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Triptolide for cardio-cerebrovascular diseases: efficacy-toxicity paradox and translation

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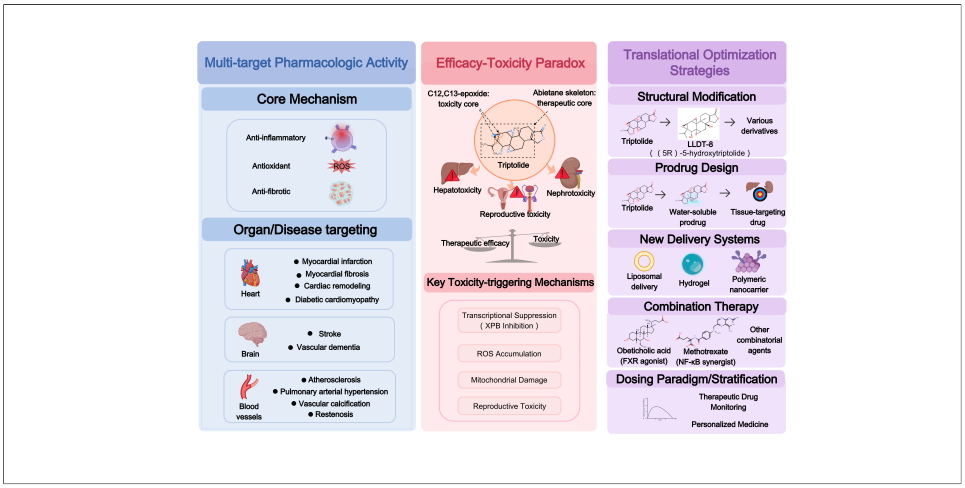

Abstract

Cardiovascular and cerebrovascular diseases remain the leading causes of death and disability worldwide. Triptolide (TP), an epoxy diterpene lactone from *Tripterygium wilfordii* Hook F, exhibits potent anti-inflammatory, immunomodulatory, antioxidant, and anti-fibrotic activities, yet its clinical use is severely limited by marked toxicity within a narrow therapeutic window, an efficacy-toxicity paradox. This review synthesizes evidence for TP's protective effects across myocardial infarction, atherosclerosis, myocardial fibrosis, cardiac remodeling, diabetic cardiomyopathy, ischemic stroke, and vascular dementia. We delineate the context-dependent regulation of its core pathways, particularly the nuclear factor kappa-light-chain-enhancer of activated B cells/NOD-like receptor protein 3 inflammatory axis and the nuclear factor erythroid 2-related factor 2/heme oxygenase-1

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antioxidant system, in which the same molecule shifts from cytoprotection to cytotoxicity according to concentration and cellular context. A major focus is the efficacy-toxicity duality: we summarize the cellular and molecular mechanisms underlying TP-induced hepatotoxicity, nephrotoxicity, and reproductive toxicity, and discuss how these toxicities constrain its clinical translation. To address these translational roadblocks, we critically evaluate optimization strategies, including novel drug delivery systems, water-soluble prodrugs, structural modification of the reactive C12, C13-epoxide toxicity core, and rational combination therapies. By integrating mechanistic insights with practical translational strategies, this review provides a roadmap for transforming TP from a potent but hazardous natural compound into a safer, effective therapeutic for cardio-cerebrovascular diseases.

INTRODUCTION

Cardiovascular diseases (CVDs) and cerebrovascular diseases (CBVDs) remain the leading causes of death and disability worldwide. Epidemiological projections indicate that by 2050, the prevalence of CVDs will increase by 90.0%, and the number of cardiovascular deaths will rise by 73.4%, reaching an estimated 35.6 million[1]. Cardiometabolic factors, such as obesity and hypertension, drive systemic metabolic dysregulation and vascular injury, whereas behavioral and environmental exposures including smoking, unhealthy diet, and air pollution provoke chronic low-grade inflammation. These drivers interact with genetic susceptibility and psychosocial stress to accelerate the pathogenesis of cardio-cerebrovascular diseases[2]. Currently, first-line therapies such as statins and antiplatelet agents are widely used to control these risk factors. Although statins have been shown to exert various pleiotropic effects, including anti-inflammatory and plaque-stabilizing properties, high residual cardiovascular risks and long-term adverse effects (e.g., statin-associated muscle symptoms or elevated liver enzymes) remain significant clinical challenges[3]. Furthermore, their capacity to fully reverse advanced pathological changes, such as established fibrosis and structural remodeling, often remains limited in clinical practice[3]. These limitations provide a rationale for identifying agents that target multiple pathways and disease stages. Natural compounds, such as herbal extracts and their purified constituents, have therefore gained widespread attention as alternative or adjunctive treatments for cardio- cerebrovascular diseases[4].

Tripterygium wilfordii Hook F (TWHF) has a documented medicinal history dating back to the Compendium of Materia Medica. Traditionally used to relieve joint swelling, treat rheumatic pain, and manage eczema, it is a quintessential herb for dispelling wind-dampness in traditional Chinese medicine (TCM)[5]. Triptolide (TP; chemical structure shown in Figure 1), a diterpenoid triepoxide featuring a unique abietane skeleton with three epoxy groups and an α,β-unsaturated γ-lactone ring, is the principal bioactive diterpenoid epoxide isolated from TWHF and embodies a striking pharmacological duality. While exhibiting multiple potent activities, including anti-inflammatory, immunosuppressive, and anti-tumor effects, TP also carries significant toxicity, particularly hepatotoxicity, which has greatly hindered its clinical application[6,7]. Due to its outstanding research value, TP has been highlighted by Cell as one of the natural compounds with potential for modern drug development[8]. Given its inherent efficacy-toxicity duality, studies on TP must shift beyond descriptive observation toward precise mechanistic investigations, with a focus on benefit-risk assessment and feasible translational strategies.

In this review, the term "efficacy-toxicity paradox" refers specifically to the translational dilemma in which TP's potent multi-target efficacy is inseparable from its narrow therapeutic window and idiosyncratic organ toxicity within a clinically usable dose range, rather than to the generic pharmacological principle that dose determines effect. This review provides a holistic and critical analysis of TP's potential in cardio-cerebrovascular diseases [Figure 1]. We first present an updated overview of TP's pharmacokinetic limitations, which underlie its translational challenges. We then deconstruct its core pharmacological effects, emphasizing the context-dependent nature of its actions, particularly in oxidative stress. A central and novel

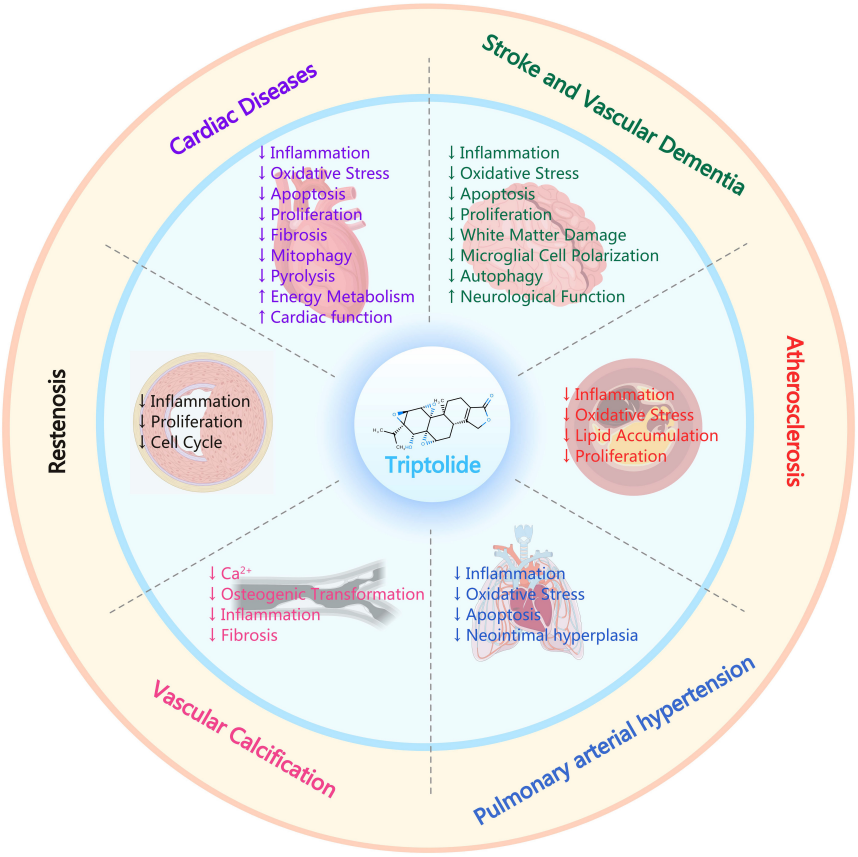

Figure 1. Schematic illustration of the pleiotropic protective effects of TP across the cardio-cerebrovascular diseases spectrum. TP exerts multi-target pharmacological actions through its anti-inflammatory, antioxidant, anti-fibrotic, anti-apoptotic, and neuroprotective mechanisms. These integrated effects ameliorate a wide range of disorders, including cardiac disease, cerebrovascular injury, atherosclerosis, pulmonary arterial hypertension, vascular calcification, and restenosis. The diagram highlights the broad therapeutic potential of TP in addressing the complex pathological processes underlying cardio-cerebrovascular diseases. (Created with MedPeer (https://www.medpeer.cn/), ID: 1dcfc1xkynzfd34s3h1791713633).

component of this review is the systematic dissection of its toxicity, where we not only detail the molecular mechanisms across key organs but also, for the first time integrate available clinical trial evidence to underscore the severity of its clinical limitations. We subsequently provide a synthesized overview of its therapeutic mechanisms across the entire spectrum of cardio-cerebrovascular diseases. Finally, we critically evaluate the latest optimization strategies, including nano-formulations, prodrugs, and combination therapies, and offer a forward-looking perspective on how to overcome the efficacy-toxicity paradox and translate this promising compound into clinical practice.

