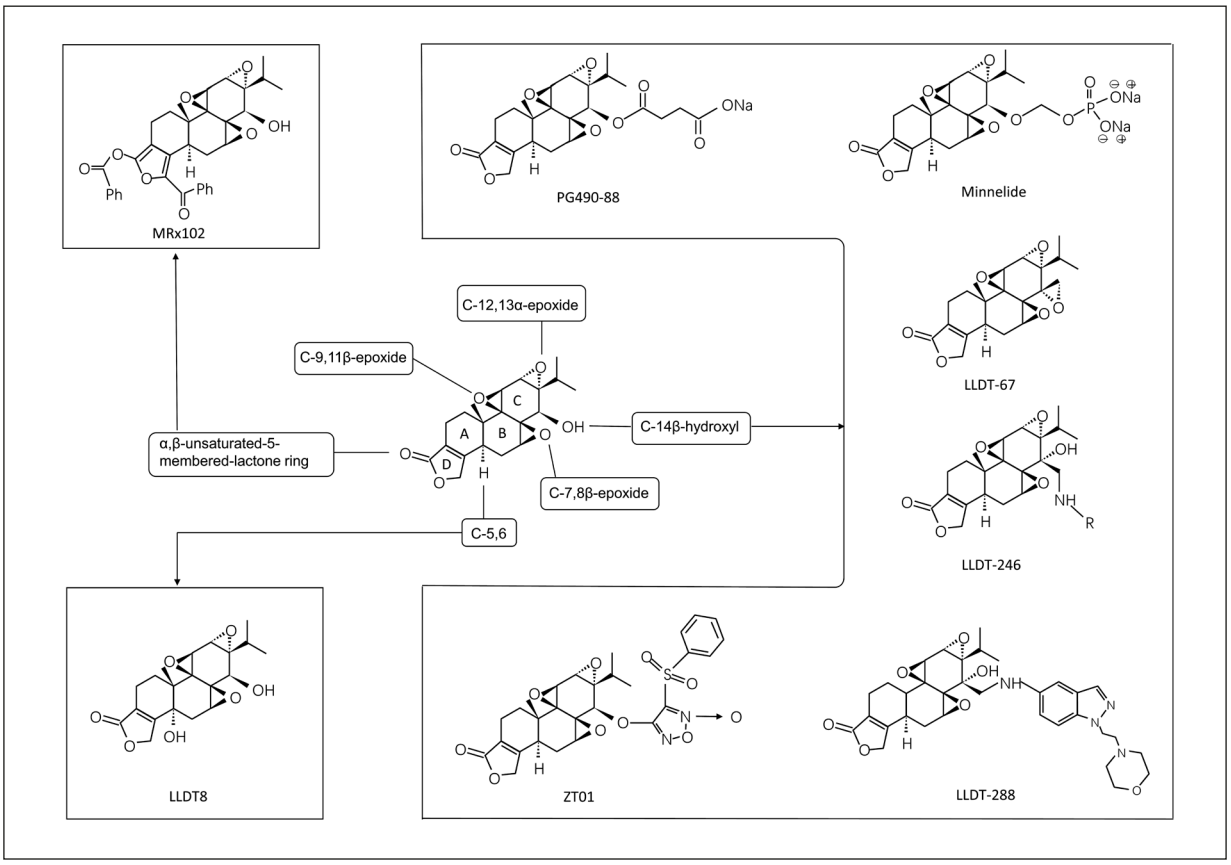

Figure 1. SARs of triptolide and chemical structure of some triptolide derivatives.

triptolide. It is therapeutically indicated for the treatment of persistent aberrant immune activation, including rheumatoid arthritis and AIDS, and is now in the phase II clinical stage[14]. Minnelide has successfully passed a phase II clinical trial for refractory pancreatic cancer and is now the triptolide medicine that is progressing the fastest in clinical trials[15]. Minnelide is even more effective than the traditional first-line drug gemcitabine in the treatment of pancreatic cancer[83]. In addition, newly developed derivatives, such as MRx102[16], LLDT-246[17], LLDT-288[18], ZT01[19] have also exhibited great potential in antitumor, anti-inflammatory, immunosuppressive effects in recent years.

Many molecules and signaling pathways are associated with the pharmacological mechanism of triptolide. As many triptolide derivatives are structurally similar to triptolide (some of which are prodrugs that are converted to TPL *in vivo*), they may have the same mechanism of action as triptolide. Therefore, in order to get a complete understanding of this subject and make recommendations for future triptolide research, this article reviews the medicinal chemistry progress and the bioactivity, preclinical, and clinical status of triptolide derivatives. In addition to a brief overview of existing research on the derivatives of triptolide, we have also proposed some new ideas. It is hoped that this review will contribute to a better understanding of the progress in this field. We also hope that our suggestions will be helpful for further research and rational development of new derivatives of triptolide.

Chemical Structure and Structure-Activity Relationships of Triptolide

In 1972, Kupchan S.M. extracted the first epoxy diterpenoid lactone compound triptolide from the root of *Tripterygium Wilfordii* Hook F[20], and the molecular structural formula was shown in (Figure 1), the relative molecular mass was 360.4, and the melting point was around 226°C[20]. Comprehensive and systematic structure modifi-

cation and structure-activity relationship studies of TP have been conducted by research groups at home and abroad, mainly focusing on C-14 β-OH, unsaturated five-membered lactone ring (D-ring), C-5, C-6, and 3 epoxide bond sites. As a result of these discoveries, a variety of triptolide derivatives have been produced and tested in various target or phenotypic screens. Through the analysis of these structural analogues of triptolide, the literature provides a comprehensive summary of the structure-activity relationship of triptolide[12,21-25]. We have preliminarily summarized the structure-activity relationships (SARs) of some triptolides (Figure 2):

