Review

DOI: 10.5582/bst.2026.01256

Traditional Chinese medicine for diabetic lower extremity arterial disease: A review of recent advances

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SUMMARY: Diabetic lower-extremity arterial disease (LEAD) is a prevalent macrovascular complication of diabetes and a critical pathological foundation for diabetic foot lesions. Its pathogenesis involves glycolipid metabolic disturbance, excessive oxidative stress, persistent vascular inflammation, and endothelial dysfunction, leading to limb ischemia, refractory foot ulcers, and increased amputation risk. Current standard treatments, including glycemic and lipid control, antiplatelet therapy, and endovascular revascularization, have improved clinical outcomes but still face challenges in fully ameliorating microcirculatory impairment and preventing long-term restenosis. Traditional Chinese medicine (TCM) exerts multi-component and multi-target protective effects against diabetic LEAD. This review summarizes pharmacological advances in representative TCM agents, including *Salvia miltiorrhiza*, *Astragali Radix*, and their bioactive constituents (*e.g.*, tanshinone IIA sulfonate, salvianolic acid B, astragaloside IV, and Astragalus polysaccharide), as well as classical formulas and patent medicines such as Huangqi Guizhi Wuwu Decoction, Tongxinluo capsule, Tangbi capsule, and Danggui Sini Decoction. Their mechanisms involve protecting vascular endothelium, regulating glycolipid metabolism, suppressing vascular inflammation *via* NF-κB and NLRP3 pathways, and activating Nrf2-mediated antioxidant defense, HIF-1α/VEGF, PI3K-AKT, and Ang-1/Tie-2 signaling to restore microcirculation and promote angiogenesis. Clinically, TCM-assisted endovascular intervention reduces postoperative restenosis and improves lower-limb perfusion; external preparations promote diabetic foot ulcer healing; acupuncture, moxibustion, and mind-body exercises improve microcirculation and long-term management. TCM is a promising adjunctive strategy for diabetic LEAD, and further mechanistic and clinical studies are needed to advance its standardized application and improve patient prognosis.

Keywords: Diabetic lower-extremity arterial disease (LEAD), Traditional Chinese medicine (TCM), endothelial dysfunction, oxidative stress, vascular inflammation, angiogenesis

1. Introduction

Lower extremity arterial disease (LEAD) is a prevalent macrovascular complication of diabetes and serves as a critical pathological foundation for diabetic foot lesions (*1*). Multiple risk factors, including prolonged diabetic duration, suboptimal glycemic control, hypertension, and dyslipidemia, are strongly correlated with development of LEAD, the predominant lower-extremity manifestation of peripheral arterial disease (PAD). Its pathophysiological progression involves glycolipid metabolic disturbance, excessive oxidative stress, persistent vascular inflammation, and endothelial dysfunction (Figure 1) (*2*). In recent years, the rising incidence, disability rate, and mortality of LEAD among diabetic patients have imposed a substantial socioeconomic burden on patients' families and society (*3*). Despite its high prevalence in the Chinese diabetic population, LEAD remains substantially underdiagnosed and undertreated. A national multicenter cross-sectional study demonstrated that LEAD prevalence among high-risk patients with type 2 diabetes reached 21.2%, whereas only 10.6% of affected individuals received a formal diagnosis before study enrollment (*4*). In addition, pharmacological management targeting glycemic, blood pressure, and lipid control in this patient population frequently fails to meet guideline-recommended targets.

Current mainstream therapeutic strategies for diabetic LEAD consist of glycemic regulation, lipid-modifying therapy, antiplatelet agents, and vascular revascularization (*5*). Nevertheless, these conventional interventions exhibit limited efficacy in ameliorating microcirculatory impairment and chronic vascular inflammation (*6*). Furthermore, long-term pharmacotherapy may induce diverse adverse reactions, and revascularization remains hampered by a high incidence of long-term

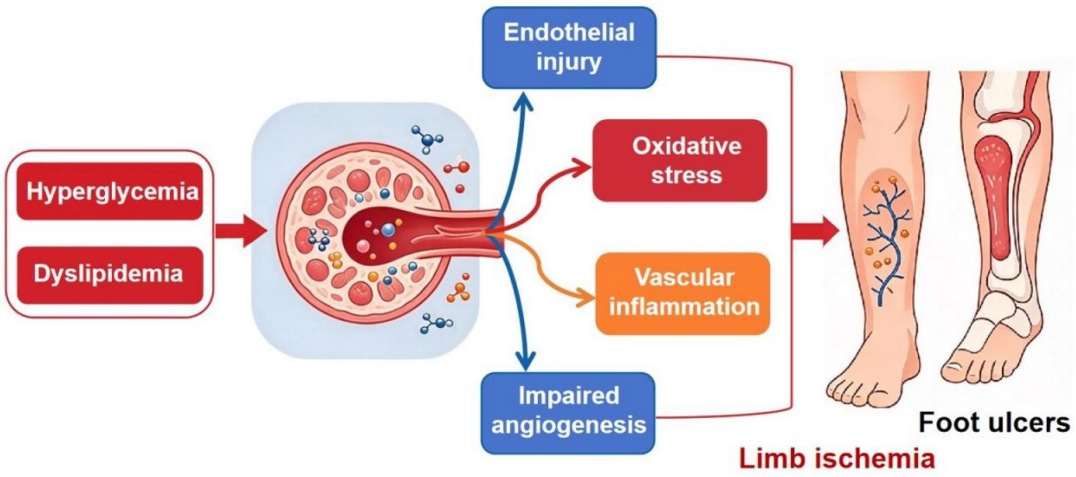


Figure 1. Pathogenesis of diabetic lower-extremity arterial disease (LEAD). Hyperglycemia and dyslipidemia induce endothelial injury, oxidative stress, vascular inflammation, and impaired angiogenesis, ultimately causing limb ischemia and diabetic foot ulcers.