PHARMACOKINETIC PROFILE OF TP AND ITS TOXICOLOGICAL IMPLICATIONS

The pharmacokinetic (PK) properties of TP present significant obstacles to its clinical application, yet they also provide important insights for translational development. TP is poorly water-soluble (0.017 mg/mL at 20 °C) but is highly absorbed upon oral administration, with an oral bioavailability of 63.9%-72.1% in rats[9,10] and 75.0% in dogs[11,12]. Following oral administration to male Sprague-Dawley (SD) rats, TP is rapidly distributed to the liver, spleen, lungs, and kidneys, with moderate levels in the spleen and lungs, and relatively low concentrations in the kidneys, heart, and testes[9]. Notably, TP accumulates predominantly in the liver, rendering this organ the primary site of its severe toxicity and a major cause of mortality in experimental animals[13,14]. Furthermore, TP is rapidly eliminated in rats, with a half-life of approximately 0.42 h after oral administration and 0.19 h after intravenous injection[9,10]. In dogs, the terminal half-life was

2.5 h following intravenous administration of 0.05 mg/kg TP[11,12]. These PK characteristics make it very difficult to maintain effective systemic concentrations. TP is primarily metabolized in the liver by cytochrome P450 (CYP450) enzymes, particularly cytochrome P450 2C19 (CYP2C19) and cytochrome P450 3A4 (CYP3A4)[15-17]. Its metabolic pathways involve hydroxylation, as well as conjugation with sulfate, glucuronic acid, N-acetylcysteine (NAC), and glutathione (GSH)[18,19]. After administration to rats, TP is excreted mainly as metabolites *via* bile and feces, with nearly 39% of the parent drug cleared through bile[20,21]. In summary, the distinctive PK profile of TP, which is characterized by high bioavailability, rapid hepatic distribution, swift clearance, and biliary excretion, presents major hurdles for maintaining therapeutic levels and managing toxicity, while simultaneously providing a critical foundation for its clinical translation.

CORE PHARMACOLOGICAL EFFECTS AND BIOLOGICAL TOXICITY OF TP

Anti-inflammatory action: systematic inhibition of core inflammatory cascades

The anti-inflammatory effects of TP arise from its synergistic inhibition of multiple key inflammatory signaling nodes. Its core mechanism involves potent inhibition of the Toll-like receptor 4 (TLR4)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, which not only suppresses the activation of the upstream TLR4 receptor but also blocks the activity of the downstream IKK complex, and stabilizes inhibitor of nuclear factor kappa B (IκB)[22]. Consequently, nuclear translocation and transcriptional activity of NF-κB are inhibited, leading to downregulation of downstream pro-inflammatory mediators such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6)[23,24]. Concurrently, TP exerts a dual inhibitory effect on the NOD-like receptor protein 3 (NLRP3) inflammasome pathway. By inhibiting the NF-κB pathway, TP reduces the transcriptional synthesis of NLRP3 inflammasome components and their substrates pro-IL-1β and pro-IL-18, thereby attenuating inflammasome activation. It also directly interferes with the assembly and activation of the NLRP3 inflammasome, inhibiting caspase-1-mediated maturation of interleukin-1 beta (IL-1β) and interleukin-18 (IL-18) as well as the cleavage of Gasdermin D (GSDMD), a pyroptosis execution protein[25,26]. In addition, TP inhibits the phosphorylation of p38 mitogen-activated protein kinase (p38 MAPK)[27], thereby reducing the transcriptional upregulation of its downstream target genes, including inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2)[28,29]. This inhibition decreases iNOS levels, reducing nitric oxide production, a potent inflammatory and vasodilatory mediator. Simultaneously, COX-2 transcription is significantly weakened, thereby blocking the synthesis pathways of key inflammatory mediators such as prostaglandin E2 (PGE2)[28,29]. Furthermore, TP also interferes with the Janus kinase (JAK)-signal transducer and activator of transcription (STAT)[30,31] and phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)[32,33] pathways, reducing the levels of key pro-inflammatory cytokines in models such as rheumatoid arthritis, and inhibiting VEGFA expression to interfere with pathological angiogenesis[33]. Studies have also shown that TP exerts anti-inflammatory effects by directly targeting novel proteins such as the RNA-binding protein IGF2BP3[34]. In terms of immune regulation, TP reduces neutrophil infiltration and inhibits the formation of neutrophil extracellular traps[35], while simultaneously restoring immune homeostasis by increasing regulatory T (Treg) and B (Breg) and suppressing pro-inflammatory Th1/Th17 responses[36-38]. Beyond these classical cascades, emerging evidence indicates that TP also modulates non-coding RNAs (ncRNAs), extending its anti-inflammatory actions to the post-transcriptional level. Specifically, TP downregulates the pathogenic lncRNA RP11-83J16.1, which inactivates URI1 and interrupts β-catenin signaling, thereby mitigating synoviocyte inflammation[39]. Furthermore, TP suppresses inflammation-associated ncRNAs, such as lincRNA-p21[40] and hsa-miR-20b[41], which in turn crosstalk with the PI3K/Akt, NF-κB, and p53 pathways to cooperatively reinforce the suppression of inflammatory responses. Thus, by targeting both canonical signaling nodes and ncRNA-mediated regulatory networks, TP achieves a multilayered control of inflammation that complements its direct inhibition of TLR4/NF-κB, NLRP3, and MAPK cascades.

Bidirectional regulation of oxidative stress: from cytoprotection to toxicity

The role of TP in oxidative stress is context and concentration-dependent. In pathological states such as ischemia-reperfusion injury, low/therapeutic concentrations of TP exert antioxidant effects. TP directly inhibits the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, particularly by interfering with the assembly or electron transfer functions of its catalytic subunits, NADPH oxidase 2 (NOX2) and NADPH oxidase 4 (NOX4), thereby reducing the production of reactive oxygen species (ROS) such as superoxide[42]. Concurrently, TP acts as an activator of the nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) pathway. It modifies key cysteine residues on the kelch-like ECH-associated protein 1 (Keap1) protein, causing a conformational change that impairs Keap1's ability to bind Nrf2, allowing the released Nrf2 to translocate into the nucleus[26,43,44]. In the nucleus, Nrf2 binds to the ARE and drives transcription of antioxidant and cytoprotective genes, including heme oxygenase-1 (HO-1), quinone oxidoreductase 1 (NQO1), and glutamate-cysteine ligase catalytic subunit (GCLC), thereby systematically enhancing the cellular detoxification and antioxidant defenses[26,43,44]. These dual actions, which involve inhibition of exogenous ROS generation and activation of endogenous antioxidant defenses, underpin TP's cytoprotection under oxidative stress. Yet this benefit is concentration-dependent and reversible. When TP exceeds a threshold, the balance tips toward pro-oxidation through at least three converging events. First, TP covalently binds to peroxiredoxin 2 (PRDX2), an endogenous antioxidant peroxidase, and impairs its peroxide-scavenging function[45]. Second, by binding the xeroderma pigmentosum complementation group B (XPB) subunit of transcription factor II H (TFIIH), TP broadly arrests transcription and blocks Nrf2 nuclear translocation, thereby silencing, antioxidant genes such as HO-1 and NQO1[46,47]. Third, TP disrupts mitochondrial electron transport chain complexes (METCC), leading to abnormal electron leakage and mitochondrial ROS overproduction[48]. Together, impaired peroxide clearance, dismantled antioxidant gene programs, and unabated ROS production drive massive intracellular ROS to overwhelming levels. The resulting lipid peroxidation, compounded by GSH depletion and glutathione peroxidase 4 (GPX4) inhibition, leaves damaged lipids unrepaired and culminates in ferroptosis[49,50]. Thus, TP's biological outcome, cytoprotection or cytotoxicity, is dictated by its concentration and cellular milieu, a duality that requires explicit consideration in both mechanistic interrogation and translational design.

Anti-fibrotic action: targeted intervention in extracellular matrix deposition

Fibrosis is a common pathological endpoint in the progression of many cardiovascular and cerebrovascular diseases. The anti-fibrotic effects of TP are primarily achieved through the direct inhibition of the transforming growth factor-beta 1 (TGF-β1)/Sma and mad related proteins (Smad) pathway. TP effectively downregulates the expression of TGF-β1, thereby suppressing its functional activity and blocking the phosphorylation of Smad2 and Smad3 downstream of the TGF-β1 receptor. This molecular blockade prevents activated Smad2/3 from forming complexes with Smad4 and translocating into the nucleus, thereby inhibiting the transdifferentiation of fibroblasts into myofibroblasts and suppressing the overproduction of extracellular matrix components such as collagen[51,52]. Furthermore, TP can synergistically inhibit the Wnt/β-catenin pathway by stabilizing the β-catenin degradation complex or interfering with its nuclear translocation, thereby reducing β-catenin-mediated transcription of pro-fibrotic and pro-proliferative genes[53]. Moreover, TP directly inhibits the activation and proliferation of key effector cells such as hepatic stellate cells[54,55], induces their apoptosis, and synergistically limits fibrosis progression by inhibiting auxiliary pathways such as PI3K/Akt/mechanistic target of rapamycin (mTOR)[56] and MAPK[57], while simultaneously inhibiting the epithelial-mesenchymal transition process and regulating macrophage polarization[58,59]. Its anti-fibrotic effects also involve the regulation of cellular autophagy, as well as the modulation of histone modifications and miR-141-3p. By downregulating miR-141-3p, TP relieves its inhibition of phosphatase and tensin homolog (PTEN), thereby suppressing the Akt/mTOR pathway, reactivating autophagic flux, and alleviating fibrosis[60]. Collectively, these interventions lead to a significant downregulation of key fibrosis

