Drug Design, Development and Therapy

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REVIEW

Research Progress of Triptolide Against Fibrosis

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Abstract: Fibrosis leads to organ failure and death, which is the final stage of many chronic diseases. Triptolide (TPL) is a terpenoid extracted from the traditional Chinese medicine *Tripterygium wilfordii Hook. F* (TwHF). Triptolide and its derivatives (Omtriptolide, Minnelide, (5R)-5-hydroxytriptolide) have been proven to have a variety of pharmacological effects. This study comprehensively reviewed the antifibrotic mechanism of TPL and its derivatives, and discussed the application of advanced nanoparticles (NPs) drug delivery system in the treatment of fibrotic diseases by TPL. The results show that TPL can inhibit immune inflammatory response, relieve oxidative stress and endoplasmic reticulum stress (ERS), regulate collagen deposition and inhibit myofibroblast production to play an anti-fibrosis effect and reduce organ injury. A low dose of TPL has no obvious toxicity. Under pathological conditions, a toxic dose of TPL has a protective effect on organs. The emergence of TPL derivatives (especially Minnelide) and NPs drug delivery systems promotes the anti-fibrosis effect of TPL and reduces its toxicity, which may be the main direction of anti-fibrosis research in the future.

Keywords: triptolide, derivatives, anti-fibrosis, nanoparticles

Introduction

Fibrosis is a pathological deviation from injury repair caused by various causes, like autoimmunity, chronic viral infection, and toxicity (such as drugs, radiation, chronic ischemia, or alcohol), which is usually accompanied by over-deposition of extracellular matrix (ECM) (primarily collagen) and organ function damage.[1,2] Almost every organ system is affected by fibrosis, which can include the heart, liver, kidneys, pulmonary system, and skin.[3] However, the results of clinical treatment of fibrosis are not satisfactory. Tissue fibroproliferative disorders are responsible for nearly 45% of annual deaths from all diseases.[4]

TwHF (Figure 1) was first documented in the Compendium of Materia Medica and is an essential Chinese medicine.[5] It has a long-term clinical application and functions in dispelling wind and dehumidification, promoting blood circulation and dredging collaterals, killing insects and detoxifying, and reducing swelling and pain. Many clinical researches have confirmed the therapeutic effects of TwHF on various diseases including interstitial pneumonia, systemic lupus erythematosus, multiple sclerosis, oral lichen planus, and rheumatoid arthritis.[6–8] Triptolide (TPL) (Figure 2), as the most abundant terpenoid constituent of TwHF, is regarded as the active component with the greatest potential for translation from traditional to modern medicine.[9] Previous investigations have shown that TPL has beneficial roles such as anticancer, anti-inflammatory, and regulation of immunity.[10–12] In recent years, it has also been found to have therapeutic effects on fibrotic diseases, such as renal fibrosis (RF) caused by diabetic nephropathy.[13] However, TPL has limited water solubility, oral bioavailability, and high doses cause serious toxicity, so a variety of TPL derivatives (Figure 2) have been exploited, such as Minnelide, Omtriptolide (PG490-88), (5R)-5-hydroxytriptolide (LLDT-8).[14,15] In addition, the development of advanced technologies such as NPs has completely changed the drug delivery of TPL.[16] In this review, we not only systematically review the pharmacological mechanism of TPL and its derivatives (Table 1, Figure 3), but also introduce the application of the cutting-edge NPs delivery system in TPL anti-fibrosis (Table 2), hoping to provide help for the future research and application of TPL.

Received: 8 March 2024
Accepted: 1 July 2024
Published: 25 July 2024

Figure 1 *Tripterygium wilfordii Hook. F* and its pieces of traditional Chinese medicine.