restenosis, which ultimately limits comprehensive and effective management of diabetic LEAD (*7*). Therefore, identifying adjunctive or alternative therapies that can effectively improve microcirculation, suppress vascular inflammation, and delay progression of atherosclerosis has become a research priority.

Characterized by the holistic concept and syndrome differentiation and treatment, traditional Chinese medicine (TCM) has been widely applied in prevention and intervention of diabetes and its related vascular complications for thousands of years (*8*). It exerts multi-target and multi-pathway regulatory effects, exhibiting prominent advantages in ameliorating lower limb blood perfusion, alleviating vascular inflammatory response and preventing development of arteriosclerotic lesions (*9*). A Bayesian network meta-analysis revealed that Chinese herbal injections, such as Dan Shen injection, Danhong injection, and Chuanxiongqin injection, in combination with conventional therapy, significantly improved the ankle-brachial index (ABI), dorsalis pedis artery blood flow, and hemorheological indices, indicating that TCM could be a valuable adjunctive treatment for diabetic LEAD (*10*). Furthermore, modern pharmacology has demonstrated that some Chinese herbal medicines, such as *Salvia miltiorrhiza* (Danshen), and *Astragali Radix* (Huangqi), can exert anti-atherosclerotic actions *via* improving hemorheology, suppressing platelet aggregation, modulating oxidative stress, reducing lipid levels and ameliorating lipid metabolism, and protecting both the endothelium and basement membrane (*11*). These findings provide scientific evidence for use of TCM in treatment of diabetic LEAD.

In recent years, although clinical evidence and molecular mechanistic studies on TCM for diabetic LEAD have accumulated rapidly, a systematic synthesis of these findings is still lacking. In this review, we therefore aim to comprehensively summarize recent advances regarding the pharmacological mechanisms and clinical applications of bioactive constituents, classical TCM formulas, and patent medicines for the prevention and treatment of diabetic LEAD. By integrating these data, we hope to provide a solid scientific basis for optimizing clinical therapeutic regimens and ultimately improving long-term patient outcomes.

2. Modern pharmacological mechanisms of TCM in the treatment of diabetic LEAD

Diabetic LEAD represents a multifactorial vascular complication. Chronic hyperglycemia, dyslipidemia, inflammation, and oxidative stress, together with impaired angiogenesis, synergistically trigger endothelial injury, arterial stiffening and limb ischemia. TCM bioactive constituents, classical formulas, and patent medicines exert promising vascular-protective effects against diabetic LEAD through multi-component and multi-target regulatory mechanisms (Table 1 and Table 2). This section reviews recent advances in modern pharmacological research on TCM against diabetic LEAD, focusing on four interrelated domains: vascular endothelial protection, modulation of glucose and lipid metabolism, suppression of vascular inflammatory responses, and improvement of microcirculation coupled with pro-angiogenic effects (Figure 2). Collectively, these mechanisms support TCM as a potential adjunctive therapy for diabetic LEAD and lay a foundation for subsequent mechanistic exploration and clinical investigation.

2.1. Protection of vascular endothelial function

Vascular endothelial dysfunction is widely recognized as the initiating step in pathogenesis of diabetic LEAD (*12*). Under chronic hyperglycemic conditions, the endothelium undergoes a series of pathological alterations, including reduced nitric oxide (NO) bio-

Table 1. Pharmacological mechanisms of bioactive constituents from traditional Chinese medicine (TCM) in the treatment of diabetic lower-extremity arterial disease (LEAD)