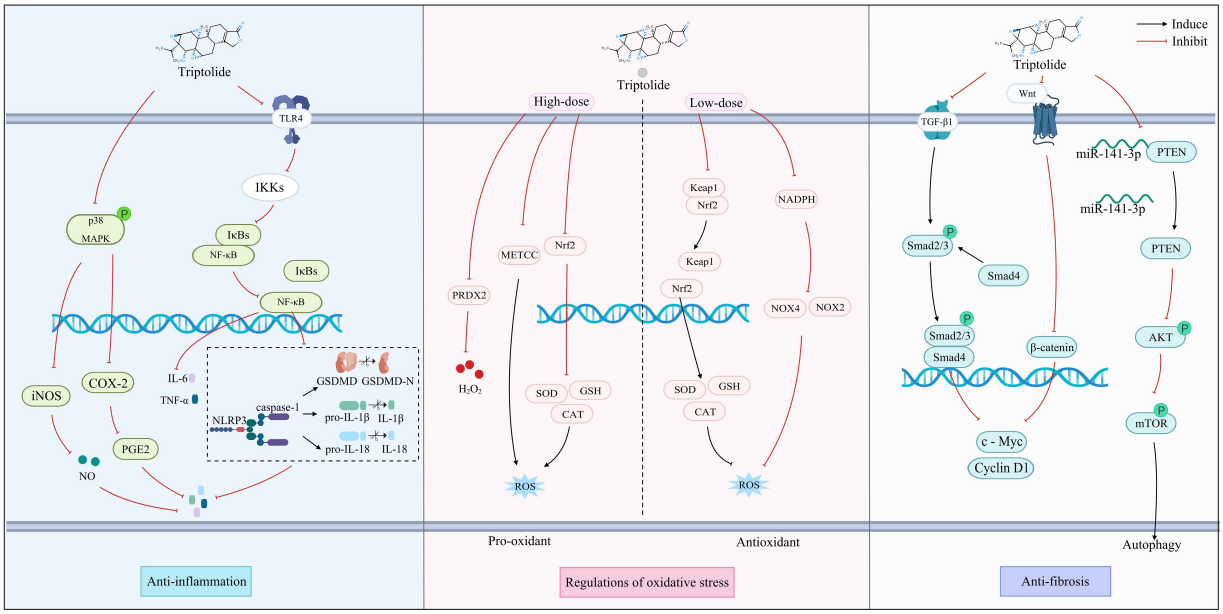

Figure 2. Signaling pathways mediating the core pharmacological effects of TP. The schematic delineates the major molecular cascades through which TP exerts its pleiotropic actions. Anti-inflammatory effects (A) TP suppresses the release of pro-inflammatory mediators primarily by inhibiting the TLR4/NF-κB pathway, blocking NLRP3 inflammasome activation, and attenuating p38 MAPK signaling. Regulation of oxidant stress (B) TP reduces oxidative stress by promoting Nrf2 nuclear translocation *via* disruption of the Keap1-Nrf2 interaction, leading to upregulation of antioxidant enzymes (SOD, CAT, GSH), while downregulating pro-oxidant factors (NOX2, NOX4). At high-doses, TP disrupts cellular redox balance by inhibiting antioxidant defenses (e.g., targeting PRDX2 and suppressing Nrf2) while promoting mitochondrial ROS accumulation (e.g., *via* METCC dysfunction). Anti-fibrotic effects (C) TP attenuates fibrosis through multiple axes, including inhibition of the TGF-β/Smad2/3 signaling pathway, modulation of autophagy *via* the miR-141-3p/PTEN/AKT/mTOR axis, and interference with the Wnt/β-catenin/c-Myc/ Cyclin D1 cascade. These integrated actions synergistically suppress fibroblast activation, extracellular matrix deposition, and myofibroblast transdifferentiation. (Created with MedPeer (https://www.medpeer.cn/), ID: 24c5byr4ak886eabd01791809203).

markers such as α-smooth muscle actin (α-SMA) and type I and III collagen, demonstrating TP's potential in combating complex myocardial and vascular fibrosis. TP exerts multi-target pharmacological effects, as detailed in Figure 2.

Biological toxicity: from bench to clinic

TP represents a distinctive double-edged sword. Despite its prominent pharmacological efficacy, it also exhibits substantial toxicity that has severely hindered its clinical application. The core mechanism underlying TP-induced toxicity lies in its ability to irreversibly suppress transcription. Specifically, TP covalently binds to the XPB subunit of the TFIIH complex, directly impairing XPB function and thereby arresting RNA polymerase II-dependent transcription. This process is facilitated by the three epoxides present on the TP molecule, which subsequently disrupt DNA repair mechanisms and trigger programmed cell death[47,61]. This biological toxicity lacks satisfactory selectivity on normal tissues, including the liver, kidneys, and reproductive system. Hepatotoxicity represents the most prominent toxic feature, as TP is primarily metabolized by hepatic CYP3A4/CYP3A enzymes, and its covalent binding to XPB in hepatocytes provokes ROS burst and GSH depletion, triggering apoptosis, pyroptosis, ferroptosis and subsequent extensive hepatocyte injury[62,63]. Nephrotoxicity is equally concerning, as TP and its secondary metabolites are excreted *via* renal tubules, leading to sustained high-level exposure of proximal tubular epithelial cells, where organic cation transporter 2 (Oct2) mediates toxic accumulation, rendering these cells highly susceptible to oxidative stress, mitochondrial damage and inflammatory responses, ultimately resulting in tubular necrosis, proteinuria and elevated serum creatinine[64]. Furthermore, TP induces severe reproductive organ damage by penetrating the blood-testis barrier, and TP-mediated down-regulation of testicular breast

Table 1. Reported adverse events associated with TP-containing preparations in clinical settings

Drug entity	Subjects	Major toxic effects	References
Tripterygium glycosides tablets	Patients with lupus nephritis	Exhibits potent reproductive toxicity	[67]
Tripterygium glycosides tablets	Patients with systemic lupus erythematosus	Reproductive toxicity, hepato-renal toxicity, and hematological toxicity	[68]
Tripterygium wilfordii decoction	Female patients with kidney diseases	At the conventional dosage, severe bone marrow suppression occurred, leading to end-stage kidney disease, and ultimately death due to infection	[69]
Tripterygium wilfordii preparations	Patients with rheumatoid arthritis	Increased liver transaminase (liver damage), abnormal urine test (kidney damage), myocardial injury, decreased white blood cells	[70,71]
Tripterygium wilfordii preparations	Patients with psoriasis	Reproductive toxicity, hepato-renal toxicity, and hematological toxicity	[72]

cancer resistance protein (BCRP) efflux transporter contributes to intratesticular drug accumulation. Ovarian granulosa cells, spermatogenic cells and Sertoli cells are highly sensitive to TP, which suppresses global transcription *via* the TFIIH-XPB complex, directly disrupting spermatogenesis and follicular development. Activation of the ROS/JNK-dependent mitochondrial apoptotic pathway gives rise to Sertoli cell injury, blood-testis barrier disruption, follicular apoptosis and decreased sex-hormone synthesis[7,65,66]. Thus, the liver suffers toxicity because of metabolic enrichment, the kidney due to excretory enrichment, and the reproductive system owing to barrier penetration, dysregulated transporters and the high dependency of germ cells on XPB-mediated transcription. Given this intrinsic toxicity and the narrow therapeutic window, pure TP monomer has not been approved as a standalone clinical therapy, and clinical trial data specific to the pure monomer remain scarce, human investigations are largely confined to early-phase trials of synthetic derivatives or prodrugs such as PG490-88. Assessment of human safety margins therefore relies predominantly on standardized *Tripterygium wilfordii*-containing preparations, including *Tripterygium* glycosides tablets and *T. wilfordii* decoctions. Although TP is recognized as a principal bioactive and toxic constituent of these preparations, these formulations contain multiple other active compounds. Adverse reactions reported for them in patients with lupus nephritis, rheumatoid arthritis, psoriasis, and various cancers consistently document elevated liver transaminases, renal dysfunction, severe bone marrow suppression, and occasional fatal outcomes [Table 1][67-73]. Importantly, these clinical adverse reactions cannot be attributed exclusively or directly to purified TP, as the multi-component nature of Tripterygium wilfordii preparations may involve synergistic or additive toxicities. Accordingly, in this review, these clinical data are regarded as safety signals for standardized Tripterygium wilfordii-containing preparations rather than as direct evidence of the clinical toxicity of purified TP. These safety signals from TP-containing preparations, together with preclinical evidence on purified TP, indicate that toxicity remains a critical barrier to the clinical application of TP-containing preparations and underscore the urgent requirement for mitigation strategies that separate therapeutic efficacy from inherent toxicity. Direct clinical safety data for the purified TP monomer remain scarce and should not be inferred from studies of multi-component preparations.

PLEIOTROPIC MECHANISMS OF TP ACROSS THE CARDIO-CEREBROVASCULAR DISEASES SPECTRUM

Comprehensive cardioprotection

Myocardial infarction (MI) and ischemia/reperfusion (I/R) injury

MI arises from an imbalance between myocardial perfusion and energy metabolism, and the extent of myocardial necrosis and I/R injury largely determines subsequent cardiac dysfunction[74]. Percutaneous coronary intervention (PCI) restores perfusion after MI but frequently aggravates I/R injury[75]. Limiting myocardial necrosis and preserving cardiac function are therefore the principal therapeutic goals. In rat

cardiac I/R models, TP markedly reduces infarct size and preserves left ventricular performance[43]. This protection is accompanied by activation of the Nrf2/HO-1 pathway, with elevated superoxide dismutase (SOD), glutathione peroxidase (GPx) and GSH, and reduced lipid peroxidation [malondialdehyde (MDA)], indicating attenuated oxidative stress[43].TP also reduces myocardial inflammatory cell infiltration and lowers TNF-α, IL-1β and IL-6[43]. In H_2O_2-induced H9c2 cardiomyocytes, TP blocks apoptosis by inhibiting extracellular signal-regulated kinase 1/2 (ERK1/2) and caspase-3, and restrains inflammation through NF-κB suppression, collectively attenuating I/R damage[76]. These acute protective effects would be expected to confine myocardial necrosis and sustain cardiac function.