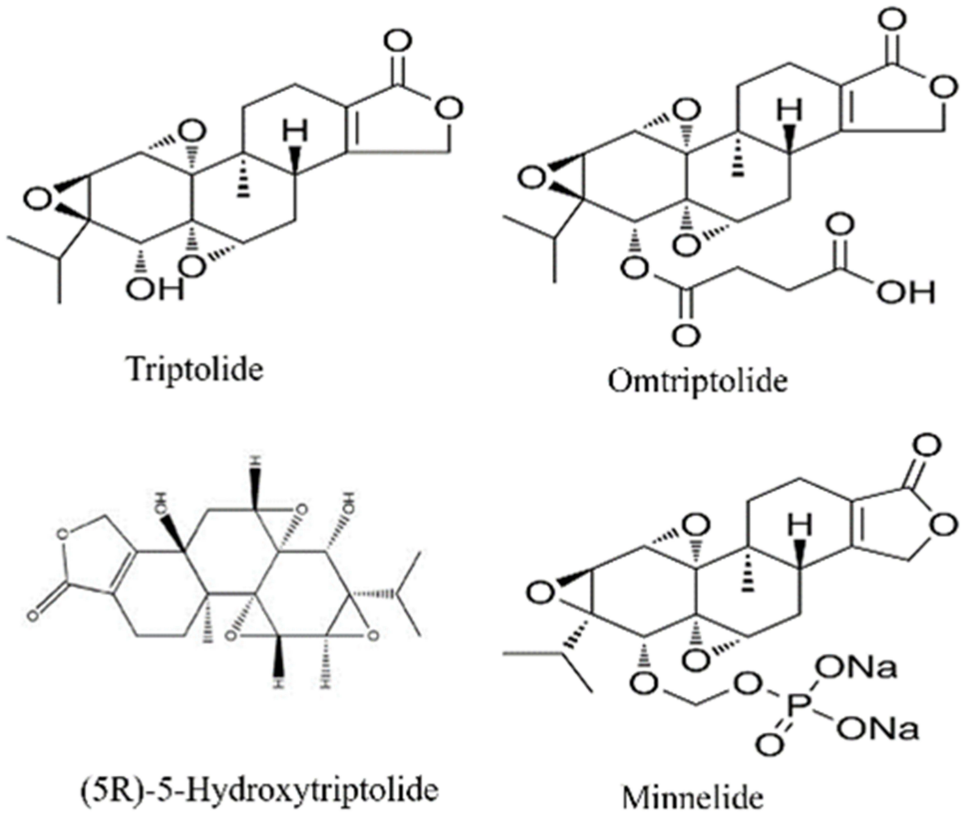

Figure 2 The structures of triptolide and its derivatives.

Table 1 Pharmacological Mechanism of TPL and Its Derivatives

Models	In vitro/In vivo	Effects and Related Mechanisms	Organ	Drug	References
Streptozotocin (STZ) induced DCM in rats, H9c2 cells	Both in vitro and vivo	Inhibit inflammation: NF-κB↓	Cardiac	TPL	[17]
high-sucrose-fat diet induced DCM in rats	In vivo	Inhibit inflammation and fibrosis: TLR4/NF-κB↓	Cardiac	TPL	[18]
Isoproterenol (ISO) induced MF in rats	In vivo	Inhibit inflammation and fibrosis: NF-κB / NLRP3↓	Cardiac	TPL	[19]
Transverse aortic constriction induced MF in rats	In vivo	Inhibit inflammation and fibrosis: TGF-β1/Smad 3, NLRP3↓	Cardiac	TPL	[20]
rat CFbs	In vitro	Inhibit cell proliferation and fibrosis: TGF-β1 /Smad3↓	Cardiac	TPL	[21]
suprarenal abdominal aorta constriction induced MF in rats	In vivo	Inhibit inflammation and fibrosis: Ang II, TGF-β, NF-κB↓	Cardiac	TPL	[22]
Ang II-induced cardiac fibrosis in mice, mouse CFbs	Both in vitro and vivo	Inhibit fibrosis: CyPA / CD147, NLRP3, NOX2, TGF-β/MAPK, TGF-β/Smad2/ Smad3↓	Cardiac	TPL	[23]
ISO induced MF in rats	In vivo	Inhibit myocardial damage and fibrosis: Foxp3↓	Cardiac	TPL	[24]
Transverse aortic constriction induced MF in mouse, Mouse Cardiac Muscle Cell Line	Both in vitro and vivo	Inhibit EndMT: USP14/Keap1/Nrf2, Snail, Slug and Twist↓	Cardiac	TPL	[25]
ISO induced MF in rats	In vivo	Inhibit fibrosis: PTEN↑	Cardiac	TPL	[26]
RIPF in rats, mouse AMs isolated from the BALM model, NIH3T3 cells	Both in vitro and vivo	Inhibit oxidative stress and fibrosis: AMs /NADPH oxidase /ROS/myofibroblasts ↓	Pulmonary	TPL	[27]
HFL-1 cells	In vitro	Inhibit cells proliferation, migration and fibrosis: FAK/calpain↓	Pulmonary	TPL	[28]
BLM induced PF in rats, primary mouse lung fibroblasts	Both in vitro and vivo	Inhibit fibrosis: TGF-β/SMAD, MMPs/LOX/integrin, integrin-β1/FAK/YAP↓	Pulmonary	TPL	[29]
Radiation induced PF in mouse	In vivo	Inhibit fibrosis: IKKβ/NFκB, LOX↓	Pulmonary	TPL	[30]
Radiation induced PF in mouse, NIH3T3 cells	Both in vitro and vivo	Inhibit the activation of myofibroblasts: TGF-β1/ERK/Smad3↓	Pulmonary	TPL	[31]
Paraquat induced PF in mouse, BEAS–2B cells	Both in vitro and vivo	Inhibit cells migration and EMT: TGF-β↓	Pulmonary	TPL	[32,33]
BLM induced PF in mouse	In vivo	Inhibit EMT: NF-κB/Twist 1↓	Pulmonary	TPL	[34]
BLM induced PF in mouse	In vivo	Relieve ERS: GRP 78, CHOP↓	Pulmonary	TPL	[35]
BLM induced PF in mice, NHLF cells	Both in vitro and vivo	Inhibit fibrosis: TGF-β↓	Pulmonary	PG490-88	[36]
DMN induced HF in rats, HSC-T6 cells	Both in vitro and vivo	Inhibit inflammation and fibrosis: NF-κB↓	Hepatic	TPL	[37]
CCL4 induced HF in mouse, mouse PBMCs,	Both in vitro and vivo	Regulates immunity and fibrosis: Th1, Th2, Th17 cells↓, Treg cells↑	Hepatic	TPL	[38]
Bile duct ligation induced HF in mice, Human intrahepatic biliary epithelial cells	Both in vitro and vivo	Inhibit tissue necrosis, inflammation and fibrosis: RelB↓	Hepatic	TPL	[39]
obese db/db mice and methionine/choline-deficient diet-induced nonalcoholic fatty liver disease in mice	In vivo	Inhibit inflammation and fibrosis: AMPK↑	Hepatic	TPL	[40]
DOCA-salt hypertension induced renal injury in mice	In vivo	Inhibit inflammation: NF-κB↓	Renal	TPL	[41]
NRK-49F cells	In vitro	Inhibit fibrosis: p38, ERK1/2↑Smad2↓	Renal	TPL	[42]
STZ induced diabetes in rats	In vivo	Inhibit fibrosis: RANTES↓	Renal	TPL	[43]
high-fat diet and STZ induced DKD in rats, HMCs	Both in vitro and vivo	Regulate autophagy and fibrosis: Akt, mTOR, PTEN↑, miR-141-3p↓	Renal	TPL	[44]
high-fat diet induced DKD, HK-2 cells	Both in vitro and vivo	Inhibit EMT: miR-188-5p /PTEN /PI3K/AKT↓	Renal	TPL	[45]
db/db diabetic mice, SV40-MES-13 cells	Both in vitro and vivo	Inhibit oxidative stress and fibrosis: Nrf2, HO-1, SOD↑ ROS, NOX4, GSK3β, p-GSK3β↓	Renal	TPL	[46]