(1) The replacement of C2 with a hydroxyl group decreased its anti-inflammatory, immunosuppressive, and antitumor activities, whereas its toxicity increased.
(2) Introducing suitable functional groups at the C-5 and C-6 positions, such as replacing hydrogen at the C-5 position with hydroxyl groups, significantly reduces toxicity but does not disrupt its immunosuppressive and anticancer activities.
(3) α-Type epoxide group of positions C-12, C-13 is an important part of triptolide. When it changes, the immune suppression, anti-male fertility, and physiological toxicity of triptolide will be affected. When the ortho hydroxyl groups were introduced at C-12, C-13, triptolide only showed significant anti-inflammatory activity. The disconnection of C-12 and C-13 of triptolide will lose its anticancer and immunosuppressive activity, but it can retain its anti-inflammatory effect. After the introduction of the chlorine atom at C-12 position, its toxicity evidently decreased.
(4) C-14 β-OH is an essential active group and an important modification site of triptolide. The purpose of drug targetability can be achieved by linking esterification with a targeted chemical structure, and the water solubility of drugs can also be improved by linking water-soluble groups. When fluorine replaces the hydroxyl group in C-14 of triptolide, the product obtained also has good anticancer activity. The hydroxyl at the C-14 position is oxidized to a ketone, and its anti-inflammatory and immunosuppressive activities markedly decline. The activity was also weak after the hydroxyl at the C-14 position was acetylated.
(5) The epoxy groups of triptolide are key sites for their biological activity. Therefore, the epoxy bonds of C-9 and C-11 of triptolide can be modified to increase its biological activity. However, opening the C-7 and C-8 epoxy groups will significantly reduce the biological activity of triptolide.
(6) The trans conformation of the A/B ring is crucial, and derivatives with cis A/B ring systems have very weak cytotoxicity.

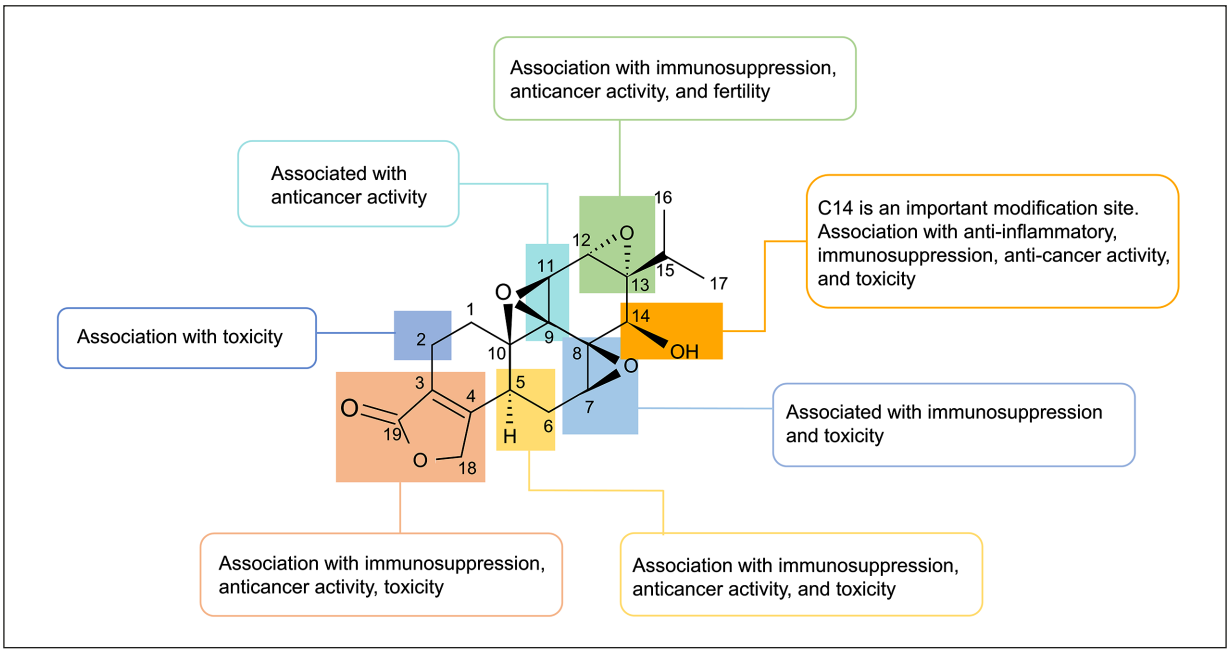

Figure 2. Structure-activity relationships of triptolide.

(7) The D-ring of triptolide is crucial for its biological activity, and modification of the D-ring will significantly reduce its efficacy in various aspects.

The above structure-activity relationships can be used to guide the design of new derivatives of triptolide, providing low toxicity, high efficiency, and broad treatment window candidate drugs for clinical research.

Triptolide and Diseases

In recent decades, triptolide has attracted increased attention due to its pharmacological activities, such as powerful anti-inflammatory[26], immunomodulatory[27], anti-oxidative stress[28], anti-proliferation, promoting apoptosis[29], anti-osteoporosis[30], neuroprotection[31]. Therefore, triptolide is widely used in the treatment of cancer (**Supplementary Table I**), inflammatory diseases and autoimmune diseases (Table I).

Triptolide and Cancer

Triptolide has been proven in numerous studies to regulate autophagy, induce apoptosis[32], inhibit angiogenesis[33], arrest cell cycle progression[34], and inhibit tumor migration, invasion and metastasis[35]. Triptolide exerts its anti-cancer activity by regulating a variety of key molecular mechanisms and signal pathways, such as NF-kB[36], Jak/Stat3[37], Bcr-abl[38], XPB, HSP70[39], TFIIH[40], RNA polymerase I and II[41], Rac1, reactive oxygen species[42], and caspase-3[43], MKP-1, and Bcl-2[44]. Triptolide has been demonstrated to be effective in treating a variety of cancers, including pancreatic cancer, lung cancer, ovarian cancer, breast cancer, and leukemia. In addition, triptolide not only can directly inhibit tumor growth, but also can be combined with other chemotherapeutic drugs to produce synergistic anticancer effects[45]. Therefore, triptolide has emerged as a broad-spectrum anti-cancer drug capable of multitarget inhibition of cancer cell proliferation and induction of apoptosis.