During post-MI remodeling that follows the initial necrotic injury, local delivery of TP *via* a hydrogel to the infarct zone shifts macrophage polarization from the pro-inflammatory M1 phenotype toward the reparative M2 phenotype, thereby alleviating post-infarction inflammation[77]. TP also attenuates interstitial fibrosis by normalizing the collagen I/III ratio, which helps preserve cardiac structure and function[77]. In addition, TP lowers endothelial cell apoptosis by downregulating miR-24-3p and enhances mitochondrial biogenesis and function through activation of PPARs-PGC1α [peroxisome proliferator-activated receptors (PPARs)-peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α)] pathway, improving energy metabolism and maintaining vascular endothelial integrity[78].

Myocardial fibrosis (MF)

MF, characterized by excessive extracellular matrix (ECM) deposition, is an integral pathological component of adverse cardiac remodeling and myocardial hypertrophy rather than an isolated entity[79,80]. Under chronic mechanical overload or metabolic stress, cardiac fibroblast activation and myofibroblast transdifferentiation co-occur alongside cardiomyocyte hypertrophy and tissue inflammation, driven by interconnected signaling networks including TGF-β, TNF-α/NF-κB, and Wnt/β-catenin[79,80].

In angiotensin II (Ang II)-induced primary cardiac fibroblasts and mouse myocardial fibrosis models, TP disrupts the interaction between cyclophilin A (CyPA) and its receptor cluster of differentiation 147 (CD147), which blocks NLRP3 inflammasome activation and TGF-β signaling, thereby downregulating the expression of fibrosis markers such as α-SMA, connective tissue growth factor (CTGF), and type I collagen[42]. In an isoproterenol (ISO)-induced rat model of myocardial injury, TP suppresses the NF-κB/NLRP3 axis and TGF-β expression, conferring dual protection that alleviates left ventricular dilation and reduces both left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD), with overall improvement in cardiac performance[81]. To assess whether TP possesses a direct anti-fibrotic capacity independent of cardiomyocyte protection, its effects were evaluated in ISO-stimulated primary cardiac fibroblasts (CFs). In these cells, TP inhibits the Wnt/β-catenin pathway and downregulates cellular myelocytomatosis oncogene (c-Myc) and Cyclin D1, thereby suppressing fibroblast proliferation and ECM synthesis[53]. In pressure overload models such as MF induced by abdominal aortic constriction (AAC) surgery, TP significantly reduces local myocardial IL-1β and IL-6 levels by inhibiting NF-κB phosphorylation and nuclear translocation[24]. Combining TP with methotrexate (MTX) exhibits synergistic NF-κB inhibition, proving more effective than either monotherapy in improving left ventricular remodeling[82].

Cardiac remodeling (CR)

CR is a maladaptive process central to cardiovascular disease progression, involving neuroendocrine activation, cell death, inflammation, and fibrosis[83]. Ang II acts as a core mediator during this process. In Ang II-treated H9c2 cells and neonatal rat ventricular cardiomyocytes, TP inhibits excessive mitophagy by upregulating forkhead box P3 (FoxP3). It also competitively inhibits activating transcription factor 4 (ATF4) binding to DNA, suppressing its transcriptional activity and downregulating the key mitophagy protein

Parkin, which alleviates excessive mitophagy and CR[84,85]. Concurrently, TP corrects the pathological myosin imbalance by upregulating alpha-myosin heavy chain (α-MHC) and downregulating beta-myosin heavy chain (β-MHC), directly inhibiting myocardial hypertrophy[84,85]. Transverse aortic constriction (TAC) is a well-established animal model for studying pressure overload-induced CR. In TAC mouse models and Ang II-induced HL-1 mouse cardiomyocytes, TP activates Nrf2 by inhibiting USP14 and Keap1 expression, and downregulates the expression of cleaved-caspase-1, NLRP3, and GSDMD, thereby blocking pyroptosis and reducing myocardial fibrosis[26]. In TGF-β1-induced human coronary artery endothelial cells (HCAECs), TP similarly inhibits key endothelial-mesenchymal transition (EndMT) transcription factors (Slug, Snail, and Twist) *via* the USP14/Keap1/Nrf2 pathway, maintaining endothelial homeostasis[26]. Additionally, TP disrupts the vicious cycle of inflammation and fibrosis by simultaneously inhibiting the NLRP3 inflammasome and TGF-β1/Smad3 pathways, reducing pro-inflammatory factors (IL-1β, IL-18) and adhesion molecules [vascular cell adhesion molecule-1 (VCAM-1)], thereby preventing macrophage infiltration into myocardial tissue[25]. In an ISO-induced CR rat model, TP alleviates fibrosis and improves cardiac function by downregulating the p38 MAPK and TGF-β1/Smad3 signaling pathways. Notably, TP at a dose of 100 μg/kg/day achieves cardiovascular pharmacological activity comparable to captopril at 15 mg/kg/day[86]. Across both TAC and ISO models, TP consistently lowers β-MHC and collagens I and III, reduces B-type natriuretic peptide (BNP) levels, and inhibits inflammatory mediators. These changes are accompanied by improved left ventricular systolic and diastolic performance, as characterized by increased ejection fraction and fractional shortening, together with reduced LVEDD/LVESD and filling pressures[25,26,86].

Diabetic cardiomyopathy (DCM)

DCM is featured by diabetes-specific structural and functional abnormalities of the myocardium that occur independently of hypertension or coronary artery disease. Its pathogenesis is driven by hyperglycemia - induced insults, including oxidative stress, inflammatory activation, renin-angiotensin-aldosterone system dysregulation, metabolic disorders, and immune dysfunction. These interconnected processes ultimately lead to myocardial fibrosis, adverse ventricular remodeling, and declining cardiac function[87,88].

In streptozocin (STZ)-induced diabetic rat models, TP demonstrates clear cardioprotection. It significantly downregulates pro-inflammatory factors (TNF-α, IL-1β), inhibits macrophage infiltration, and suppresses key molecules in the TGF-β/Smad and TGF-β1/α-SMA/vimentin pathways (e.g., TGF-β1, monocyte chemoattractant protein-1 (MCP-1), collagen I and III), thereby reducing collagen deposition and improving cardiac function[57,89]. Notably, TP targets the core metabolic disturbance in DCM. Under hyperglycemia-induced insulin resistance or deficiency, impaired cardiac energy metabolism severely contributes to myocardial damage and fibrosis. TP addresses this critical issue by suppressing aberrant p38 MAPK signaling, which subsequently mitigates metabolic stress, helps restore myocardial ATP synthesis, and improves overall myocardial energy metabolism[23,57].

Multifaceted protection against cerebrovascular damage

Stroke

Stroke remains a leading global cause of death and disability, with a prevalence ranging from 0.25% to 4% and a case-fatality rate of approximately 30%[90]. The pathogenesis of ischemic stroke primarily involves occlusion of the middle cerebral artery territory, leading to insufficient cerebral perfusion. Neuroinflammation is a key driver of injury, while cerebral edema directly affects patient prognosis during the hyperacute phase (within 6 h of onset)[91].

TP protects against ischemic brain injury by intervening at multiple acute pathological junctures. In rat models of transient middle cerebral artery occlusion (MCAO)-induced cerebral ischemia-reperfusion injury (CIRI), TP inhibits NF-κB nuclear translocation, downregulates inflammatory factors such as COX-2, iNOS,

TNF-α, IL-6, and IL-1β, and reduces astrocyte hyperactivation[92-95]. By blocking the NF-κB/p53-upregulated modulator of apoptosis (PUMA) axis and inhibiting MAPK pathways, TP upregulates the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2), downregulates the pro-apoptotic protein Bcl2-associated X protein (Bax), and suppresses caspase-3, exerting anti-inflammatory and anti-apoptotic effects. These actions protect the blood-brain barrier, reduce cerebral edema and infarct volume, and improve neurological function[92-95]. Additionally, TP modulates the Wnt/β-catenin pathway, downregulating the downstream effectors c-Myc and Cyclin D1 to suppress pro-inflammatory cytokines (TNF-α, IL-6, IL-8, IL-1β) in rat brain tissue, thereby alleviating neuroinflammation. Concurrently, it enhances antioxidant capacity by increasing SOD activity, reduces MDA and ROS levels, mitigates neuronal damage, and decreases neurological deficit scores, cerebral infarction volume, and the severity of cerebral edema[96]. Beyond acute protection, TP promotes post-injury neural repair. It inhibits the neurite outgrowth inhibitor A (NogoA)/nogo-66 receptor (NgR)/rho-associated protein kinase (ROCK) pathway, which is a key inhibitor of axonal regeneration and synaptic repair, while upregulating postsynaptic density protein 95 (PSD-95) and growth-associated protein 43 (GAP43) to facilitate synaptic remodeling and functional recovery[97]. Regulating microglial polarization represents another core mechanism. TP inhibits pro-inflammatory M1 polarization and promotes anti-inflammatory M2 transition in microglia by blocking of the cathepsin S (CTSS)/Fractalkine/C-X3-C motif chemokine receptor 1 (CX3CR1) pathway, thereby mitigating neuroinflammation and accelerating tissue repair[98]. The therapeutic efficacy of TP is dramatically enhanced through synergistic drug combinations that leverage complementary mechanisms. One effective strategy is its combination with the anti-inflammatory adjuvant drug 2,4-diamino-6-hydroxypyrimidine (DAHP). This combination more potently reduces neuronal apoptosis and suppresses glial activation by synergistically activating the protective PI3K/Akt/mTOR pathway while inhibiting the pro-inflammatory ERK1/2 pathway[99,100]. Another promising approach involves co-administration with the colony stimulating factor 1 receptor (CSF1R) inhibitor Ki20227. This regimen suppresses CSF1R signaling, upregulating brain-derived neurotrophic factor (BDNF), p-Akt, and survival-related ERK1/2. It also modulates autophagy markers, lowering the ratio of LC3-II/LC3-I and Atg5 while raising p62, and promotes synaptic proteins such as PSD-95 and synaptophysin (SYN), ultimately increasing dendritic spine density[101]. Collectively, these combined pharmacodynamic actions work synergistically to improve neurological dysfunction following cerebral ischemia.