(*Continued*)

https://doi.org/10.2147/DDDT.S467929 DovePress

Table 1 (Continued).

Models	In vitro/In vivo	Effects and Related Mechanisms	Organ	Drug	References
db/db diabetic mice	In vivo	Inhibit EMT: Kindlin-2, TGF-β/Smad3↓	Renal	TPL	[47]
Adriamycin induced AN in mice, primary mouse podocytes	Both in vitro and vivo	Relieve injury: ROS, cytochrome c↓	Renal	Minnelide	[48]
Adriamycin induced AN in Angptl3 knockout (Angptl3-/-) mice	In vivo	Inhibits apoptosis, inflammation and fibrosis: TGF-β1/Smad2 and p53↓	Renal	Minnelide	[49]
subepithelial myofibroblasts from patients undergoing a partial colectomy for carcinomas	In vitro	Inhibit inflammation and fibrosis: NF-κB↓	Intestinal	TPL	[50]
C3H/HeJBir IL-10−/− and wild-type mice, intestinal fibroblasts from anastomotic tissue specimens from Crohn's patients and paired normal tissues adjacent to the anastomosis	Both in vitro and vivo	Inhibit cells proliferation and migration, inflammation and fibrosis: miR-16-1/HSP70↓	Intestinal	TPL	[51,52]
C3H/HeJBir IL-10−/− mice	In vivo	Inhibit inflammation: miR-155↓, SHIP-1↑	Intestinal	TPL	[53]
Laser photocoagulation induced CNV in mice, THP-1 cells, ARPE-19 cells, EA.hy926 cells	Both in vitro and vivo	Inhibit inflammation and fibrosis: TGF-β/Smad↓	Retina	TPL	[54]
Wild-type and systemic Hic-5 knockout C57BL/6 mice, PSCs from pancreas of Hic-5 knockout C57BL/6 mice	Both in vitro and vivo	Inhibit fibrosis: NF-κB/p65↓	Pancreatic	TPL	[55]
Human fibroblasts, laminectomy induced epidural fibrosis in rats	Both in vitro and vivo	Regulates cell proliferation, migration, apoptosis, autophagy and fibrosis: PI3K/AKT/mTOR↓	Epidural	TPL	[56]