Bioactive constituent	Source	Target/signaling pathway	Main mechanism	Protective effect	*Ref.*
Sodium Tanshinone IIA sulfonate	*Salvia miltiorrhiza* (Danshen)	miR-133a↓/GCH1↑/NO↑	Enhancing NO bioavailability and reducing oxidative injury	Protecting vascular endothelium and improving perfusion in diabetic ischemia	(*16*)
Salvianolic acid B	*Salvia miltiorrhiza* (Danshen)	BMP4↓/ROS↓/NO↑	(i) Inhibiting apoptosis/mitophagy; (ii) Enhancing NO bioavailability	(i) Protecting diabetic endothelial function; (ii) Accelerating wound healing	(*18-20*)
Curcumin+Baicalein	*Curcuma longa* (Jianghuang); *Scutellaria baicalensis* (Huangqin)	Nrf2/HO-1↑; p38/JNK MAPK↓	Mitigating oxidative-mediated endothelial damage	Enhancing endothelial viability and ameliorating diabetic angiopathy	(*23*)
Astragaloside IV	*Astragali Radix* (Huangqi)	AMPK/PI3K/Akt↑; METTL3/m6A/SIRT1↑	(i) Correcting glucose-lipid homeostasis; (ii) Triggering epigenetic modulation	(i) Ameliorating glycolipid disorders and IR; (ii) Attenuating peripheral arterial stiffness and AGE-triggered vascular injury	(*30-33*)
Astragalus polysaccharide	*Astragali Radix* (Huangqi)	miR-721↓/PPAR-γ↑/PI3K/Akt↑; ROS↓	Regulating glycolipid metabolism and scavenging ROS	Restoring insulin sensitivity and promoting angiogenesis	(*35-37*)
		M1↓/M2↑, TNF-α↓, IL-1β↓, IL-6↓, IL-10↑	Regulating M1 to M2 macrophage polarization and reducing pro-inflammatory cytokines	Alleviating local inflammatory responses in diabetic wounds	(*45*)
		VEGF/VEGFR↑, Ang-1/Tie-2↑	Activating VEGF/VEGFR and Ang-1/Tie-2 signaling pathways	Enhancing angiogenesis in diabetic hindlimb ischemia	(*54*)
Resveratrol	Grapevine, berries, and other plants	NF-κB↓, TNF-α↓, IL-1β↓, IL-6↓, ICAM-1↓, MCP-1↓	(i) Inhibiting NF-κB nuclear translocation; (ii) Down-regulating pro-inflammatory cytokines and adhesion molecules	Attenuating vascular inflammatory injury in type 2 diabetes	(*47*)
		PI3K/AKT/Nrf2↑, Ferroptosis↓	Inhibiting high-glucose-induced ferroptosis by activating the PI3K-AKT-Nrf2 signaling pathway	Promoting angiogenesis and accelerating diabetic wound healing	(*55*)
Pseudostellaria heterophylla polysaccharides	*Pseudostellaria heterophylla* (Taizishen)	NLRP3↓, PANoptosis↓	Inhibiting NLRP3 inflammasome assembly and PANoptosis	Improving blood perfusion and microvascular density in diabetic lower limb ischemia	(*48*)
Heterophyllin B	*Pseudostellaria heterophylla* (Taizishen)	SMOX↓, Nrf2↑, TNF-α↓, IL-6↓, IL-1β↓, TGF-β↓	Inhibiting SMOX to reinforce Nrf2-dependent antioxidant defense and suppress pro-inflammatory signaling	Rescuing high-glucose-induced endothelial dysfunction and promoting angiogenesis	(*56*)

Note: Abbreviations: GCH1, GTP cyclohydrolase 1; NO, nitric oxide; BMP4, bone morphogenetic protein 4; ROS, reactive oxygen species; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; METTL3, methyltransferase-like 3; m6A, N6-methyladenosine; SIRT1, sirtuin 1; GNG, hepatic gluconeogenesis; AGE, advanced glycation end-product; ICAM-1, intercellular adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; NLRP3, nucleotide-binding oligomerization domain-like receptor protein 3; Ang-1, angiopoietin-1; Tie-2, tyrosine kinase with immunoglobulin-like and EGF-like domains 2; SMOX, spermine oxidase.

Table 2. Pharmacological mechanisms of classical formulas and patent medicines from traditional Chinese medicine (TCM) in the treatment of diabetic lower-extremity arterial disease (LEAD)

Classification	Common name	Target/signaling pathway	Main mechanism	Protective effect	Ref.
Classical formula	Huanggi Guizhi Wuwu Decoction	HIF-1α/VEGF↑, TNF-α↓, IL-16↓, ET-1↓, NO↑	Regulating HIF-1α/VEGF signaling and suppressing vascular inflammation	Ameliorating arterial inflammation and endothelial function	(*42*)
Patent medicine	Tongxinluo capsule	ROS/NLRP3/Caspase-1/GSDMD↓, IL-1β↓, IL-18↓; Jagged-1/Notch-1/ephrin-B2↑	Inhibiting endothelial pyroptosis and enhancing endothelial-smooth muscle cell interactions	(i) Restoring hindlimb blood flow; (ii) Protecting endothelial barrier and suppressing vascular inflammation	(*43,44*)
Patent medicine	Danhong injection	VEGF-A/VEGFR-2↑, PPAR-δ↑	Activating VEGF-A/VEGFR-2 and PPAR-δ signaling axes to enhance EPC-driven endothelial repair	Improving peripheral arterial repair and angiogenesis; lowering limb necrosis risk	(*52*)
Classical formula	Danggui Sini Decoction	VEGF/PI3K/Akt↑, ET-1↓, eNOS↑	Activating VEGF/PI3K/Akt-driven angiogenesis and rebalancing the ET-1/eNOS vasomotor axis	Restoring hindlimb perfusion and functional recovery in diabetic ischemia	(*53*)

Note: Abbreviations: HIF-1α, hypoxia-inducible factor-1α; ET-1, endothelin-1; NO, nitric oxide; ROS, reactive oxygen species; NLRP3, nucleotide-binding oligomerization domain-like receptor protein 3; GSDMD, Gasdermin D; EPC, endothelial progenitor cell; eNOS, endothelial nitric oxide synthase.

availability, excessive oxidative stress, over activated inflammation, and endothelial-to-mesenchymal transition (EndMT), which collectively disrupt vascular homeostasis and predispose the arterial wall to atherosclerotic lesion formation. In the context of lower extremity arterial disease, impaired endothelial function exacerbates local ischemia, thereby contributing to progression of limb-threatening conditions and increasing risk of amputation, disability, and mortality in diabetic patients (*13*). Therefore, protecting the vascular endothelium and preserving its functional integrity may represent a fundamental therapeutic strategy for prevention and treatment of diabetic LEAD.