To address the inherent toxicity and poor water solubility of TP, the structural analog LLDT-8 was developed by introducing a hydroxyl group at the C5 position[102]. In both *in vivo* CIRI mouse models and *in vitro* lipopolysaccharide (LPS)-treated BV-2 cells, LLDT-8 exhibits potent anti-inflammatory and neuroprotective properties. Mechanistically, it inhibits TLR4 activation, which in turn reduces IκBα phosphorylation and degradation, thereby preventing NF-κB activation and subsequent nuclear translocation[103]. This targeted suppression ultimately leads to decreased nitric oxide (NO) release, lowered levels of pro-inflammatory cytokines, and reduced iNOS expression[103].

Vascular dementia

Vascular dementia (VD) is a syndrome of cognitive impairment resulting from hemorrhagic or ischemic cerebrovascular diseases, pathologically characterized by chronic cerebral hypoperfusion that leads to oxidative stress, chronic inflammation, white matter damage, and synaptic dysfunction[104,105]. In mice, TP attenuates vascular dementia induced by permanent bilateral common carotid artery occlusion (BCCAO) by enhancing antioxidant capacity. This protective effect is achieved through increasing sirtuin 1 (SIRT1) levels and promoting PGC1α deacetylation while simultaneously increasing SOD activity. TP also reduces hippocampal neuronal apoptosis by decreasing caspase-3 levels and increasing the Bcl-2/Bax ratio, and lowers blood-brain barrier (BBB) hyperpermeability, eventually improving cognitive function[106].

Subcortical ischemic vascular dementia is another common subtype of VD, with core pathology involving white matter damage caused by chronic cerebral hypoperfusion, where oligodendrocyte apoptosis and microglial-mediated neuroinflammation serve as key contributing factors[107]. In right unilateral common carotid artery occlusion (rUCCAO) mice and oxygen-glucose deprivation/reperfusion (OGD/R)-exposed oligodendrocytes, TP alleviated white matter injury by directly inhibiting oligodendrocyte apoptosis through activation of Src/Akt signaling and increased inhibitory phosphorylation of phosphor-glycogen synthase kinase 3 beta (p-GSK3β), consistent with reduced GSK3β activity, upregulating Bcl-2 and downregulating cleaved-caspase-3. In BV-2 microglia exposed to OGD/R and in rUCCAO mice, TP also suppressed microglial activation and proinflammatory cytokine expression, which contributed indirectly to white matter protection[108].

Multi-pronged intervention of TP in vascular pathologies

Atherosclerosis (AS)

AS development involves endothelial dysfunction, lipid infiltration, inflammation, and plaque formation. Rupture of an unstable plaque can subsequently trigger acute thrombosis, resulting in severe clinical events such as MI and stroke[109,110]. TP demonstrates multi-target potential across these steps. In human umbilical vein endothelial cells (HUVECs) injured by LPS or oxidized low-density lipoprotein (ox-LDL), TP alleviates oxidative stress and inflammatory responses by inhibiting NF-κB nuclear translocation, reducing NADPH oxidase activity, and upregulating SOD[111,112]. It also inhibits NF-κB transcriptional activity, which downregulates downstream targets including Cyclin D1, urokinase-type plasminogen activator (uPA), and VEGF, thereby suppressing excessive endothelial proliferation, migration, and pathological intra-plaque angiogenesis[113]. In a TiO_2 nanoparticle-triggered vascular endothelial injury, TP protects against vascular damage by concurrently reducing inflammation and lipid accumulation in vascular smooth muscle cells (VSMCs), demonstrating its efficacy across diverse etiological agents[114]. TP can increase ABCA1 expression, lower total cholesterol and total triglyceride levels, and improve lipid disorders in $ApoE^{-/-}$ mice[115]. Finally, TP has also shown promise in mitigating graft coronary arteriosclerosis (GCA) by downregulating PDGF-A mRNA expression, which ultimately reduces intimal hyperplasia[116].

Pulmonary arterial hypertension (PAH)

Network pharmacology analysis indicates that TP may intervene in PAH by modulating multiple pivotal biological pathways, including interleukin 17 (IL-17), TNF, toll-like receptor signaling, and apoptosis. Molecular docking studies reveal that TP exhibits strong binding affinities to key apoptotic regulators, caspase-3 and Poly(ADP-ribose) polymerase 1 (PARP1), with docking scores of -7.67 and -8.35 kcal/mol, respectively, suggesting its potential to directly influence apoptotic processes[117]. Whether initiated early or as a delayed intervention, TP attenuates the pathological progression of pulmonary hypertension, right ventricular hypertrophy, and pulmonary arterial occlusion, and even demonstrated the capacity to reverse established neointimal formation in pulmonary vessels in SD rats[118,119]. Additionally, TP significantly downregulates the expression of several mast cell-derived proteases, such as mast cell protease-7, mast cell protease-1, and mast cell chymase-1, which have been implicated in neointimal development and vascular occlusion[118,119]. Although TP has shown potential in experimental pulmonary vascular injury and PAH models, its poor water solubility limits its bioavailability and clinical application. To address this, its water-soluble derivative PG490-88 was developed. In a pulmonary ischemia-reperfusion injury model, PG490-88 attenuated pulmonary edema and pulmonary hypertension by inhibiting the MAPK and NF-κB pathways, thereby reducing apoptosis and inflammation[120]. However, direct evidence for PG490-88 in established PAH remains limited, and this finding should be interpreted within the context of ischemia-reperfusion-associated pulmonary vascular injury rather than as evidence of efficacy in established PAH.

Vascular calcification (VC)

VC is an actively regulated pathological mineralization process closely associated with increased CVDs risk and adverse prognosis. Disturbances in calcium homeostasis serve as a prerequisite for VC development, while osteogenic transdifferentiation of VSMCs and activation of inflammatory pathways represent key drivers of calcification progression[121]. During VC, aberrant overexpression of osteogenic factors such as bone morphogenetic protein 2 (BMP2) and transcription factors like runt-related transcription factor 2 (RUNX2) drives VSMCs to synthesize and secrete bone matrix-related proteins, including osteopontin (OPN), bone sialoprotein (BSP), osteocalcin (OCN), eventually leading to mineral deposition[122]. Emerging evidence highlights the innovative potential of TP in halting this process. In a vitamin D3 plus nicotine-induced VC rat model, TP has been shown to upregulate miRNA-204 expression, which subsequently suppressed BMP2 and RUNX2, directly blocking the osteoblastic transdifferentiation of VSMCs and mitigating calcification[123]. Similarly, in an adenine-induced chronic kidney disease (CKD) mouse model of VC, TP significantly reduced abdominal aortic calcium deposition. Mechanistically, TP suppresses NF-κB-driven inflammatory and osteogenic signaling in VSMCs, thereby preventing Krüppel-like factor 4 (KLF4)-dependent osteogenic reprogramming and resulting in sustained suppression of VSMCs osteogenic programming and a specific reduction in VC[124]. Concurrently, TP decreases the release of pro-inflammatory cytokines such as TNF-α and IL-6, thus alleviating high-phosphate-induced myocardial fibrosis and providing multi-faceted cardiovascular protection[124].

Restenosis (RS)

RS is a common complication following vascular interventions, primarily driven by excessive proliferation of VSMCs and persistent inflammation[125]. In a rabbit iliac artery stent injury model, local delivery of TP *via* pluronic gel effectively prevents VSMC over-proliferation. This anti-proliferative effect is mediated through the downregulation of the ERK1/2- MAPK pathway and upregulation of the cell cycle inhibitor p21. This cascade leads to suppression of CDKs activity and inhibition of retinoblastoma protein (Rb) phosphorylation, which subsequently induces cell cycle arrest at the G1/S phase[126,127]. Importantly, TP also addresses the inflammatory component of restenosis. In a porcine coronary stent injury model, TP significantly attenuates neointimal hyperplasia, reduces luminal stenosis, and lowers the expression of pro-inflammatory factors (TNF-α, IL-6)[128]. Together, TP exerts its therapeutic effects by simultaneously targeting pathological VSMCs proliferation and the underlying inflammatory microenvironment. TP exerts multi-target pharmacological effects in cardiovascular diseases, as detailed in Figure 3 and Table 2.

OPTIMIZATION STRATEGIES FOR OVERCOMING THE EFFICACY-TOXICITY PARADOX: FROM PRODRUG DESIGN TO CLINICAL TRANSLATION

The severe biological toxicity and unfavorable PK properties of TP including poor water solubility (0.017 mg/mL at 20 °C), rapid *in vivo* elimination ($t_{1/2}$ < 1 h in rats), and extensive hepatic accumulation, which constitute the fundamental barriers to its clinical translation[9-11]. However, these features collectively form the PK basis for its dose-limiting toxicities while also providing valuable insights for rational structural optimization. In recent years, researchers have developed a variety of formulation modification strategies based on TP's structural features, such as the C-14 hydroxyl group, the epoxy group, and its hydrophobic scaffold, aiming to achieve reduced toxicity and enhanced therapeutic efficacy. These strategies can be broadly categorized into prodrug design, advanced drug delivery systems, structural modification, and rational combination therapy.