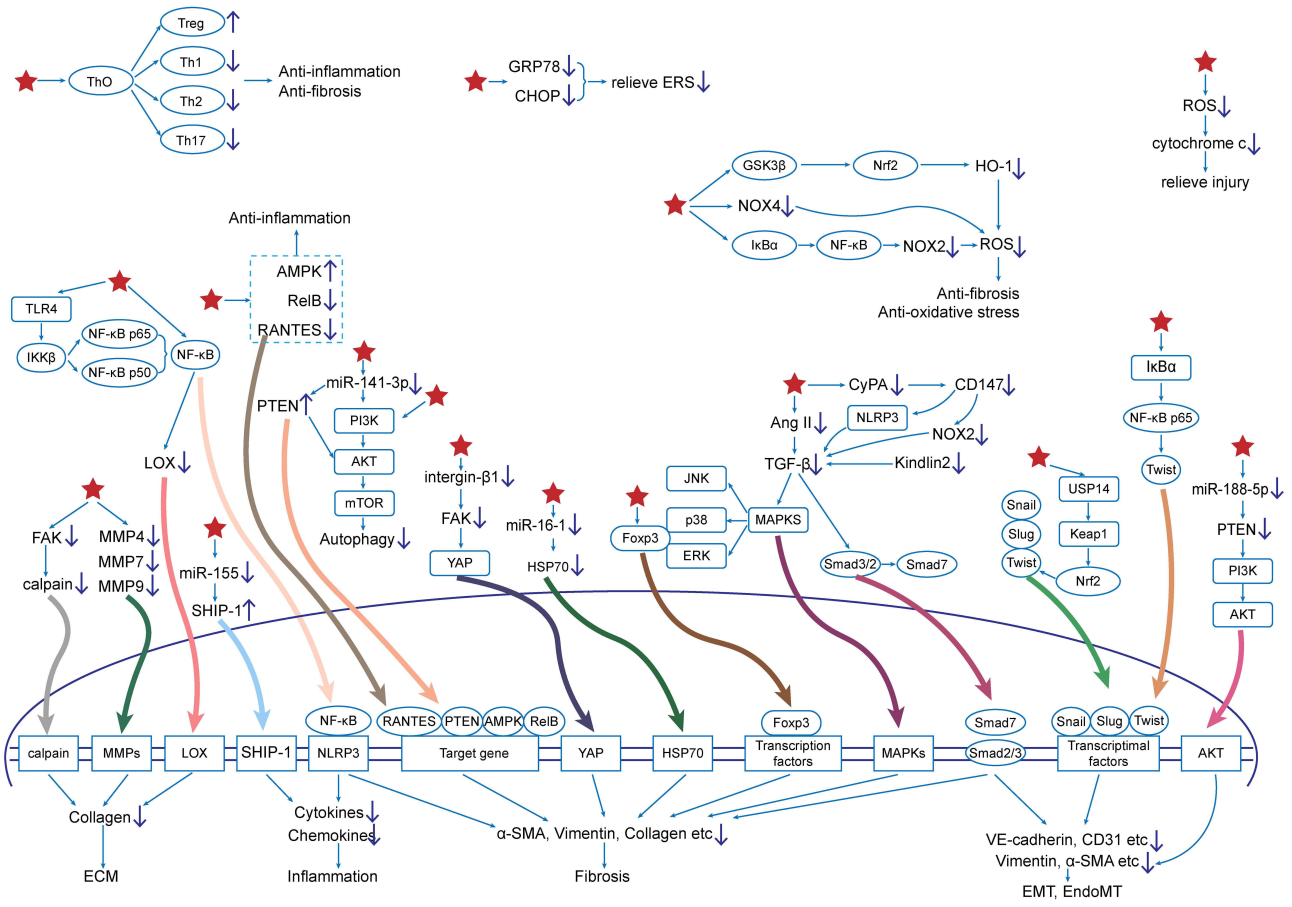

Figure 3 Mechanism diagram of triptolide and its derivatives against fibrosis. Star indicates TPL and its derivatives.

Anti-Fibrotic Effect of TPL

Heart

Myocardial fibrosis (MF) exists in almost all chronic heart diseases, and damages heart function, playing a crucial role in the progression and consequences of heart failure. Abnormal proliferation and activation of cardiac fibroblasts (CFbs), deposition of ECM, and formation of scar tissue are its major pathological features.[59,60]

Inflammatory mediators are implicated in the pathogenesis of MF. Long-term chronic inflammation may lead to cardiomyocyte necrosis, and necrotic cardiomyocytes are replaced by collagen scars to cause reparative fibrosis.[61] NF-κB pathway is a classic inflammatory pathway. It has been shown that TPL can inhibit Toll-like receptor 4 (TLR4) /NF-κB and NF-κB pathways to improve cardiac immune inflammatory response and alleviate myocardial fibrosis in rats with diabetic cardiomyopathy (DCM).[17,18] TPL can improve the expression of fibrosis-associated factors, such as transforming growth factor (TGF)-β1, type I collagen (Col I), and type III collagen (Col III) mRNA, in rats by inhibiting the activation of NOD-like receptor thermal protein domain associated protein 3(NLRP3) inflammasome mediators downstream of the NF-κB pathway.[19] TPL also depresses pro-fibrotic TGF-β1 pathways and inflammatory mediators downstream of NLRP3 inflammasome, such as IL-1β, IL-18, monocyte chemotactic protein (MCP)-1 and vascular cell-adhesion molecule −1, and inhibits infiltration of macrophages in a dose-dependent manner.[20]