Salvia miltiorrhiza (Danshen) is a highly valued herb used in TCM. According to ancient Chinese medical documents, *Salvia miltiorrhiza* was believed to be highly potent in dispersing stasis and activating circulation. It is commonly used to treat various circulatory disturbance-related diseases, owing to its pharmacological actions, including vasodilation, anti-coagulation, anti-inflammatory effects, and free radical scavenging activity (*14*).

Tanshinone IIA, a major lipophilic bioactive constituent of *Salvia miltiorrhiza*, exerts a vascular-protective effect. However, its low aqueous-solubility restricts oral bioavailability and hinders clinical application. To overcome this, sodium Tanshinone IIA sulfonate (STS) was developed with greatly improved solubility. STS retains multiple pharmacological activities (anti-oxidant, anti-inflammatory, anti-apoptotic) and has been approved by the China State Food and Drug Administration (CFDA) for treating cardiovascular diseases (*15*). STS protects vascular endothelium under hyperglycemic ischemia. In diabetic mice with hindlimb ischemia, STS improved perfusion recovery, increased capillary density, and decreased reactive oxygen species (ROS) levels and miR-133a expression (*16*). It also reduced malondialdehyde (MDA) content while elevating GTP cyclohydrolase 1 (GCH1) and cyclic guanine monophosphate (cGMP) levels in ischemic muscle, indicating an enhanced anti-oxidative and vascular-protective status. To validate direct endothelial effects, primary endothelial cells were cultured under high-glucose and hypoxic conditions to mimic the diabetic ischemic micro-environment. STS markedly promoted tube formation and increased nitric oxide (NO) production, while also lowering intracellular ROS and miR-133a. Collectively, these findings demonstrate that STS exerts pro-angiogenic effects in diabetic ischemia by suppressing miR-133a and up-regulating GCH1, thereby enhancing NO bio-availability and reducing oxidative injury.

Salvianolic acid B (SalB) is another pivotal bioactive constituent of *Salvia miltiorrhiza* and possesses a vascular-protective effect. It has an extensive range of pharmacological properties, including antioxidant, anti-inflammatory, anti-thrombotic, anti-apoptotic, anti-aging,