Prodrug design for tissue-specific targeting

Conjugating TP with functional ligands *via* appropriate linkers has been shown to significantly improve its PK and tissue selectivity. For example, TP-glucose or TP-glucosamine conjugates achieve renal-targeted delivery through glucose transporters expressed in the proximal tubules of the kidney, thereby reducing

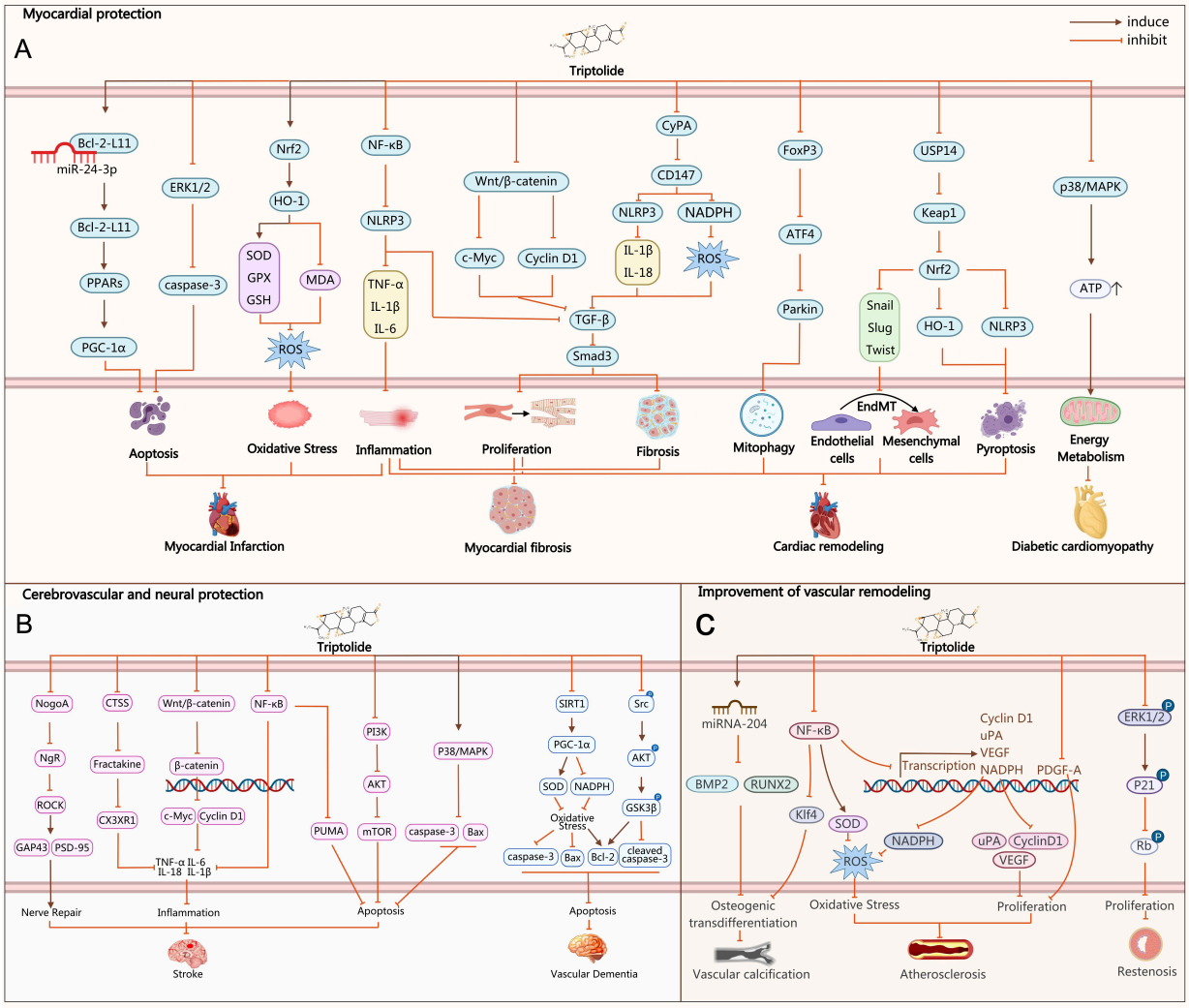

Figure 3. Multi-target mechanisms of TP in myocardial, cerebrovascular, and vascular pathologies. (A) Myocardial protection. TP elicits cardioprotection through multiple mechanisms, including anti-oxidation (Nrf2/HO-1 pathway, SOD/GSH upregulation), anti-apoptosis (Bcl-2/Bax regulation, caspase-3 inhibition), anti-inflammation (NF-κB/NLRP3 suppression, macrophage M2 polarization), anti-fibrosis (TGF-β/Smad and Wnt/β-catenin inhibition), and improvement of myocardial energy metabolism (PPARs/PGC1α activation). These integrated actions contribute to therapeutic benefits in myocardial infarction, ischemia/reperfusion injury, myocardial fibrosis, pathological cardiac remodeling, and diabetic cardiomyopathy. (B) Cerebrovascular and neural protection. In the cerebrovascular system, TP provides neuroprotection *via* anti-inflammatory (TLR4/NF-κB inhibition, microglial M2 polarization), anti-apoptotic (Bcl-2/Bax regulation), and pro-repair (NogoA/NgR/ ROCK inhibition, PSD-95/GAP43 upregulation) mechanisms. These effects support its therapeutic utility in ischemic stroke and vascular dementia. (C) Improvement of vascular remodeling. TP mitigates vascular calcification by inhibiting osteogenic transdifferentiation (BMP2/RUNX2 suppression *via* miRNA-204 upregulation), alleviates atherosclerosis through suppression of oxidative stress, inflammation, and pathological angiogenesis (NF-κB, VEGF, uPA inhibition) and ameliorates vascular restenosis by restraining excessive VSMCs proliferation (ERK1/2 inhibition and p21-mediated cell cycle arrest). (Created with MedPeer (https://www.medpeer.cn/), ID: 50bc1wltb6eaxen111791808861).

reproductive and immune toxicity while retaining anti-inflammatory activity[129,130]. Furthermore, conjugating TP with biomacromolecules or functional peptides endows it with active targeting capabilities. TP-lysozyme conjugates achieve targeting of renal tubular epithelial cell *via* megalin-mediated endocytosis, resulting in reduced hepatic, reproductive, and immune toxicity[131,132]. Similarly, TP conjugated with the human serum albumin active peptide (PF-A299-585) enables efficient renal accumulation through the cubilin/megalin receptor pathway, with a 10-fold reduction in cytotoxicity at 24 h and low risk of immunogenicity[133]. The water-soluble derivative PG490-88, developed through structural modification, attenuated pulmonary edema and pulmonary hypertension in a pulmonary ischemia-reperfusion injury model by inhibiting the MAPK

Table 2. Comprehensive summary of TP's multi-target mechanisms across the cardio-cerebrovascular disease spectrum in preclinical studies

Diseases	Animal model *in vivo*	*In vivo* concentration (routes of administration)	Cell model *in vitro*	*In vitro* concentration	Effects	Mechanisms	References
MI	Wistar rats (I/R)	25, 50, 100 μg/kg (i.p.)	NA	-	Anti-inflammation; Antioxidant.	↓TNF-α, IL-1β, IL-6, MDA; ↑Nrf2/HO-1, SOD, GPx, GSH	[43]
	Rats (I/R)	100, 200, 400 μg/kg (i.p.)	H9c2 (NAC, PDTC and H_2O_2)	10, 30, 50 ng/mL	Anti-inflammation, Antioxidant; Anti-apoptosis	↓NF-κB ROS ERK1/2, Bax, LOX1, TNF-α, IL-1β, IL-6 MDA, iNOS, caspase3, IκBα; ↑Bcl2	[76]
	Rats (ligation of the left anterior descending coronary artery)	0.125 mg/kg (i.m.)	RAW264.7	20 nM	Anti-inflammation; Anti-apoptosis	↓cleaved-caspase-3 TNF-α; ↑IL-10	[77]
	C57BL/6 J mice (Ang II)	100 mg/kg (i.p.) [see note]	CFs (Ang II)	10 μg/L	Anti-inflammation; Anti-fibrosis; Inhibition of proliferation	↓CyPA/CD147, NLRP3, NADPH, TGF-β, α-SMA, collagen I, CTGF, p-Smad2, p-Smad3, Nox2, p-ERK, p-p38, p-JNK	[42]
MF	SD rats (ISO)	200 μg/kg (i.p.)	NA	-	Anti-inflammation; Anti-fibrosis	↓NF-κB, NLRP3, IL-1β, IL-18, TNF-α, TGF-β1, COL1, COL3	[81]
	SD rats (ISO)	10, 50, 150 μg/kg (i.p.)	CFs (ISO)	10 μg/L	Anti-fibrosis; Inhibition of proliferation	↓Wnt/β-catenin, COL1, COL3, HYP, c-Myc, Cyclin D1	[53]
	SD rats (suprarenal abdominal aorta constriction)	9 μg/kg (i.p.)	NA	-	Anti-inflammation; Anti-fibrosis; Inhibition of proliferation	↓NF-κB, IL-1β, IL-6, Ang II, TGF-β	[24]
	NA	-	HUVECs (Ox-LDL)	25 nM	Anti-inflammation; Inhibition of proliferation; Anti-apoptosis	↓miR-24-3p, BCL2L11, bax, caspase3; ↑PPARs, PGC1α, bcl-2	[78]
	C57 mice and FoxP3^{DTR} mice (ISO)	10, 30, 100 μg/kg (i.p.)	H9c2 and NRVMs (Ang II)	10 μg/L	Inhibition of mitophagy	↓Pink1, Parkin, LC3, β-MHC; ↑FoxP3, ATF4, α-MHC	[84,85]
	Wistar rats (ISO)	20, 100 μg/kg (i.p.)	NA	-	Anti-fibrosis	↓p38 MAPK, TGF-β1, Smad3, CVF, PVCA, VW/BM, HYP	[86]
CR	C57BL/6 J mice (TAC)	10, 30, 90 μg/kg (i.p.)	HL-1 (Ang II)	10 μg/L	Anti-fibrosis; Antioxidant; Inhibition of EndMT	↓USP14, Keap1, NLRP3, c-caspase-1, GSDMD, BNP, β-MHC, COL1, COL3, IL-1β, IL-18, Snail, Slug, Twist; ↑Nrf2, HO-1	[26]
	C57BL/6 mice (TAC)	20, 100 μg/kg (i.p.)	NA	-	Anti-inflammation	↓NLRP3, TGF-β1, Smad3, IL-1β, IL-18, MCP-1, VCAM-1	[25]
DCM	SD rats (streptozotocin)	50, 100, 200, 400 μg/kg (i.g.)	NA	-	Anti-inflammation; Anti-fibrosis	↓p38 MAPK, TLR4, NF-κB, VCAM-1, TGF-β1, α-SMA, Vimentin, TNF-α, IL-1β, MCP-1, COL1, COL3	[23,57]
	Rats (streptozotocin)	100, 200, 400 μg/kg (i.p.)	H9c2 (streptozotocin)	20 ng/L	Anti-inflammation; Anti-fibrosis	↓NF-κB, COL1, COL3, ICAM-1, VCAM-1, TNF-α, IL-1β	[89]