Via direct and TGF-β-mediated actions, the local release of angiotensin II (Ang II) plays an effective role in activating and stimulating cardiac fibrosis.[62,63] In vitro, TPL inhibited Ang II-induced CFbs proliferation and decreased Ang II-induced fibrosis signaling TGF-β1 /Smad3 expression.[21] In vivo, TPL treatment could inhibit the generation of pro-fibrosis factors such as Ang II and TGF-β induced by pressure overload, and significantly suppress left ventricular end-diastolic pressure, myocardial collagen volume fraction (CVF), and Col I/III deposition.[22] The down-regulation of pro-inflammatory cytokines

Table 2 Application of NPs Delivery System in TPL Anti-Fibrosis

Models	In vitro/In vivo	Effects	Organ	Drug	References
CM (M-0531) induced autoimmune myocarditis in mice	In vivo	Increase the solubility and bioavailability of TPL, Inhibit fibrosis and inflammation: NF-κB↓	Cardiac	TPL nanosuspensions	[57]
RAW 264.7 cells, H9C2 cells, myocardial infarction induced by ligation of left anterior descending coronary artery in mice	Both in vitro and vivo	Relieve TPL toxicity, inhibit fibrosis and cardiomyocytes apoptosis, long-term anti-inflammatory	Cardiac	TPL@PLGA@F127	[58]
Laser photocoagulation induced CNV in mice, THP-1 cells, ARPE-19 cells, EA.hy926 cells	Both in vitro and vivo	Enhance the anti-inflammatory and anti-fibrosis effects of TPL	Retinal	TPL-nanolip-PEG	[54]

Abbreviations: TPL, triptolide; TwHF, Tripterygium wilfordii Hook. F; ERS, endoplasmic reticulum stress; NPs, nanoparticles; ECM, extracellular matrix; RF, renal fibrosis; MF, Myocardial fibrosis; CFbs, cardiac fibroblasts; TLR4, Toll-like receptor 4; DCM, diabetic cardiomyopathy; Col I, type I collagen; Col III, type III collagen; NLRP3, NOD-like receptor thermal protein domain associated protein 3; MCP, monocyte chemotactic protein; Ang II, angiotensin II; TGF, transforming growth factor; CyPA, Cyclophilin A; Foxp3, forkhead box protein P3; USP14, Ubiquitin-Specific Protease 14; Keap1, Kelch-like ECH-Associated Protein 1; CVF, collagen volume fraction; PF, pulmonary fibrosis; RIPF, radiation-induced pulmonary fibrosis; AMs, alveolar macrophages; NADPH, Nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; FAK, focal adhesion kinase; MMPs, matrix metalloproteinases; IKKβ, inhibitor of kappa B kinase; LOX, lysyl oxidases; EMT, epithelial-mesenchymal transdifferentiation; EndMT, endothelial-mesenchymal transition; α-SMA, α-smooth muscle actin; AEC II s, alveolar type II epithelial cells; GRP78, glucose-regulated protein 78; CHOP, C/EBP homologous protein; HF, Hepatic fibrosis; HSCs, hepatic stellate cells; DMN, dimethylnitrosamine; CCL4, carbon tetrachloride; AMPK, AMP-activated protein kinase; DOCA, deoxycorticosterone acetate; RANTES, regulation upon activation of normal T-cell expressed and secreted; DKD, diabetic kidney disease; PTEN, phosphatase and tensin homologue; NOX, NADPH oxidase; GSK3β, glycogen synthase kinase 3 beta; Nrf2, nuclear factor E2-related factor 2; HO-1, heme oxygenase-1; HSP70, heat shock protein 70; CNV, choroidal neovascularization; CD, Crohn's disease; AN, Adriamycin Nephropathy; Angptl3, anti-angiogenin-like protein 3; mAb, monoclonal antibody; STZ, Streptozotocin.