Triptolide and Inflammatory and Immune-Related Diseases

Triptolide not only inhibits cancer cell proliferation and induces cell apoptosis, but also inhibits inflammation and stimulates cell protection by inhibiting pro-inflammatory cytokines and chemokines, including PMA, THF-a, IFN-r, MCP-1, MIP-1a, MIP-1B, RANTES, TARC, IP-10, MCP-1, G-CSF, IL-1B, IL-6, IL-8, Cxcl-1, COX-2, and NO[46-51]. Triptolide is a promising medication for the treatment of inflammatory illnesses because of its strong anti-inflammatory and immunosuppressive effects. It has been shown that triptolide plays an important therapeutic role in inflammatory diseases, such as membranous nephropathy (MN), kidney transplantation, inflammatory bowel disease (IBD), asthma, acute lung injury (ALI), and diabetic nephropathy (DN). Meanwhile, triptolide also played an important therapeutic role in many autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus (SLE), and CIA-induced arthritis, by regulating immune-related cells and inflammatory mediators. Triptolide is also a possible medicine for the treatment of several neurodegenerative illnesses, such as Parkinson's disease (PK) and Alzheimer's disease (AD), as it reduces neuroinflammation and has neuroprotective pharmacological effects. Triptolide has also been demonstrated to effectively inhibit HIV-1 replication *in vitro* at nanomolar doses by favoring the breakdown of Tat protein, which is expressed by the virus[52].

Pharmacological Activity and Clinical Progress of Triptolide Derivatives

Based on the progress of structural modification of triptolide, some derivatives such as PG490-88Na (F6008), (5R)-5-hydroxytriptolide (LLDT-8), and Minnelide have made progress in the treatment of rheumatoid arthritis (RA), autoimmune diseases, and cancer (Figure 3). Their chemical synthetic route is shown in the figure (Figure 4). These compounds are less poisonous and have improved oral bioavailability and water solubility.

(5R)-5-Hydroxytriptolide (LLDT-8)

(5R)-5-hydroxytriptolide (LLDT-8) is an analog structurally modified from triptolide. Compared to TP, its hydrogen at the C-5 position is replaced by a hydroxyl group[53]. The pharmacological action of LLDT-8, a structural homolog of triptolide, is comparable to that of triptolide. Pharmacological experiments have shown that LLDT-8 exhibits strong immunosuppressive activity in both cellular and humoral immune responses, and exhibits strong anti-inflammatory and immunosuppressive activities *in vitro* and *in*

Table I. The potential mechanism of triptolide in the treatment of inflammatory and immune diseases.

Disease	Mechanism of action	Signaling pathways	Effects	Ref.
Rheumatoid arthritis	1. Immunosuppression, 2. Anti-inflammatory 3. Apoptosis, 4. Anti-angiogenesis, 5. Cartilage and bone protective, effects 6. Inhibit the proliferation of FLSs	↓NF-κB signaling pathways, MAPK signaling pathways, JNK/MAPK signal pathway, PI3-K/Akt signaling pathways, RANKL/RANK/osteoprotegerin signaling pathway, JAK/STAT3 signaling pathway, cGAS-STING pathway, ↑Notch signaling pathway,	↓ FLS, IL-18, IL-1, IL-6, IL-17, IL-10, IL-12, TNF-α, NF-κB, TGF-β1, COX-2, PGE2, MMPs, STAT3, Th17, DCs, CCR5, (MIP)-1α, MIP-1β, (MCP)-2, GM-CSF, VEGF, ↑ Redox balance, Tregs,	117, 186, 216-228
SLE	1. Immunosuppression 2. Anti-inflammatory	↓ The TLR7/NF-κB signaling pathway, the JAK/STAT1 signaling pathway	↓miR-146a, TLR7, MyD88, p-IRAK1, p-NF-κBp65, IFN-γ, IL-6, IL-8, TNF-α, CXCL1, TNF, MCP-1 ↑Treg, the miR-125a-5p,	62, 229-233
Ankylosing spondylitis	1. Anti-inflammatory 2. Immunosuppression 3. Stimulation of osteoclast genesis 4. Improved platelet activation 5. Inhibition of proliferation differentiation 6. Induction of osteoblast apoptosis	↓ NF-κB signaling pathway, MAPK signaling pathway, the BMP/Smad pathway	↓circRNA-0110634, IL-1β, TNF-α, VEGFA, VEGFR and SDF-1, CXCR4, TNF-α, IL-6β, IL-1, BMPRII, Smad1, Smad4 and Smad5 ↑ IL-4, IL-10	198, 234-237
Inflammatory bowel disease	1. Anti-inflammatory 2. Immunosuppression 3. Anti-oxidative stress 4. Decreased ECM deposition and collagen production 5. Pro-apoptotic	↓ TNF-alpha/TNFR2 signal pathway, the IL-6/STAT 3 signaling pathway, the mTOR/ STAT3 signaling, the PDE4B/ AKT/NF-κB signaling, IL-6/ STAT3/SOCS3 signaling pathway. ↑the NRF2/HO-1 signaling pathway	↓ TNF-α, IFN-γ, IL-17, IL-6, IL-10, PGE2 (prostaglandin E2), ROS, Bcl-2, Bcl-xl, f IL-12, IL-23	53, 207, 238-244
Intestinal fibrosis	1. Anti-inflammatory 2. Decreased ECM deposition and collagen production	↓ The miR 16 1/HSP70 signaling pathway	↓ IL 6, TNF α, TGF β1	153, 245
Hepatic fibromatosis	1. Anti-inflammatory 2. Suppressed collagen deposition	↓ The NF-κB signaling pathway	↓ TNF-α, MCP-1, Fibronectin, α-SMA, Collagens, TGF-β, RelB	241, 246, 247
Membranous nephropathy	1. Immunosuppression 2. Anti-oxidative stress 3. Anti-inflammatory 4. Podocyte protection	↓ p38 MAPK pathway, the NF-κB signaling pathway, ERK and JNK pathways, NF-κB	↓ ROS, malondialdehyde (MDA), Cleaved caspase-3 and cleaved poly ADP-e ribos polymerase (PARP) ↑ superoxide dismutase (SOD)	229, 248-250
Lupus nephritis	1. Anti-inflammatory 2. Immunosuppression	↓ The JAK/STAT1 signaling pathway	↓ IP-10, Mig, RANTES, IFN-γ, IL-6, IL-8, TNF-α, CXCL1, TNF, MCP-1 ↑ Treg, miR-125a-5p	62, 230-232
Renal fibrosis	1. Inhibit macrophage and myofibroblast infiltration 2. Reducing interstitial collagen deposition 3. Regulation of autophagy 4. Anti-fibrotic	↓ The TGF-β1-smad2 and p53 pathways, the miR-141-3p/PTEN/ Akt/mTOR pathway	↓ α-SMA, TGF-β1, TGF-β1, CTGF (connective tissue growth factor), MCP-1 and osteopontin, TNF-α, IL-6, IL-1β	94, 251-253

Continued

Table I *(Continued)*. The potential mechanism of triptolide in the treatment of inflammatory and immune diseases.