Stroke	SD rats (MCAO)	0.1, 0.5, 1, 5 mg/kg (i.p.)	SH-SY5Y (OGD/R)	40 ng/mL	Anti-inflammation; Anti-apoptosis	↓NF-κB, p38 MAPK, bax, TNF-α, IL-6, IL-1β; ↑bcl-2	[92,93]
	SD rats (MCAO)	0.2 mg/kg (i.p.)	NA	-	Anti-inflammation; Antioxidant; Anti-apoptosis	↓NF-κB, bax, caspase3, iNOS, COX-2, GFAP; ↑bcl-2	[94]
	SD rats (MCAO)	5 mg/kg (i.p.)	NA	-	Anti-apoptosis	↓NF-κB, PUMA, caspase3	[95]
	SD rats (CIRI)	12.5, 25, 50 mg/kg (i.p.)	NA	-	Anti-inflammation; Antioxidant; Anti-fibrosis	↓Wnt/β-catenin, TNF-α, IL-6, IL-8, IL-1β, ROS, MDA, c-Myc, Cyclin-D1; ↑SOD	[96]
	SD rats (CIRI)	0.2 mg/kg (i.p.)	SH-SY5Y (OGD/R)	1 nM	Promote nerve repair	↓NogoA, NgR, ROCK; ↑PSD-95, GAP43	[97]
	C57BL/6 mice (MCAO)	0.4 mg/kg (i.p.)	BV-2 (LPS)	50 ng/mL	Inhibit the polarization of microglia; Anti-apoptosis	↓CTSS, Fractalkine, CX3CR1, TNF-α, IL-1β, Arg-1; ↑iNOS	[98]
VD	SD rats (BCCAO)	5 μg/kg (i.p.)	NA	-	Anti-apoptosis; Antioxidant	↓bax, caspase3, MDA; ↑SIRT1, PGC1α, bcl-2, SOD	[106]
	C57BL/6 mice (rUCCAO)	5, 20 μg/kg (i.p.)	BV-2 (OGD/R)	0.001, 0.01, 0.1 nM	Anti-inflammation; Anti-apoptosis	↓c-caspase3, bax, TNF-α, IL-6; ↑Src, Akt, p-GSK3β, bcl-2	[108]
	NA	-	HUVECs (LPS)	25, 50, 100 nM	Anti-inflammation	↓NF-κB, TNF-α, IL-6, MCP-1, ICAM-1, VCAM-1	[111]
	NA	-	HUVECs (Ox-LDL)	25, 50, 100 nM	Anti-inflammation; Antioxidant	↓NF-κB, TNF-α, IL-6, MCP-1, ICAM-1, VCAM-1, 8-isoprostane, MDA, superoxide; ↑SOD	[112]
AS	NA	-	VSMCs (TiO2 nanosheets)	100 nM	Anti-inflammation	↓IL-6, MCP-1	[114]
	NA	-	HUVECs (VEGF)	60 nM	Inhibition of proliferation	↓NF-κB, Cyclin D1, uPA, VEGF	[113]
	ApoE$^{-/-}$ mice (High-fat diet)	25, 50, 100 μg/kg (i.p.)	NA	-	Anti-inflammation	↓TNF-α, IL-1β, IL-6, IL-8, TC, TG; ↑ABCA1	[115]
	Lewis rats (Intraabdominal heterotopic heart transplantation)	3.75, 37.5 μg/kg (i.p.)	NA	-	Inhibition of proliferation	↓PDGF-A mRNA	[116]
PAH	SD rats (pneumonectomy-monocrotaline)	0.25 mg/kg (i.p.)	NA	-	Inhibition of neointimal hyperplasia	↓mPAP, RVSP	[118,119]
VC	SD rats (Vitamin D3 plus nicotine)	10, 20, 40 mg/kg (i.p.)	NA	-	Inhibition of osteoblastic transdifferentiation	↓BMP2, RUNX2; ↑miRNA-204	[123]
	DBA/2 mice (adenine)	70 μg/kg (i.p.)	NA	-	Inhibition of osteoblastic transdifferentiation	↓NF-κB, RUNX2, Spp1, phosphate, Calcium, TNF-α; ↑Acta2, Tagln	[124]
RS	Rabbit (metal stent)	5.6, 56 μg/stent (drug-eluting stent)	VSMCs (Serum post-starvation stimulation)	1, 10, 50 nM	Inhibition of proliferation; Cell cycle arrest	↓ERK1/2, pRb; ↑P21	[126,127]
	Pigs (metal stent)	100 μg/stent (drug-eluting stent)	NA	-	Anti-inflammation	↓TNF-α IL-6	[128]

The dose of TP (100 mg/kg, i.p.) reported in Ref.[42] is pharmacologically implausible, as it far exceeds the known LD50 of TP in rodents. This discrepancy most likely represents a typographical error in the original publication (e.g., μg *vs.* mg). Although the authors have verified that the original text reports this value, it should not be regarded as established data, and readers are advised to interpret this specific dosage with caution. MI: Myocardial infarction; MF: myocardial fibrosis; CR: cardiac remodeling; DCM: diabetic cardiomyopathy; VD: vascular dementia; AS: atherosclerosis; PAH: pulmonary arterial hypertension; VC: vascular calcification; RS: restenosis; Ang II: angiotensin II; TP: triptolide; I/R: ischemia-reperfusion; NAC: N-acetylcysteine; GSH: glutathione; ROS: reactive oxygen species; MDA: malondialdehyde; iNOS: inducible nitric oxide synthase; ISO: isoprenaline; α-SMA: alpha-smooth muscle actin; SD: sprague-dawley; CFs: cardiac fibroblasts; VSMCs: vascular smooth muscle cells.

and NF-κB pathways, thereby reducing apoptosis and inflammation[120]. However, direct evidence for PG490-88 in established PAH remains limited, and this finding should be interpreted within the context of ischemia-reperfusion-associated pulmonary vascular injury rather than as evidence of efficacy in established PAH. More recently, Kang *et al.* discovered a novel water-soluble, rapid-release TP prodrug with improved drug-like properties and high efficacy in human acute myeloid leukemia[134], while Wang *et al.* developed TP-CSO, a TP prodrug for pancreatic cancer treatment[135]. These recent advances demonstrate that rational prodrug design represents a promising avenue for improving TP's therapeutic index.

Advanced nano-delivery systems for controlled release and targeting

Leveraging the strong hydrophobicity of TP, various nanocarriers have been constructed through self-assembly or covalent conjugation strategies. For instance, TP loaded into PEG-PDLLA block copolymers and modified with the AS1411 aptamer enables both passive and active dual targeting in a pancreatic cancer model, thus reducing accumulation in normal tissues[136]. Liposomes modified with an anti-carbonic anhydrase IX antibody or with TRX-20 have been developed to deliver TP to the lungs and kidneys, respectively[137,138]. Moreover, covalent grafting of TP onto carboxymethyl chitosan or dendrimers not only improves the water solubility of TP to 5 mg/mL but also achieves sustained release, effectively alleviating injection site reactions, hepatotoxicity, and cardiotoxicity[139,140]. In the context of myocardial infarction, Wang *et al.* demonstrated that local delivery of TP *via* a thermosensitive hydrogel to the infarct zone promotes macrophage polarization from the pro-inflammatory M1 phenotype toward the reparative M2 phenotype, effectively mitigating early-stage inflammation while minimizing systemic toxicity[77]. In the context of vascular restenosis, local delivery of TP *via* pluronic gel in a rabbit iliac artery stent injury model effectively prevents VSMC over-proliferation through downregulation of the ERK1/2-MAPK pathway and upregulation of the cell cycle inhibitor p21[126,127]. These nanoformulation strategies effectively reduce toxicity and enhance efficacy *in vitro* and *in vivo* by improving solubility, enabling controlled release, optimizing biodistribution, and conferring active targeting, all while preserving TP's pharmacological activity.

Structural modification and analog development

Synthesizing TP analogs represents another important strategy for improving solubility and overall PK properties. The most notable example is LLDT-8 ((5R)-5-hydroxytriptolide), developed by introducing a hydroxyl group at the C5 position, which exhibits potent anti-inflammatory and neuroprotective properties with reduced toxicity[102,141]. In both *in vivo* CIRI mouse models and *in vitro* LPS-treated BV-2 cells, LLDT-8 inhibits TLR4 activation, reduces IκBα phosphorylation and degradation, prevents NF-κB activation and nuclear translocation, ultimately leading to decreased nitric oxide release and reduced pro-inflammatory cytokine levels[103]. Beyond LLDT-8, Noel *et al.* systematically reviewed TP and its derivatives as cancer therapies and highlighted the potential of structural modification to generate analogs with improved drug-like properties[141]. These structural strategies aim to uncouple the reactive C12, C13-epoxide toxicity core from the anti-inflammatory diterpenoid therapeutic core to broaden the therapeutic window. The reactive C12, C13-epoxide moiety is the primary toxicity core responsible for irreversible global transcription inhibition *via* XPB binding[142]. The polycyclic diterpenoid skeleton mediates the anti-inflammatory therapeutic core. Structural modification of the epoxide or its steric environment such as C5-hydroxylation in LLDT-8 enables partial uncoupling of toxicity from efficacy while preserving pharmacological activity[102,141]. These structural optimization efforts provide a foundation for developing safer TP-based therapeutics.