(IL-1β and IL-6) in serum and NF-κB in myocardial tissue was also observed in the TPL group.[22] Further studies have shown that TPL can alleviate MF by attenuating Ang II-induced TGF- β signal by inhibiting intracellular and extracellular Cyclophilin A (CyPA) / CD147.[23] Transcriptional factors participate in the modulation of MF. TPL can improve myocardial injury and myocardial fibrosis score and inhibit cardiac hypertrophy by up-regulating the expression of forkhead box protein P3 (Foxp3).[24] TPL can also significantly improve endothelial-mesenchymal transition (EndMT) and alleviate MF by regulating Ubiquitin-Specific Protease 14 (USP14)/ Kelch-like ECH-Associated Protein 1 (Keap1)/ Nuclear factor erythroid 2-related factor 2 (Nrf2) pathway and transcription factors such as Snail, Slug and Twist.[25] In addition, the effect of TPL on reducing myocardial collagen content, perivascular collagen area, and myocardial CVF was related to the up-regulation of phosphatase and tensin homologue (PTEN).[26]

Lung

A group of chronic lung conditions known as pulmonary fibrosis (PF) causes progressive damage to the pulmonary interstitium, impairing gas exchange, producing dyspnea, lowering quality of life, and ultimately leading to respiratory failure and death.[64]

Studies have confirmed that inflammation and oxidative stress are closely associated with the occurrence and development of PF.[65] Yang et al[66] found that TPL can inhibit the production of pro-fibrotic cytokines (IL-1β, TGF-β1, and IL-13) in the radiation-induced pulmonary fibrosis (RIPF) model, and improve the 5-month survival rate, lung density, and function. Subsequent studies have identified alveolar macrophages (AMs) as a major source of reactive oxygen species (ROS) in RIPF, and TPL exerts its antifibrotic effects by inhibiting myofibroblast activation and collagen accumulation via the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-ROS axis in AMs.[27] TPL also represses migration and invasion of lung fibroblasts and inhibits the expression of fibrosis factors Col I and Col III and the production of inflammatory factors IL-6 through the focal adhesion kinase (FAK)/troponin axis.[28]

The increase in myofibroblast production and ECM protein deposition are some pathological features associated with the development of PF.[67] It has been shown that TPL can not only regulate matrix metalloproteinases (MMPs), which are involved in ECM deposition but also mediate TGF-β1/Smad fibrosis signal pathway to inhibit the transformation of lung fibroblasts into myofibroblasts.[29,68] It was also found that TPL could block integrin-β1/FAK/YAP signal transduction in the biomechanical stress transduction pathway and attenuate the pro-fibrotic effect of fibrogenic ECM on fibroblasts via integrin suppression.[29] In addition, TPL can inhibit PF through inhibitor of kappa B kinase (IKKβ)/NFκB pathway and

reduce the production of lysyl oxidases (LOX) which catalyzes matrix protein cross-linking.[29,30] Zhang et al[31] found that TPL can inhibit TGF-β1/ERK/Smad3 pathway and reduce myofibroblast activation both in vivo and in vitro. In addition, in PF, myofibroblasts can also originate from cell sources other than fibroblasts, such as epithelial and endothelial cells, which gain a mesenchymal phenotype through epithelial-mesenchymal transdifferentiation (EMT) or EndMT, and show classic markers of myofibroblast differentiation, like vimentin, α-smooth muscle actin (α-SMA) expression and others.[69,70] Many studies demonstrated that TPL inhibits the migration and invasion of human lung epithelial cells and inhibits the expression of EMT-related factors through TGF-β1 signal.[32,33] TPL can reverse the EMT of alveolar type II epithelial cells (AEC II s) and relieve PF by regulating NF-κB/Twist1 signal.[34] TPL can also inhibit the expression of glucose-regulated protein 78 (GRP78) and C/EBP homologous protein (CHOP) in AEC II s, relieve ERS, reduce collagen deposition in lung tissue, and significantly improve lung function in mice.[35]

Liver

Hepatic fibrosis (HF) is mainly induced by chronic hepatotoxic injury (such as chronic hepatitis and non-alcoholic steatohepatitis) and cholestatic injury (such as primary and secondary cholangitis, primary sclerosing cholangitis and biliary atresia).[71]

The main mesenchymal cells in the liver are hepatic stellate cells (HSCs), and activated HSCs is a key factor in the pathological progression of HF.[72] Chong et al[37] have shown that TPL can inhibit the expression of fibrosis factor α-SMA through anti-NF-κB activation pathway. In addition, TPL treatment significantly reduced the increase of inflammatory cytokines (TNF-α and IL-6) induced by dimethylnitrosamine (DMN) in rats. Immune regulation is a key factor in the pathological process of fibrosis. Jiang et al[38] reported for the first time that TPL attenuates carbon tetrachloride (CCL4)-induced HF by modulating the differentiation of CD4+T (Th2, Th1, Th17, and Treg) cells. RelB is related to liver fibrosis. By lowering the expression of RelB in bile duct cells, TPL can suppress the bile duct response brought on by common bile duct ligation, hence lowering liver damage, fibrosis, and inflammation.[39] TPL can also improve liver lipogenesis, HF, and fatty acid oxidation in nonalcoholic fatty liver disease mice by activating AMP-activated protein kinase (AMPK).[40]

Kidney

RF, particularly tubulointerstitial fibrosis, is the primary indicator and dependable prognostic index of renal insufficiency, including glomerulosclerosis, renal tubule atrophy, and renal interstitial fibrosis.[73,74] It is also a common marker and pathway of several progressive chronic kidney diseases.