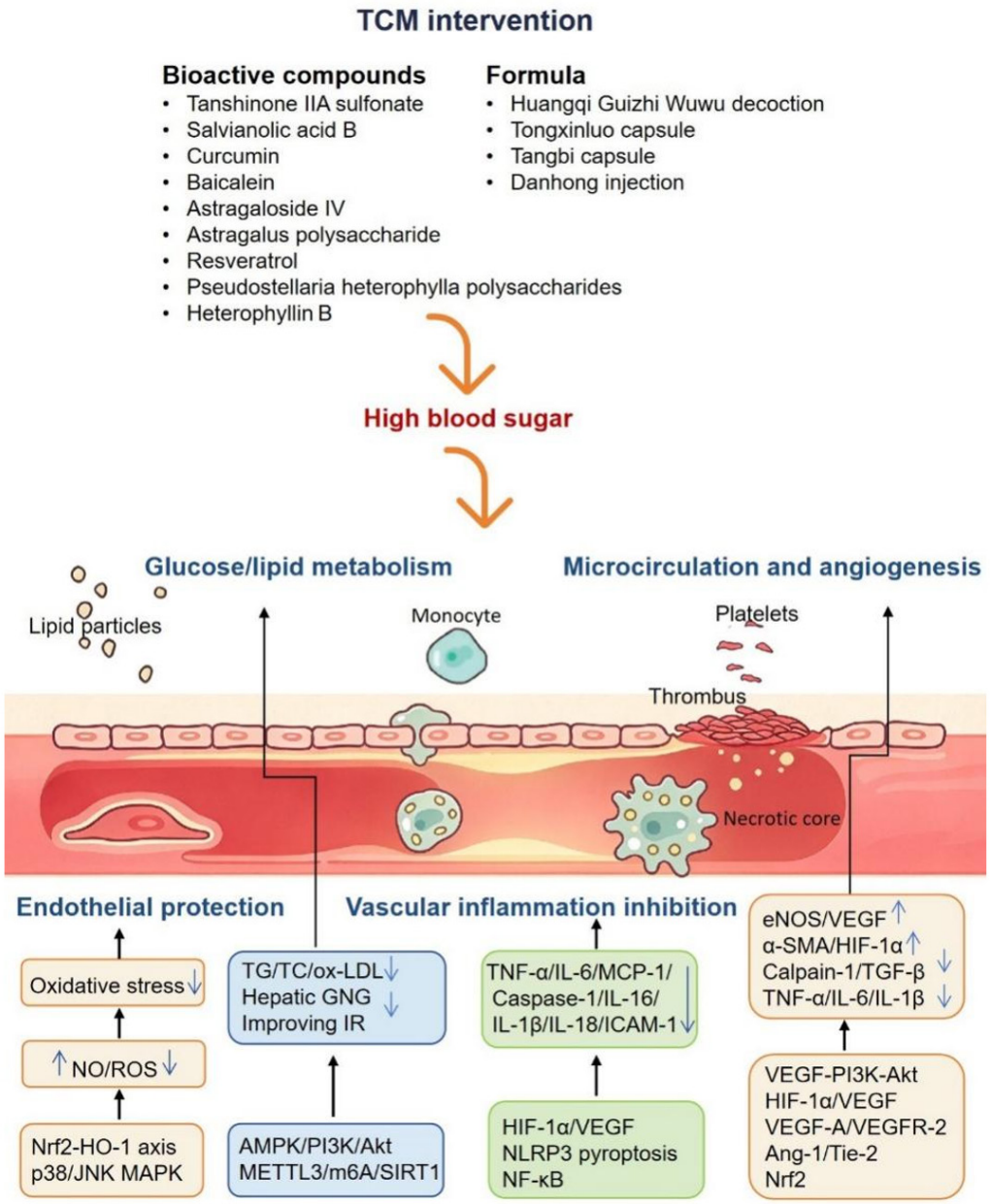


Figure 2. Molecular mechanisms of traditional Chinese medicine (TCM) for diabetic lower-extremity arterial disease (LEAD). Bioactive constituents, classical formulas, and patent medicines of TCM ameliorate hyperglycemia-induced vascular lesions *via* endothelial protection, glycolipid metabolism regulation, anti-inflammation, and promotion of microcirculation and angiogenesis, by modulating multiple intracellular signaling cascades. (Note: Abbreviations: IR, insulin resistance; TG, triglyceride; TC, total cholesterol; ox-LDL, oxidized low-density lipoprotein; GNG, gluconeogenesis; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; METTL3, methyltransferase-like 3; m6A, N6-methyladenosine; SIRT1, sirtuin 1; MCP-1, monocyte chemoattractant protein-1; ICAM-1, intercellular adhesion molecule-1; NLRP3, nucleotide-binding oligomerization domain-like receptor protein 3; HIF-1α, hypoxia-inducible factor-1α; VEGFR-2, vascular endothelial growth factor receptor 2; eNOS, endothelial nitric oxide synthase; α-SMA, α-smooth muscle actin; Ang-1, angiopoietin-1; Tie-2, tyrosine kinase with immunoglobulin-like and EGF-like domains 2.)

and vascular and mitochondrial protection (*17*). Sal B exhibited a potential to ameliorate diabetes-induced endothelial and mitochondrial dysfunction through inhibition of endothelial-cell apoptosis and excessive mitophagy (*18*). It rescues mitochondrial membrane potential, curtails ROS accumulation and improves NO bio-availability, hence maintaining vascular endothelial homeostasis under hyperglycaemia conditions, as confirmed in high-glucose-stimulated endothelial cells and diabetic mice. Moreover, Sal B ameliorates vascular endothelial dysfunction in diabetic mice by disrupting the bone morphogenetic protein 4 (BMP4)-ROS vicious cycle (*19*). It inhibits BMP4 over-expression, suppresses ROS production, restores NO bio-availability, and improves endothelium dependent aortic relaxation, thereby protecting against hyperglycemia-induced endothelial injury in diabetic mice. In addition, Building on Sal B's endothelial benefits, a metal-polyphenol

nanocomposite hydrogel loaded with Sal B was engineered for diabetic foot ulcers (*20*). It reprogrammed the metabolic microenvironment *via* ROS scavenging, angiogenesis promotion, M2 macrophage polarization, and glucose depletion, collectively accelerating wound healing in diabetic models.

Curcuma longa (Jianghuang) and *Scutellaria baicalensis* (Huangqin) are commonly used herbal medicines in TCM. Both herbs have been investigated for treatment of diabetes and its vascular complications in modern TCM pharmacological research (*21,22*). Curcumin and Baicalein, their respective main bioactive components, possess vascular protective properties. One study has demonstrated synergistic vascular protection conferred by combined curcumin-baicalein treatment (*23*). In H_2O_2-damaged EA.hy926 endothelial cells and Goto-Kakizaki diabetic rats, this combination enhanced endothelial viability, decreased fasting blood glucose and serum lipid levels, preserved aortic structural integrity, and diminished vascular TNF-α. Mechanistically, the Curcumin-Baicalein mixture activated the Nrf2-HO-1 antioxidant axis and inhibited p38/JNK MAPK phosphorylation, thereby mitigating oxidative-mediated endothelial damage. Collectively, this herbal-derived combination represents a promising multi-target strategy for managing diabetic angiopathy.

In summary, vascular endothelial dysfunction is the initiating event in pathogenesis of diabetic LEAD, and TCM-derived bioactive constituents exert robust endothelial protection. These include STS and SalB from *Salvia miltiorrhiza*, as well as the Curcumin–Baicalein combination from *Curcuma longa* and *Scutellaria baicalensis*. They preserve vascular integrity by attenuating oxidative stress and apoptosis, enhancing NO bioavailability and angiogenic capacity, and remodeling the metabolic microenvironment. These multi-target endothelial-protective properties position TCM-derived bioactive constituents as promising therapeutic candidates for management of diabetic vascular complications, warranting further investigation through rigorously designed clinical trials and mechanistic studies.