Disease	Mechanism of action	Signaling pathways	Effects	Ref.
Kidney transplant	1. Anti-inflammatory 2. Immunosuppression 3. Inhibited the differentiation of B cells 4. Inhibiting complement activation and T-cell infiltration	↓ TGF-βsignaling pathway	↓VCAM-1, TGF-β, C3, CD40, IgA, IgG, IgM	97, 99,254-257
Diabetic nephropathy	1. Anti-inflammatory 2. Anti-oxidative stress 3. Prevent the epithelial-mesenchymal transition (EMT)	↓ The NLRP3 inflammasome pathway, the microRNA-155-5p, the TGF-β1/Smads signaling pathway, Wnt3α/β-catenin signaling pathway, the notch1 pathway ↑ the Nrf2/HO-1 pathway	↓IL-1β, IL-6, TNF-α, TNF-α, IL-1, IL-1β, TGF-β3, Smad7, caspase-1, IL-1β, IL-18, NLRP 3 (Nod-like receptor protein 3), ASC (apoptosis-associated speck-like protein), OCP (oxidative carbonyl protein) ↑BDNF (brain-derived neurotrophic factor), IL-4, Smad7, MicroRNA-137	5, 125, 258-266
Diabetic cardiomyopathy	1. Immunosuppression 2. Anti-inflammatory 3. Increases cardiac energy metabolism	↓ TLR4-induced NF-κB/IL-1β immune pathway, NF-κB/TNF-α/ VCAM-1, TGF-β1/α-SMA/ Vimentin fibrosis pathway, the NF-κB signaling pathway. ↑ MAPK signaling pathway	↓TLR4, NF-κB, p65, MCP-1, VCAM-1, TNF-α, IL-1β, α-SMA, TGF-β1	54, 267, 268
Psoriasis	1. Immunosuppression 2. Anti-inflammatory	↓ The IL-36α signaling pathway, the Interferon-gamma (IFN-γ) signaling pathway	↓ STAT3, IL-36α ↑microRNA-204-5p, microRNA-181b-5p	57, 269-272

vivo, with significantly reduced toxic side effects (*in vitro* cytotoxicity is 122 times lower than triptolide, and *in vivo* acute toxicity is 10 times lower)[54,55]. The researchers constructed the first *lncRNA-TFmRNA* coexpression network, further explaining the changes in lncRNA and mRNA expression across the entire genome before and after LLDT-8 treatment. The authors suggest that *lncRNAs* may serve as biomarkers and therapeutic development targets in LLDT-8[25]. LLDT-8 exhibits superior drug formation, higher solubility, and lesser toxicity when compared to triptolide. It is clinically intended for the treatment of various chronic aberrant immune activations and is currently in phase II clinical trials[14]. LLDT-8 may be a suitable clinical alternative to triptolide.

LLDT-8 and tumor diseases

LLDT-8 has broad-spectrum antitumor activity and can exert antitumor activity by inhibiting transcription. As a novel transcriptional inhibitor, LLDT-8 has potential therapeutic effects on P-glycoprotein-mediated drug-resistant tumors[56]. LLDT-8 also demonstrated strong antitumor activity against human and mouse cancer cell lines, including P-388, HL-60, A-549, MKN-28, and MCF-7, with half inhibitory concentration values ranging from 0.04 to 0.20 nM, according to an *in vitro* anticancer activity evaluation. In addition, *in vivo* experiments have shown that LLDT-8 is effective against both ovarian cancer and prostate cancer[53]. These results suggest that LLDT-8 should be a promising anticancer drug candidate.

LLDT-8 and inflammatory diseases

Previous studies[55] have shown that LLDT-8 may be closely related to its anti-inflammatory, antioxidant, and cytokine effects. A recent study[57] found that LLDT-8 inhibits the IL-36α signaling pathway and significantly alleviates psoriasis-like skin inflammation induced by imiquimod (IMQ, TLR7 agonist), suggesting that LLDT-8 may be a potential drug for the treatment of psoriasis. LLDT-8 can exert anti-inflammatory effects by inhibiting its production of IFN-γ, and it may be a potential interferon-γ (IFN- γ) inhibitor.