TPL has multiple protective effects on RF, including reducing inflammatory cell infiltration and fibrosis, reducing the expression of many chemokines and cytokines, and reducing renal injury. It was shown that TPL significantly decreased macrophage and myofibroblast infiltration and collagen deposition in the renal interstitial fibrosis model.[75] Similarly, in the model of renal injury induced by deoxycorticosterone acetate (DOCA)-salt hypertension, TPL can inhibit the NF-κB pathway to protect cells from inflammatory damage and reduce renal collagen levels.[41] Zhu et al[42] found that TPL can inhibit ECM synthesis in NRK-49F cells by regulating the activities of Smad2, p38, and ERK1/2. It was shown that TPL ameliorated glomerulosclerosis and interstitial fibrosis in diabetic rats in association with inhibition of regulation upon activation of normal T-cell expressed and secreted (RANTES) overexpression in renal tissues.[43] MicroRNAs are small non-coding RNAs that play an influential role in the fight against RF. Li et al[44] found that TPL can relieve RF caused by diabetic kidney disease (DKD) by restoring autophagy through miR-141-3p/ PTEN/Akt/mTOR pathway. Subsequent studies confirmed that TPL can improve renal tubulointerstitial fibrosis by targeting miR-188-5p/PTEN/PI3K/AKT signal pathway to reverse tubulointerstitial fibrosis induced by high glucose.[45] More importantly, TPL can delay the development of nephropathy in diabetic rats, especially in the stage of massive albuminuria, which may be related to the inhibition of monocyte-macrophage aggregation and the reduction of inflammatory factor expression by TPL.[76] Fan et al[46] have shown that TPL can not only improve the proteinuria of DKD mice, but also regulate the expression of superoxide dismutase (SOD), ROS, and prototype NADPH oxidase (NOX) 4 in kidney tissue to improve oxidative stress and alleviate RF in DKD by regulating glycogen synthase kinase 3 beta (GSK3β)/ Nrf2/heme oxygenase-1 (HO-1) signal transduction pathway. In addition, TPL was protective against structural damage and loss of function of podocytes in DKD mice.[47] TPL alleviates diabetes-induced podocyte EMT by inhibiting TGF- β1/Smad3 signal pathway and kindlin-2.[47]

Intestine

Intestinal fibrosis is a common complication of chronic inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease (CD).[77] Previous studies have shown that TPL inhibits IL-1β-induced expression of IL-8, MCP-1, and MMP-3 in human colonic subepithelial myofibroblasts by suppressing NF-κB activity.[78] In the colon fibrosis model of chronic colitis, TPL can reduce the deposition of ECM and the production of total collagen in the colon, and inhibit the expression of Col I protein and collagen Iα1 mRNA in myofibroblasts.[50] Ileocecal anastomotic fibrosis and stricture are common complications after ileocecal resection of CD. Hou et al[51] reported that TPL can improve the inflammation and fibrosis of CD anastomotic fibrosis mice through miR-16-1/heat shock protein 70 (HSP70) signal. A subsequent study showed that TPL could also inhibit the migration, proliferation, and fibrosis of fibroblasts derived from ileocolon anastomosis in CD patients by regulating miR-16-1/HSP70 pathway in vitro.[52] Similarly, TPL can also target miR-155/SHIP-1 signal pathway to reduce the expression of pro-inflammatory cytokines in CD anastomotic fibrosis mice.[53]

Others

Retinal fibrosis is one of the end-stage complications of neovascular age-associated macular degeneration, leading to severe, permanent, and high risk of irreversible visual impairment.[79] The studies of Lai et al[54] showed that TPL inhibited the production of vascular endothelial growth factor and neovascularization in retinal fibrosis mice related to choroidal neovascularization (CNV), promoted M2 macrophage polarization, and mediated TGF-β1/Smad signal pathway to improve EMT/EndoMT. In vivo studies have shown that TPL inhibits the expression of IL-6 and α-SMA mediated by the NF-κB/p65 pathway, thereby alleviating pancreatic fibrosis in mice with chronic pancreatitis.[55] Ileocolic anastomotic fibrosis and stenosis are common complications after CD ileocolic resection. TPL can improve epidural fibrosis by inhibiting PI3K/AKT/mTOR signal, inhibiting fibroblast proliferation, and stimulating apoptosis and autophagy.[56]