2.2. Regulation of glucose and lipid metabolism

Glucose and lipid metabolic disorders are well-established core risk factors driving occurrence and progression of diabetic LEAD (*24*). In the diabetic milieu, chronic hyperglycemia, insulin resistance (IR), and aberrant lipid profiles, characterized by elevated free fatty acids, oxidized low-density lipoprotein (ox-LDL), and triglyceride (TG)-rich remnants, collectively instigate a cascade of metabolic insults (*25*). These include enhanced polyol and hexosamine pathway flux, increased advanced glycation end-product (AGE) formation, and impaired lipoprotein lipase activity, which together promote intracellular lipid accumulation, mitochondrial dysfunction, and endoplasmic reticulum stress in vascular cells (*26*). Such metabolic disturbances not only exacerbate systemic inflammatory and oxidative stress but also directly fuel atherosclerotic plaque formation, plaque vulnerability, and micro-vascular rarefaction in the lower extremities. In the context of LEAD, uncontrolled glucose and lipid metabolism aggravates peripheral arterial stiffness, reduces collateral circulation, and accelerates ischemic tissue damage, thereby heightening risk of critical limb ischemia and adverse cardiovascular events (*27*). Therefore, restoring metabolic homeostasis through pharmacological regulation of glycemia and lipidemia may constitute an indispensable adjunctive strategy to halt or retard the natural history of diabetic LEAD, complementing revascularization and anti-thrombotic approaches.

Astragali Radix (Huangqi) is a classical traditional Chinese medicinal herb with inherent tonic properties, which has been widely used for treatment of diabetes, cardiovascular disorders, and refractory wounds in China and Southeast Asia over thousands of years. Accumulating pharmacological evidence demonstrates that *Astragali Radix* exerts multiple therapeutic bioactivities, including anti-inflammatory, antioxidant, and immunomodulatory effects (*28*). To date, more than 100 chemical constituents, primarily saponins, flavonoids, and polysaccharides, have been isolated and identified from this herb.

Among these bioactive constituents, Astragaloside IV (AS-IV) is regarded as a principal active ingredient responsible for its anti-diabetic efficacy (*29*). Consistent with its metabolic regulatory function, accumulating preclinical studies have validated that AS-IV effectively ameliorates diabetic glycolipid disorders by activating the AMPK/PI3K/Akt signaling cascade, suppressing hepatic gluconeogenesis (GNG), improving IR, and reducing circulating levels of TG, total cholesterol (TC), and ox-LDL (*30,31*). By inhibiting excessive lipid deposition and alleviating metabolic stress in vascular endothelial cells, AS-IV attenuates hyperglycemia and dyslipidemia induced peripheral arterial stiffness and atherosclerotic lesions, thereby retarding diabetic LEAD progression (*32*). Beyond classical metabolic pathways, AS-IV also exerts protective effects against diabetic vascular complications *via* epigenetic modulation. Mechanistically, AS-IV up-regulates methyltransferase-like 3 (METTL3) mediated N6-methyladenosine (m6A) modification to enhance Sirtuin 1 (SIRT1) mRNA stability and expression (*33*). The elevated SIRT1 further modulates the FOXO1/AMPK axis to mitigate AGE-triggered cellular injury, inhibit local inflammation, and facilitate vascular and tissue repair in diabetic lower extremity lesions. Comprehensively, AS-IV exerts a multi-level protective effect on diabetic vascular lesions not only by correcting glucose-lipid homeostasis but also by triggering epigenetic modification-dependent vascular protective effects.

Astragalus polysaccharide (APS), a major bioactive polysaccharide isolated from *Astragali Radix*, has been shown to exert anti-inflammatory, antioxidant, and hypoglycemic effects (*34*). Notably, growing evidence indicates that APS ameliorates type 2 diabetes mellitus (T2DM) by promoting glucose transport and modulating lipogenesis. In a high-fat-diet-induced T2DM rat model, APS treatment reverses aberrant hepatic expression of sweet-taste receptors and downstream glycolipid-metabolism genes, including glucose transporters and lipogenic enzymes, thereby restoring hepatic insulin sensitivity and correcting systemic hyperglycaemia and dyslipidaemia (*35*). These metabolic-restoring effects may reduce lipotoxic injury to peripheral arterial walls and retard progression of diabetic LEAD. At the cellular level, adipocyte-based experiments demonstrate APS counteracts TNF-α provoked IR by inhibiting miR-721 expression, which subsequently activates PPAR-γ and the PI3K/AKT signal pathway to facilitate glucose uptake in adipose tissue (*36*). Improved insulin sensitivity within adipose tissue may further mitigate chronic metabolic-related inflammation and foster a favourable systemic micro-environment, which lays a foundation for vascular-protective actions. Beyond its systemic metabolic regulation, biomaterial-based local delivery of APS provides an alternative strategy targeting diabetic peripheral ischemic complications. An APS-loaded electroconductive hydrogel composed of carboxymethyl chitosan and sodium alginate can sustain local release of APS to scavenge reactive oxygen species, suppress inflammatory responses and facilitate angiogenesis in diabetic-injured tissue. Notably, this conductive dressing enables real-time electromyographic monitoring of surrounding muscle function, offering a theranostic approach for the management of ischemic-related lower-extremity lesions secondary to diabetic LEAD (*37*).