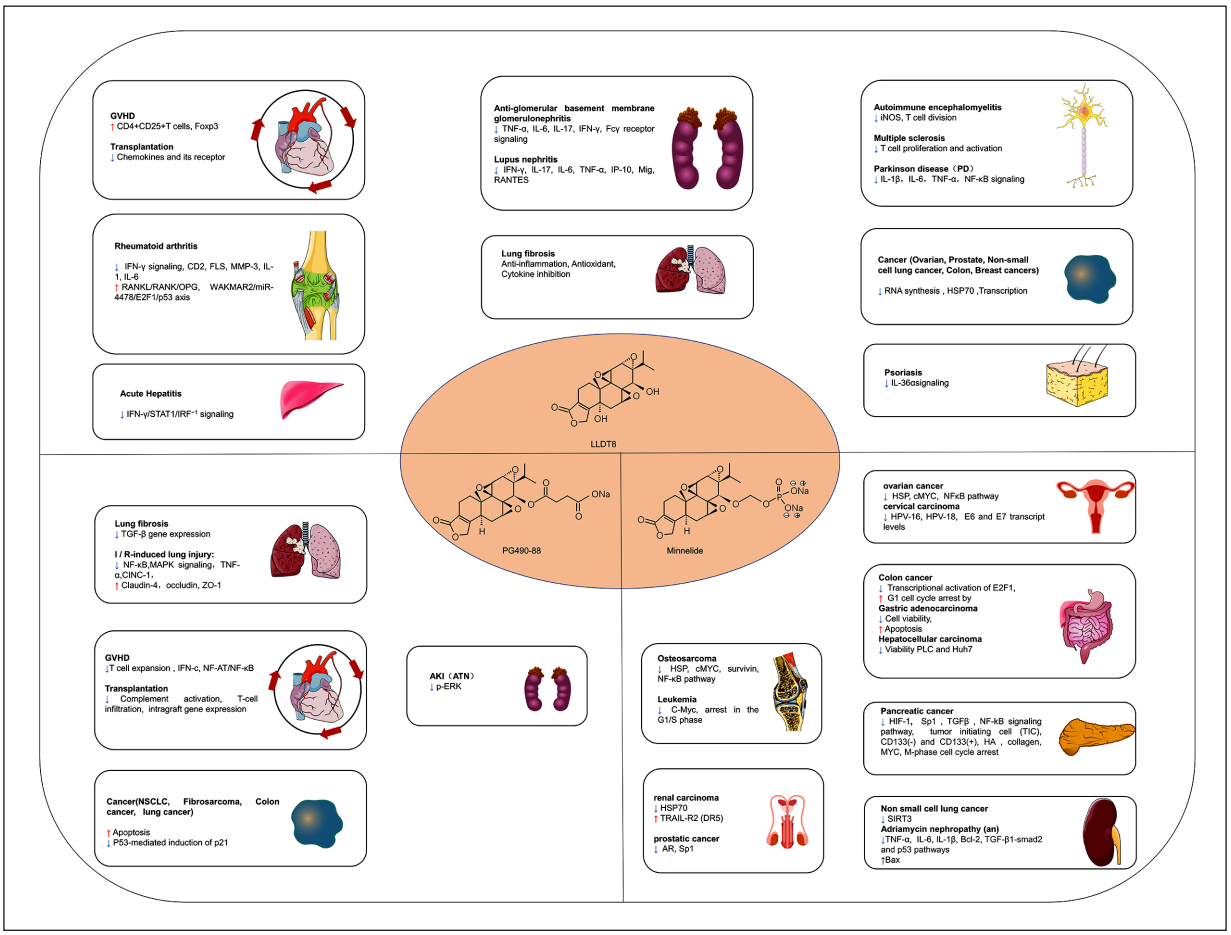

Figure 3. Schematic illustration of potential mechanisms of LLDT-8, PG490-88Na, and Minnelide in the treatment of some diseases.

LLDT-8 also has certain therapeutic effects on nervous system diseases. In the 6-hydroxydopamine (6-OHDA) hemi Parkinson's rat model, LLDT-8 attenuated activity disorders and neuroinflammation in rats, demonstrating potential therapeutic potential for Parkinson's disease (PD). Its research has shown that LLDT-8 can reduce PD-like behavior, dopaminergic neurodegeneration, and neuroinflammation in the nigrostriatal system, providing a new method and entry point for the treatment of PD[59]. Scholars[54] have studied the anti-inflammatory and neuroprotective effects of LLDT-8 on cerebral ischemia-reperfusion injury. The results indicate that it can be achieved through IκB/NF-κB cascade reaction, which inhibits neuroinflammation mediated by microglia, plays an anti-inflammatory role, and protects against acute cerebral ischemia-reperfusion injury[54]. Meanwhile, LLDT-8 can effectively inhibit pro-inflammatory factors (TNF-α and IL-1β), and suppress the NF-κB signaling pathway, thereby inhibiting the LPS-induced glial inflammatory response. Further evidence suggests that LLDT-8 may become a potential drug for the treatment of neurodegenerative diseases[60].

In certain kidney, liver, and lung diseases, it has also been shown to have some degree of therapeutic potential. Based on the powerful anti-inflammatory effect of LLDT-8, it can regulate the Fcγ signaling pathway and alleviate anti-glomerular basement membrane glomerulonephritis in NZW mice[61]. It can also inhibit the expression of renal chemokines and the infiltration of renal immune cells, thereby weakening systemic lupus nephritis in MRL/lpr mice[62]. In the IFN-γ/STAT1/IRF-1 pathway and immune disorders mediated by inflammatory cytokines, LLDT-8 can prevent ConcanavalinA-induced hepatitis[63]. According to the findings of Dong et al[64], LLDT-8 can also lower serum levels of the enzymes alanine transaminase (ALT) and aspartate transaminase (AST), as well as diminish liver fatty and bal-

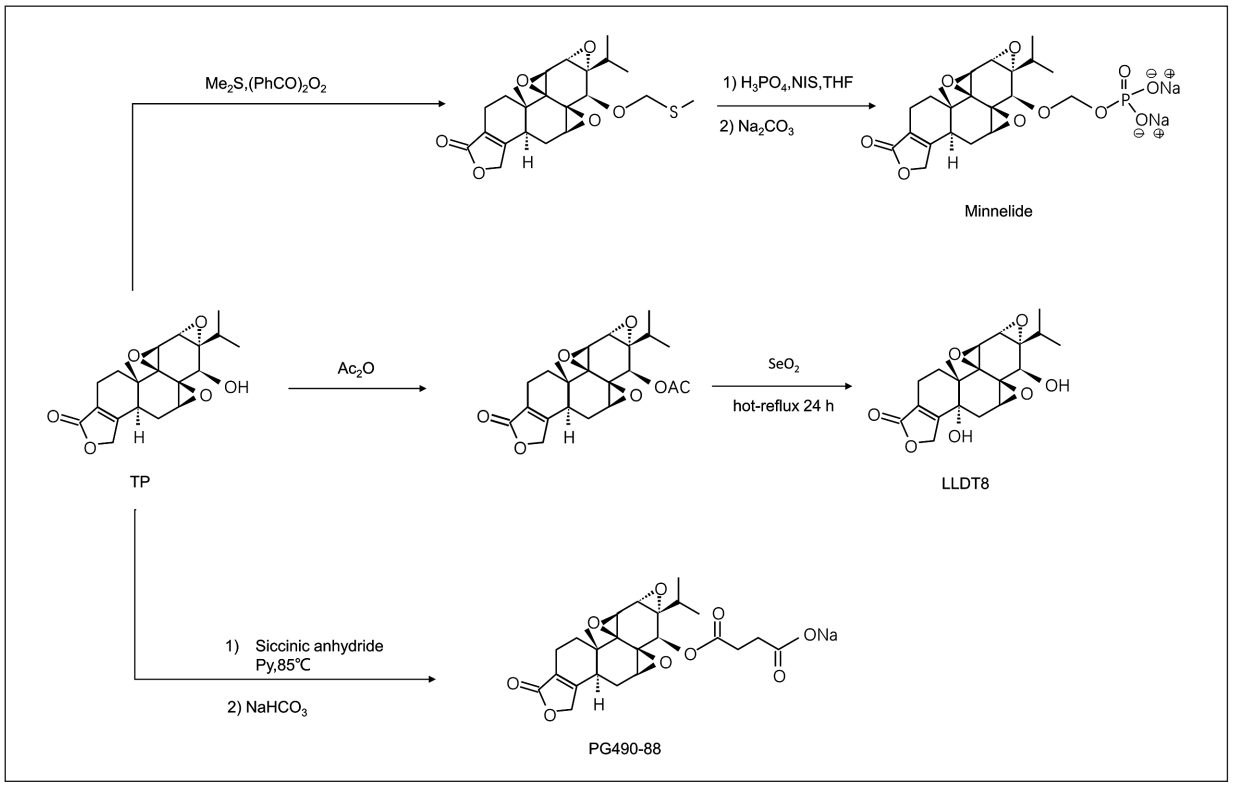

Figure 4. Synthetic route of LLDT-8, PG490-88Na, and Minnelide.