Antifibrotic Effect of Triptolide Derivatives

When a phosphate group is added to TPL, a water-soluble derivative called Minnelide is produced, which is widely used in the treatment of cancer.[10] Li et al[48] have shown that Minnelide alone can significantly alleviate proteinuria and renal injury in Adriamycin Nephropathy (AN) mice, which is related to the ROS-mediated mitochondrial pathway. However, Minnelide combined with anti-angiogenin-like protein 3 (Angptl3)-FLD monoclonal antibody (mAb) almost completely improved the proteinuria and restored the ultrastructure of podocytes in AN mice, which was associated with the promotion of podocyte autophagy and suppression of apoptosis.[80] Subsequent studies have demonstrated that Minnelide can reduce the expression of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) in Angptl3 knockout AN mice, and improve apoptosis and fibrosis through TGF-β1/Smad2 and p53 signal.[49]

Compared with TPL, LLDT-8 substituted hydrogen with a hydroxyl group at C-5 position, and PG490-88 introduced fatty acid structure at C-14 position. They play an active role in the therapy of PF. In the bleomycin (BLM)-induced PF mouse model, LLDT-8 could alleviate weight loss and increase lung index, reduce the production of inflammatory cells (neutrophils and lymphocytes) and cytokines (IL-4, TNF-α, and TGF-β), promote the activity of antioxidant factor SOD, inhibit the level of hydroxyproline and improve lung histological injury.[81] In the same model, PG490-88 significantly decreased the number of myofibroblasts and blocked the increase of TGF-β gene expression induced by BLM in human lung fibroblasts.[36] The latest studies have shown that LLDT-8 can suppress the generation of inflammatory and fibrogenic factors by macrophages to improve proteinuria and structural renal damage and delay fibrosis in DKD mice.[82]

Application of Nanoparticle Drug Delivery System in Anti-Fibrosis of TPL

Although studies have shown that low-dose TPL has no obvious toxicity, a toxic dose of TPL has a protective effect on organs under pathological conditions.[15,83] But the toxicity of TPL is still a concern. The use of NPs can not only improve the dissolution, transport and cellular uptake of bioactive components, but also reduce the toxicity of TPL.[16,84] At present, the NPs carrier technology used in TPL anti-fibrosis includes nano-suspension, nano-gel, and nano-liposome. Nanosuspensions are a versatile formulation method for improving drug delivery of hydrophobic drugs and one of the most prosperous ways to improve the performance of poorly water-soluble drugs.[85] Li et al[57] used TPL nano-suspension

to treat autoimmune myocarditis rats, delayed left ventricular remodeling, and significantly improved fibrosis indexes such as myocardial collagen proliferation, CVF, and perivascular collagen area, I/ III collagen ratio. NF-κB pathway may partially mediate the decrease of peripheral blood inflammatory factors, as IL-1, TNF- α, IL-6, and MCP-1. Wang et al[58] combined with FDA-approved polylactic acid-glycolic acid copolymer (PLGA) NPs and F127 hydrogel, prepared TPL-loaded nano-hydrogel platform (TPL@PLGA@F127), which can reduce the hepatotoxicity by releasing TPL more slowly and stably. The study has shown that TPL@PLGA@F127 can promote the polarization of macrophages to M2 (anti-inflammatory cells) on the 3rd day after myocardial infarction to play a long-term anti-inflammatory effect, inhibit myocardial fibrosis, and protect cardiomyocytes, and improve cardiac function[58] Liposome is one of the most mature nano-delivery carriers, and it is one of the few nano-preparations used in clinical treatment. Its particle size ranges from 50 to 1000nm.[86] Lai et al[54] showed that polyethylene glycol nanoliposomes (TPL-nanolip-PEG) loaded with TPL could enhance the inhibitory effect of TPL on the infiltration of retinal fibrosis and M2 macrophages, and had no toxic effect on the morphology and function of the retina.

Discussion and Prospect

TPL and its derivatives have an obvious anti-fibrosis effect and can play a role in a variety of tissues and organs. The anti-fibrosis mechanisms of TPL and its derivatives can be summarized as follows: (1) relieving oxidative stress and ERS; (2) inhibiting immune inflammatory response; (3) regulating collagen deposition (4) inhibiting myofibroblast production; (5) regulating cell migration, proliferation, apoptosis, and autophagy.

However, at present, the anti-fibrosis studies of TPL and its derivatives are based on the level of cellular and animal research, and lack of clinical data verification, so further strict large-scale randomized controlled trials and further scientific research should be carried out to fully evaluate its clinical efficacy and safety. In addition, the application of TPL derivatives, especially Minnelide, and NPs delivery systems, to overcome the water solubility and toxicity of TPL is a promising treatment and should be focused on.

Acknowledgments

This work has been supported by Henan Province Traditional Chinese Medicine Inheritance and Innovation Talent Project (Zhongjing Plan) (CZ0237-02), Henan Province Traditional Chinese Medicine Research Special Project (20-21ZY1016), Zhengzhou Collaborative Innovation Project (2023XTCX048) and Henan University of Traditional Chinese Medicine 2022 graduate research and Innovation Ability Improvement plan (2022KYCX043).

Disclosure

The authors report no conflicts of interest in this work.

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