In summary, glucose and lipid metabolic disorders are well-established drivers of diabetic LEAD, promoting IR, vascular oxidative stress, and atherosclerotic progression. *Astragali Radix* and its bioactive constituents, AS-IV and APS, exert potent glycolipid-regulating and vascular-protective effects through multiple mechanisms, including activation of the AMPK/PI3K/Akt pathway, suppression of hepatic GNG, modulation of epigenetic modifications such as METTL3/m6A/SIRT1 signaling, and regulation of glucose transport and lipogenesis. These multi-target metabolic and vascular protective properties position *Astragali Radix*-derived components as promising therapeutic candidates for ameliorating metabolic dysfunction and delaying diabetic peripheral vascular complications, warranting further investigation through rigorously designed clinical trials and mechanistic studies.

2.3. Inhibition of vascular inflammatory responses

Chronic low-grade inflammation is a central driver in the pathogenesis and progression of diabetic LEAD (*38*). Under sustained hyperglycemic conditions, the arterial wall is continuously exposed to metabolic stressors that activate multiple pro-inflammatory signaling cascades, most notably the nuclear factor-κB (NF-κB) pathway and the nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome. Aberrant activation of NF-κB promotes overexpression of inflammatory cytokines, adhesion molecules, and chemokines, thereby inducing endothelial dysfunction, lipid deposition in the vascular wall, and atherosclerotic plaque formation (*39*). Concurrently, the NLRP3 inflammasome, which is significantly upregulated in vascular cells of diabetic patients with lower extremity arterial disease, particularly in vascular smooth muscle cells, mediates maturation and release of IL-1β and IL-18, further amplifying the inflammatory milieu (*40*). Elevated circulating levels of TNF-α, IL-6, monocyte chemoattractant protein-1 (MCP-1), and soluble vascular cell adhesion molecule-1 (sVCAM-1) have been consistently documented in diabetic patients with LEAD, and these inflammatory mediators correlate with disease severity and adverse limb outcomes (*41*). Thus, pharmacological suppression of vascular inflammatory responses represents a promising therapeutic avenue for mitigating progression of diabetic LEAD. Recently, emerging evidence indicates that TCM bioactive constituents, classical formulas, and patent medicines exert substantial anti-inflammatory effects in the context of diabetic LEAD through multi-target regulation of these inflammatory pathways.

Huangqi Guizhi Wuwu Decoction is a classic traditional Chinese herbal formula documented in the "Synopsis of the Golden Chamber" (*28*). It consists of five herbal components including *Radix Astragali* (Huangqi), *Ramulus Cinnamomi* (Guizhi), *Radix Paeoniae Alba* (Baishao), *Rhizoma Zingiberis Recens* (Shengjiang), and *Fructus Jujubae* (Dazao). It is widely prescribed in China for ischemic stroke and diabetic complications. A recent study by Wang *et al.* demonstrated that Huangqi Guizhi Wuwu Decoction mitigates arterial inflammation in rats with diabetic LEAD (*42*). This decoction markedly decreased serum TNF-α, IL-16 and endothelin-1 (ET-1), and increased NO levels. Mechanistically, such protective actions were linked to regulation of the HIF-1α/VEGF signaling pathway. Collectively, these results indicate that Huangqi Guizhi Wuwu Decoction can suppress vascular inflammation and ameliorate endothelial function, which renders it a promising therapeutic candidate for diabetic LEAD.

Tongxinluo capsule is a Chinese herbal formula composed of 12 herbs containing *Ginseng Radix* (Renshen), *Hirudo* (Shuizhi), *Scorpio* (Quanxie), *Scolopendra* (Wugong) and so on (*43*). It is widely used in China for cardio-cerebrovascular diseases and has been extended to diabetes-related vascular disease. A

recent study by Gu *et al.* investigated therapeutic effects of Tongxinluo capsule on diabetic PAD (predominantly LEAD) and its underlying mechanisms (*44*). Using a *db/db* mouse model of diabetic PAD induced by femoral artery ligation, the study demonstrated that Tongxinluo capsule restored hindlimb blood flow and enhanced arteriogenesis. Specifically, Tongxinluo capsule restored endothelial cell functions, including maintaining vasodilation balance and acting as a barrier to reduce inflammation. Mechanistically, Tongxinluo capsule inhibited endothelial cell pyroptosis *via* the ROS/NLRP3/Caspase-1/GSDMD signaling pathway, thereby suppressing persistent inflammation. The study further showed that Tongxinluo capsule reduced ROS, Gasdermin D (GSDMD), cleaved caspase-1, IL-1β, and IL-18 levels in a dose-dependent manner. Additionally, Tongxinluo capsule enhanced endothelial-smooth muscle cell interactions through the Jagged-1/Notch-1/ephrin-B2 signaling pathway. These findings indicate that Tongxinluo capsule exerts anti-inflammatory effects in diabetic LEAD by protecting the endothelial barrier and inhibiting pyroptosis-mediated vascular inflammation, supporting its potential as a therapeutic candidate for diabetic LEAD.