looning degeneration, which prevents liver injury. They also found that LLDT-8 can regulate stearyl-CoA desaturase-1 (SCD1) and hepatic peroxisome proliferator-activated receptor α (PPARα). The expression level significantly promotes lipid breakdown and inhibits lipid synthesis[64]. According to a recent study[65], LLDT-8 may influence TLR4 expression and NF-B signal transduction suppresses dendritic cell activation, preventing lipopolysaccharide-induced acute lung injury. It can also protect against bleomycin-induced pulmonary fibrosis in mice[66].

LLDT-8 and immune diseases

LLDT-8 has been shown to be able to prevent EAE by inhibiting the activation of T cells, but it also has promising effects for the prevention and treatment of inflammatory and immune diseases in multiple animal models[58]. The collagenase-induced arthritis in DBA/1 mice can be slowed down by using LLDT-8 because of its anti-inflammatory and immunosuppressive properties[67]. In the rat RA model, LLDT-8 can inhibit the formation of osteoclast through the RANKL/RANK/OPG pathway[2,68], thus playing a role in treating RA. This effect has also been applied to clinical trials as the primary pharmacological effect of LLDT-8. A cellular experiment by Li et al[69] suggests that CD2 protein may play a crucial role in immune disorders in RA. Thus, CD2 may be a potential target for treating RA. They further showed that LLDT-8 can treat RA by inhibiting the expression of the T-cell surface antigen CD2 (CD2). Scholars[70] suggest that activated synovial fibroblasts, along with macrophage and lymphocyte secretion factors, play an important role in the pathogenesis of rheumatoid arthritis as part of a complex cellular network. The results of Guo et al[25] indicate that LLDT-8 mainly affects FLS cells in the treatment of RA, especially in the process of immune-related pathways. Another recent study[71] discovered that LLDT-8 provides therapeutic effects by preventing fibroblast-like synovial cells (FLS) in RA fibroblasts from proliferating and invading, as well as the production of the cytokines MMP-3, IL-1, and IL-6. They also validated that LLDT-8 acts through the WAKMAR2/miR-4478/E2F1/p53 axis in RA FLS.

In some *in vitro* experiments, LLDT-8 can be inhibited by IFN-γ and inducible nitric oxide synthetase (iNOS) expression in lipopolysaccharide (LPS) activated macrophages[72], and its use

to prevent experimental autoimmune encephalomyelitis (EAE) by inhibiting T cell division. It can serve as a potential drug for the treatment of multiple sclerosis (MS)[58]. LLDT-8 can inhibit graft-versus-host disease[73]. Even during heart transplantation in mice with major histocompatibility antigen (MHC) mismatch, LLDT-8 can also help to prevent allograft rejection. LLDT-8 can decrease the division of human peripheral blood mononuclear cells while also acting as an immunosuppressant, implying that it could be employed as a human immunosuppressant[44].

Minnelide

Minnelide, 14-O-phosphonooxymethyltriptolide disodium salt, is a water-soluble analog of TP. Phosphate groups are highly electronegative and hydrophilic, and the introduction of phosphate groups to improve drug water solubility is a relatively well-established method for the modification of drug molecules. The phosphate group can be directly attached to the hydroxyl group of the parent drug in the form of a phosphomonoester or indirectly linked to the parent drug through a linker. Minnelide is the fastest-developing derivative of triptolide. *In vitro* kinetic experiments showed that, in the presence of alkaline phosphatase, Minnelide (t1/2¼2 min) was converted to triptolide, an enzyme present in all tissues, including blood. Minnelide is inactive *in vitro* and requires conversion by phosphatase *in vivo* to its active form, triptolide. After entering the human body, it can be rapidly and completely converted to triptolide, which is beneficial for controlling the dosage of the drug and improving its safety and efficacy. Currently, Minnelide has entered clinical trials for gastrointestinal cancer and pancreatic cancer[45,74-76].

Minnelide and digestive system tumors

In recent years, Minnelide has been mainly used for the treatment of pancreatic cancer and has entered clinical trials for advanced pancreatic cancer[77]. The phase II clinical trial of Minnelide needle for refractory pancreatic cancer has been completed[15], which is currently the fastest progressing triptolide drug in clinical research. In pancreatic cell lines, the assessment of cell viability revealed that Minnelide administration had an inhibitory impact similar to triptolide in the presence as opposed to the absence of alkaline phosphatase. In addition, among several independent but complementary pancreatic cancer models *in vivo*, Minnelide is very effective in reducing the growth and spread of pancreatic tumors, improving the survival rate and lowering toxicity. Minnelide can also downregulate the expression of p3000 and reduce HIF-1α transcriptional activity of the transcription complex, which inhibits the survival-promoting signaling pathway in pancreatic cancer cells. In addition, Minnelide regulates downstream effects by reducing hypoxia and related signals[78]. A research team at the University of Minnesota found that Minnelide reduced the tumor volume and number of tumor initiation cells (TICs) derived from cd133+ in tumors[79]. This is the first report on the efficacy of Minnelide in the same gene system of immune tolerance. Subsequently, the team conducted in-depth research and established an *in vitro* model to study the characteristics of tumor stem cells and tumor-initiating cells, discovering that Minnelide has good prospects for preclinical evaluation[80]. The team also found that Minnelide can deplete extracellular matrix components by consuming hyaluronic acid and collagen to improve drug delivery and survival[81]. Minnelide can cause irreversible CAFs to have passive morphologies and diminish the generation of TGF-β and ECM to inhibit TEC proliferation, which results in tumor regression[82]. Our results indicate that, compared to conventional chemotherapy alone, the combination of low doses of Minnelide with Gemcitabine + nab-paclitaxel significantly inhibits pancreatic tumor progression and improves the survival rate of tumor bearing mice[83]. Skorupan et al[15] found that pancreatic Aden squamous carcinoma (ASCP) is a highly invasive pancreatic cancer variant, and MYC is overexpressed. Minnelide is an oral anti-super enhancer drug, which can reduce MYC expression. Minnelide has the potential to be a new treatment option for both main and metastatic colon cancer because it can kill colon cancer cells *in vitro*, slow the growth of primary colon cancer, and transfer colorectal cancer to the liver *in vivo*[84]. An *in vitro* study[85] shows that Minnelide can reduce the activity of MKN28, a moderately differentiated intestinal gastric adenocarcinoma cell line, and MKN45, a poorly differentiated diffuse gastric adenocarcinoma cell line, and that the combination of irinotecan (CPT-11) and Minnelide may be an effective treatment for gastric adenocarcinoma.