Rational combination therapy for toxicity mitigation

TP can be used in combination with agents such as crocin, isoliquiritigenin, and obeticholic acid to protect hepatic P450 enzyme systems, enhance TP efflux, reduce TP-induced hepatotoxicity, and optimize its PK

profile[143-145]. For example, obeticholic acid, a farnesoid X receptor (FXR) agonist, improved TP/lipopolysaccharide-induced hepatotoxicity by inhibiting the caspase-11-GSDMD pyroptosis pathway[143]. Crocin has been shown to attenuate the side effects of TP while preserving its therapeutic efficacy in arthritis models[144], and isoliquiritigenin protects against TP-induced hepatotoxicity through mechanisms involving Nrf2 and hepatic transporters[145]. Additionally, the combination of TP and MTX exhibits synergistic NF-κB inhibition, proving more effective than either monotherapy in improving left ventricular remodeling in autoimmune myocarditis[82]. In the context of cerebral ischemia, combination of TP with the anti-inflammatory adjuvant drug DAHP more potently reduces neuronal apoptosis and suppresses glial activation by synergistically activating the protective PI3K/Akt/mTOR pathway while inhibiting the pro-inflammatory ERK1/2 pathway[99,100]. Another promising approach involves co-administration with the CSF1R inhibitor Ki20227, which suppresses CSF1R signaling, leading to upregulation of BDNF, p-Akt, and survival-related ERK1/2, ultimately increasing dendritic spine density and improving neurological function after cerebral ischemia[101]. Furthermore, flavonoids such as catalpol have been shown to protect against TP-induced hepatotoxicity by inhibiting excessive autophagy *via* the PERK-ATF4-CHOP pathway[146]. These combination strategies offer a practical and clinically feasible approach to expanding TP's therapeutic window.

Dosing paradigm optimization and personalized medicine strategies

Beyond formulation chemistry and combination therapies, optimizing clinical dosing paradigms, particularly transient, low-dose, and intermittent administration, offers a clinically practical route to uncouple TP's efficacy from its toxicity. Pure TP monomer has not yet been approved as a standalone entity due to its narrow therapeutic index. Clinical evidence has been reported for standardized Tripterygium wilfordii-containing preparations, such as Tripterygium Glycosides Tablets; however, these data pertain to multi-component preparations and should not be equated with the clinical efficacy of purified TP. In such preparations, TP content is strictly limited to microgram levels (typically 20-100 μg daily for adults) to minimize toxicity[147,148]. In contrast, *in vivo* animal studies commonly use pure TP at 0.005-50 mg/kg [Table 2], which often exceeds the TP exposure achievable with standardized preparations when converted to human equivalent doses. This mismatch helps explain the marked toxicity observed in preclinical models and supports the necessity of low-dose, intermittent, or targeted delivery strategies. Accumulating preclinical evidence, together with limited clinical observations with TP-containing preparations, indicates that transient high-dose pulse therapy or low-dose intermittent regimens can effectively suppress pathological vascular inflammatory cascades and osteogenic transdifferentiation while keeping systemic exposure below toxic thresholds, thereby avoiding cumulative hepatic, renal, and reproductive damage[106,115,148]. Because reproductive toxicity poses a critical regulatory barrier for long-term preventative therapies, clinical translation requires precise patient stratification and indication positioning[7]. TP-based regimens should primarily target non-reproductive cohorts such as elderly populations, or acute, life-threatening conditions, such as acute myocardial infarction or cerebral ischemia-reperfusion injury, whereas short-term or localized delivery (e.g., cardiac hydrogels) yields therapeutic gains while mitigating systemic off-target risks[77].

Most preclinical TP studies have been performed in young, healthy rodents without comorbidities. The human cardio-cerebrovascular disease population, however, is characterized by aging, diabetes, dyslipidemia, hypertension, and polypharmacy. This discrepancy limits the translational predictive value of current efficacy and toxicity data. Future preclinical evaluation should incorporate comorbid and aged animal models, as well as large-animal validation, to improve the clinical relevance of benefit-risk assessments. Direct evidence for therapeutic drug monitoring- and pharmacogenomics-guided personalized TP therapy is currently lacking. Nevertheless, therapeutic drug monitoring and pharmacogenomic screening have been established for other drugs, such as perampanel[149], and provide a methodological precedent rather than direct evidence for TP. On this basis, clinical application of TP could incorporate therapeutic drug

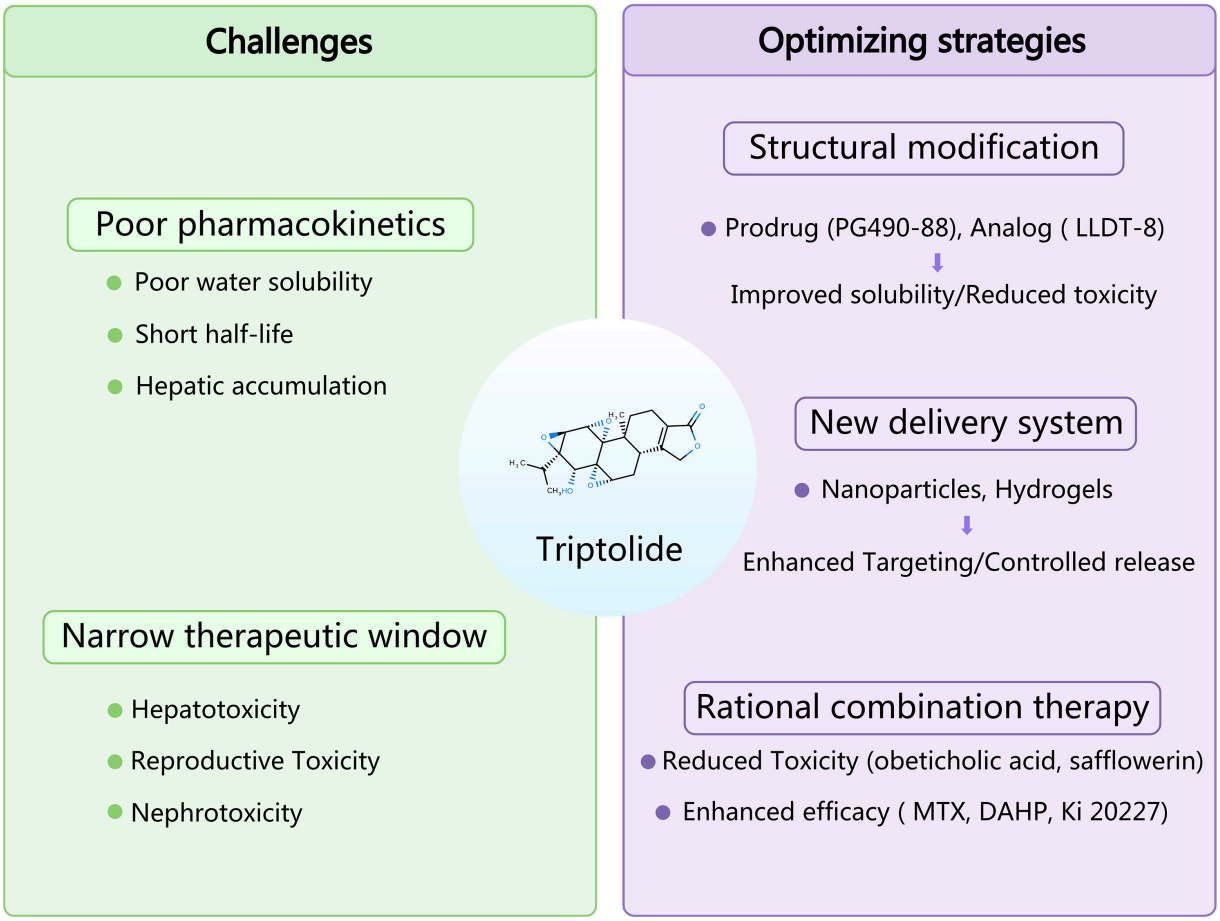

Figure 4. Strategic framework for uncoupling efficacy from toxicity to enable clinical translation of TP. The clinical potential of TP is severely hindered by its poor pharmacokinetics and narrow therapeutic window, manifesting primarily as hepatotoxicity, nephrotoxicity and reproductive toxicity. Proposed optimization strategies include structural modifications (e.g., PG490-88, LLDT-8), advanced nano-targeted or hydrogel delivery systems, and rational combination therapies (e.g., with obeticholic acid, MTX, or DAHP) to dissociate efficacy from toxicity. (Created with MedPeer (https://www.medpeer.cn/), ID: 65ac1x6y8d38yf2b51792160354).

monitoring and pharmacogenomic screening (e.g., assessing CYP3A4 metabolic activity) to tailor dosage according to individual metabolic clearance, alongside real-time tracking of sensitive toxicity biomarkers (such as urinary Kim-1 and microRNA-122)[150,151].

CONCLUSIONS AND PERSPECTIVES

These prodrug, nanoformulation, structural modification, and combination strategies discussed above provide a feasible path for clinical application. As summarized in Figure 4, the integration of molecular design (prodrugs and analogs), delivery system engineering (nanocarriers and hydrogels), and pharmacological combination (with FXR agonists, MTX, or DAHP) constitutes a comprehensive framework for dissociating TP's efficacy from its toxicity. The core challenge remains that TP's multi-target efficacy is inseparable from its narrow therapeutic window and organ-specific toxicity within a clinically usable dose range. Overcoming this dilemma requires chemical and formulation innovation as well as changes in dosing strategy, patient selection, and toxicity monitoring.

Future research should prioritize advanced drug delivery systems with improved targeting precision and controlled release, novel water-soluble prodrugs with optimized PK properties, rigorous preclinical-to-clinical translational validation using large animal models and biomarker-based trials, and predictive

biomarkers for patient stratification. Preclinical evaluation should incorporate comorbid and aged animal models that better reflect the human disease population. Clinical studies should integrate therapeutic drug monitoring and pharmacogenomic screening to enable individualized dosing. With continued innovations in formulation chemistry, prodrug design, and combination regimens, together with biomarker-guided patient stratification and exposure-toxicity monitoring, TP may evolve from a potent but hazardous natural compound into a precise and clinically viable therapeutic agent for cardiovascular and cerebrovascular diseases.

DECLARATIONS

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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