Minnelide and other systemic tumors

In addition to pancreatic cancer and gastrointestinal cancer, Minnelide can also inhibit the activity of NF-κB to prevent transfer. It can ef-

fectively reduce the tumor burden and metastasis potential of osteosarcoma, minimize the impact on osteoblasts of the tested compound, and may develop into a very effective new type of osteosarcoma chemotherapy drug[86]. A new approach for treating metastatic renal cell cancer is Minnelide in combination with anti-DR5 monoclonal antibody[87]. The experiment of Banerjee et al[88] confirmed that the combination of minocycline and sorafenib is a successful combination for the treatment of hepatocellular carcinoma models. In non-small cell lung cancer (NSCLC), Minnelide impairs mitochondrial function by controlling SIRT3 in a P53-dependent way and developing into a potent anticancer drug[89]. Minnelide can also effectively inhibit the proliferation of platinum-sensitive and resistant ovarian cancer cell lines, thereby improving the efficacy of standard chemotherapy, such as carboplatin and paclitaxel[90]. There are also studies that have confirmed that Minnelide can induce prostate cancer cell death by downregulating the androgen receptor (AR) and its splicing variants in prostate cancer cells[91]. Minnelide can dramatically lessen the burden of leukemia by causing cell cycle arrest, cell death, and decreased clonality of leukemia mother cells, according to research conducted on a number of preclinical models[92]. Our research shows that Minnelide is an effective cervical cancer drug, which can inhibit the growth of cervical cancer cells alone or be used in combination with platinum drugs to improve treatment effectiveness[93]. A recent study[94] has found that in Angptl3 gene knockout mice with doxorubicin nephropathy (AN), Minnelide can separately inhibit the TGF- β1-Smad2 and p53 pathways, improving fibrosis and apoptosis, thereby exerting protective effects on AN mice. However, several cases of reversible acute cerebellar toxicity have occurred in Minnelide's clinical trials[95]. Therefore, further research and analysis are needed during the clinical trial process.

PG490-88Na(F6008)

To boost triptolide's water solubility, early research mainly concentrated on the esterification of C-14-OH, which introduces some large polar groups, improving the parent drug's water solubility, absorption and utilization. It is generally believed that the β Orientation of C-14 hydroxyl group is necessary to maintain its strong anticancer activity. Based on this principle, for a long time, to improve water solubility and reduce adverse side effects, the structural modification of C-14 has mainly focused on the carboxylation of C-14 hydroxyl groups, enhancing the water-soluble or nitrogen-containing segments. Among them, PG490-88Na (F6008), a water-soluble prodrug, can effectively prevent acute and chronic rejection reactions in organ transplantation and has been elucidated as an effective anticancer drug[96]. PG490-88 has a stronger anti-cancer effect compared to triptolide, reducing liver and kidney toxicity, providing a reference for the clinical application of triptolide. In the human body, the conversion of PG490-88 to triptolide is unexpected. Therefore, PG490-88 is not the optimal derivative of triptolide used in clinical practice.

PG490-88 and tumor diseases

PG490-88 has been shown to be cytotoxic in tumor cell lines such as H23 (NSCLC), HT1080 (fibrosarcoma), and Colon205 (colon cancer) cells[12]. When PG490-88 is used alone, it can lead to the regression of lung cancer and colon cancer xenograft tumors, and the synergistic effect of PG490-88 and CPT-11 can also lead to tumor regression[96]. In 2003, it entered the first phase of clinical trials for the treatment of solid tumors. However, it failed in the Phase I clinical study due to delayed and insufficient biotransformation *in vivo*. Due to significant individual differences in its pharmacokinetic properties found in the Phase I clinical dose-increasing trial, the process of transforming it into TP in the human body is slow and incomplete, and the degree of transformation is difficult to predict and uncontrollable. Additionally, two deaths occurred, and the clinical trial has been suspended[13].

PG490-88 and inflammatory, immune diseases

Pan et al[97] found that PG490-88 significantly prolonged the survival time of allograft kidneys in acute rejection models in rats and prevented chronic allograft kidney rejection in rats. According to some researchers, PG490-88 can alleviate acute humoral rejection by inhibiting complement activation and T cell infiltration, thereby significantly prolonging the survival time of a canine model after kidney transplantation[98,99]. PG490-88 and tacrolimus synergistically inhibit T cell activation, reducing IFN-c production and NF-AT/NF-κB activity, thereby prolonging the survival time of transplanted kidneys in monkey models[100]. PG490-88 may reduce the release of p-ERK in cisplatin-induced acute kidney injury (AKI), thereby protecting AKI and acute tubular necro-

sis (ATN)[101]. Krishna et al[102] found that PG490-88 can block bleomycin-induced pulmonary fibrosis, which has a potential role in the treatment of idiopathic pulmonary fibrosis. Recent studies[103] have revealed that PG490-88 can block the generation of pro-inflammatory mediators and cytokines, as well as the activation of the NF-κB and MAPK signaling pathways, and eventually act as a lung protective factor in ischemia-reperfusion (I/r) injured rats. In lungs with damaged I/R, PG490-88 can inhibit inflammatory response, damage to tight junction structures, and cell apoptosis. The above experiments prove that PG490-88 has the potential to prevent lung injury induced by I/R.

Other Triptolide Analogs Showing Potential for Clinical Development

MRx102

MRx102 (18-benzoyloxy-19-benzoylfuranotriptolide) is a lactone ring derivative of TPL. MRx102, a highly hydrophobic TPL derivative, is being developed for the treatment of AML. Through the downregulation of the anti-Mcl2 apoptotic proteins XIAP and Mcl2, it can hinder RNA transcription and cause cell death. It produces *in vitro* cytotoxicity to human leukemia cells at nanomolar concentrations and reduces the activity of CD34+AML cells from patient sources[104]. It is believed that it has the least side effects in mouse AML xenotransplantation and is safer than TPL[105]. In addition, studies[16] have shown that it also plays a role in non-small cell lung cancer. IMRx102 appears to disrupt the Wnt signaling pathway in a xenograft model of non-small cell lung cancer (NSCLC), resulting in a decrease in tumor growth and metastasis.

LLDT-246

LLDT-246 inhibited the proliferation of colorectal cancer cell line HCT-116 by attenuating the NF-kB signaling pathway like triptolide. It has been shown that LLDT-246 is a unique triptolide derivative because of its somewhat more significant inhibitory action on NF-kB of colorectal cancer HCT-116 cells and cytotoxicity, which is less harmful to non-cancer cells than its parent molecule[17].

LLDT-288

LLDT-288, a C14b-heterocycle amino methyl substituent triptolide analog, exhibited promising efficacy with extremely low toxicity in a xenograft mouse model of human prostate cancer. In a human prostate (PC-3) xenograft mice model, oral treatment of LLDT-288 showed promising efficacy with relatively low toxicity. Their study also demonstrated that LLDT-288 has broad-spectrum, potent antitumor activity, and is effective against drug-resistant cancer cells, and induces apoptosis *in vitro* but with less toxicity[18].

LLDT-67

LLDT-67 was shown to enhance nerve growth factor synthesis in brain astrocytes in mice with Parkinson's disease. The neuroprotective effects of LLDT-67 have been largely attributed to its ability to enhance NGF synthesis in mesencephalic astrocytes, as well as indirectly rescue dopaminergic neurons through TrkA activation[106].

ZT01

ZT01 is a triptolide derivative with strong anti-inflammatory activity and low toxicity. By preventing the synthesis of pro-inflammatory factors, our findings demonstrated that ZT01 greatly reduced the inflammatory response to sepsis in serum or lung tissue and increased the survival rate of septic mice *in vivo*. The anti-inflammatory activity of ZT01 primarily prevents the pro-inflammatory phenotype of macrophages by blocking TAK1-TAB1 complex formation and subsequent phosphorylation of MKK4 and JNK[107]. Furthermore, by regulating the JAK-STAT signaling pathway, ZT01 significantly inhibits T cell differentiation into Th1 and/or Th17 cell subsets, as well as macrophage differentiation into inflammatory phenotypes, and ZT01 may be a potential IBD candidate for inflammatory bowel disease, warranting further research as a therapeutic approach for patients[19].

Conclusions and Future Perspectives

In the past few decades, the anticancer, anti-inflammatory, and immunosuppressive properties of triptolide have made it a promising drug for treating diseases. We found that the main research areas of triptolide are focused on its anti-inflammatory and anticancer pharmacological effects, as well as toxicity. However, the current research focus is more on its anticancer activity and toxicity. The ability of triptolide to inhibit cancer cell proliferation and induce cancer cell apoptosis in multiple targeted ways makes it a promising anticancer drug. Researchers studied the molecular mechanism of action of triptolide

using chemical biology methods and discovered that XPB/TFIIH may be a physiological target for its anticancer and immunosuppressive actions.

Two derivatives of triptolide, Minnelide and LLDT8, have entered phase II human clinical trials. To some extent, both Minnelide and LLDT8 have addressed the issues of low solubility and toxicity. However, additional effective measures are required to reduce triptolide's potential side effects further and expand its therapy window. For the study of triptolide derivatives, standard derivatization methods include hydroxylation or glycosylation, which can be achieved by cytochrome P450 and glycosyltransferases. The biosynthesis route was also studied using dioxygenases and methyltransferases, which expanded the options for studying triptolide derivatives. Many pathways and targets in the research of the pharmacological action of triptolide derivatives and triptolide are the same, which can provide new ideas for improving triptolide and its derivatives production. In addition to the derivatives obtained by structural modification, it is worth considering the search for other bioactive components with enhanced activity and low toxicity.

With the progress of total synthesis, various triptolide derivatives were synthesized and tested. Meanwhile, some molecular targets responsible for triptolide's various pharmacological actions and toxicity were identified through the design and manufacture of multiple bioactive probes. This will undoubtedly facilitate the design of new triptolide derivatives in the future. However, there are still some problems and new directions to advance triptolide derivatives into clinical treatments:

1) The traditional method of acquisition of triptolide and its derivatives cannot meet the commercial demand. Researchers examined and optimized the synthetic route of triptolide and derivatives by studying the whole synthesis of triptolide. In addition, studies on the chemical synthesis of triptolide derivatives can mainly focus on optimizing and innovative synthetic conditions to increase the amount of triptolide derivatives.
2) Although triptolide has been shown to possess diverse pharmacological activities through functional phenotypic screens *in vitro* and *in vivo*, its precise molecular targets responsible for robust biological activities have not been fully identified. Therefore, it is important to further design and synthesize new bioactive probes of triptolide to identify unexplored molecular targets and map the complete signaling network responsible for its diverse pharmacology and toxicity.
3) The development of triptolide derivatives in combination with other medications would be a useful technique. Combination medication has many advantages, including synergy to improve efficacy, delaying or reducing the incidence of drug resistance and reducing the dose of individual drugs to reduce toxic side effects.
4) In addition to the synthesis of triptolide derivatives, the development of a new triptolide loaded delivery system is a wise strategy to overcome the limitations of clinical applications. For example, small and macrocyclic ligand guided targeting have been investigated, including glucose triptolide conjugates and antibody triptolide conjugates, and demonstrated enhanced efficacy and reduced toxicity in different *in vivo* disease models. Recently, the application of nanotechnology for targeted delivery of triptolide has also shown some success.

With the development of chemical synthesis and the development of an actual synthetic route for triptolide, the future of triptolide and its derivatives as drugs to treat various human diseases seems to have a promising future.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' Contribution

LC proposed idea. LZ, PY, and YQ prepared the draft. WH draw the tables. All authors participated in the revision and finalization of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Data Availability

Data will be made available on request.

Ethics Approval and Informed Consent

Not applicable as the study is a literature review.

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