At the level of individual herbal components, several bioactive constituents derived from TCM have demonstrated potent anti-inflammatory activities relevant to diabetic LEAD. APS, a major active constituent of *Astragali Radix*, has been shown to inhibit M1 macrophage polarization and reduce expression of TNF-α, IL-1β, and IL-6 while promoting M2 macrophage polarization and elevating IL-10 levels in diabetic wound tissues, thereby effectively alleviating local inflammatory responses (*45*). Resveratrol, a non-toxic phytoestrogen found in over 70 plants including grapevine and berries, exhibits antioxidant, anti-inflammatory, and antitumor properties (46). Recent studies indicate that it protects against cardiovascular diseases and atherosclerosis and improves glucose homeostasis. Notably, Resveratrol attenuates vascular inflammatory injury in streptozotocin-induced type 2 diabetic rats by inhibiting NF-κB nuclear translocation, reducing circulating IL-1β and IL-6 levels, and down-regulating TNF-α, intercellular adhesion molecule-1 (ICAM-1), and MCP-1 expression in the vascular wall (*47*). Additionally, Pseudostellaria heterophylla polysaccharides, water-soluble polysaccharides extracted from the dried root tubers of *Pseudostellaria heterophylla* (Taizishen), have been shown to inhibit PANoptosis, a process integrating apoptosis, pyroptosis, and necroptosis, and involving NLRP3 inflammasome assembly in high glucose-exposed endothelial cells, thereby improving blood perfusion and microvascular density in diabetic lower limb ischemia (*48*).

In summary, vascular inflammation driven by the NF-κB and NLRP3 inflammasome pathways plays a pivotal role in the initiation and progression of diabetic LEAD, promoting endothelial dysfunction, vascular remodeling, and atherosclerotic lesion formation. TCM bioactive constituents, classical formulas, and patent medicines have demonstrated considerable efficacy in inhibiting these inflammatory cascades through mechanisms involving suppression of pro-inflammatory cytokine production, modulation of macrophage polarization, and inhibition of inflammasome assembly. These multi-target anti-inflammatory properties position TCM as a promising adjunctive therapeutic strategy for prevention and treatment of diabetic LEAD, warranting further investigation through rigorously designed clinical trials and mechanistic studies.

2.4. Improvement of microcirculation and promotion of angiogenesis

Microcirculatory dysfunction and impaired reparative angiogenesis represent hallmark pathological features of diabetic LEAD, and are key modulators of tissue perfusion, ischaemic injury, and long-term limb prognosis (*49*). Under sustained hyperglycaemic stress, angiogenic responses become dysregulated at multiple molecular layers: reduced HIF-1α protein stability, blunted VEGF-A production, and diminished endothelial responsiveness to pro-angiogenic stimuli. In the ischaemic lower limbs, insufficient compensatory neovascularisation fails to establish functional collateral circulation, exacerbating tissue hypoxia and driving progression toward critical limb-threatening ischaemia. Accordingly, restoring microvascular homeostasis and harnessing therapeutic angiogenesis are regarded as promising therapeutic strategies for diabetic LEAD management Frontiers. Mounting evidence indicates that TCM formulas ameliorate lower-limb microcirculatory dysfunction and enhance reparative angiogenesis in diabetic LEAD.

Tangbi capsule, a compound TCM prescription based on the classic formula Huangqi Guizhi Wuwu Decoction, consists of granules made from five herbs: *Astragali Radix* (Huangqi), *Ramulus Cinnamomi* (Guizhi), *Ligusticum Chuanxiong* (Chuanxiong), *Radix Paeoniae Alba* (Baishao), and *Caulis Spatholobi* (Jixueteng). Previous clinical studies have shown that Tangbi capsule improves clinical symptoms such as limb coldness, numbness, pain, burning, and skin dryness in diabetic LEAD patients (*50*). Mechanistically, Tangbi capsule up-regulates HIF-1α, eNOS, and VEGFA while suppressing Calpain-1 and TGF-β expression, thereby reducing endothelial apoptosis and facilitating angiogenesis in diabetic LEAD rats (*51*). Furthermore, integrated metabolomics and transcriptomics analyses indicate that Tangbi capsule modulates arginine biosynthesis, phenylalanine metabolism, and arachidonic acid metabolism, which are biological pathways closely linked to angiogenesis, immune-inflammatory cascades, and cell proliferation.

Danhong injection is a patent injection medicine derived from extracts of *Salvia miltiorrhiza* (Danshen) and *Flos Carthami* (Honghua), which are two Chinese herbal medicines with a property of activating blood circulation and removing blood stasis. It is widely prescribed for treatment of cardiovascular and cerebrovascular disease in clinical practice. Recent studies indicate that Danhong injection improves peripheral arterial repair in type 2 diabetic mice by elevating capillary density and augmenting angiogenesis through coordinated activation of the VEGF-A/VEGFR-2 and PPAR-δ signaling axes, ultimately lowering risk of limb necrosis (*52*). Notably, a defined four-component active fraction purified from DHI has been shown to be both necessary and sufficient to enhance endothelial progenitor cell-driven endothelial repair and local neovascularization.

Danggui Sini Decoction is a classic traditional Chinese medicine formula first documented in "ShangHan Lun". It consists of seven herbs, *Angelicae Sinensis Radix* (Danggui), *Ramulus Cinnamomi* (Guizhi), *Radix Paeoniae Alba* (Baishao), *Asari Radix et Rhizoma* (Xixin), *Glycyrrhizae Radix et Rhizoma* (Gancao), *Tetrapanacis Medulla* (Tongcao), and *Fructus Jujubae* (Dazao). Danggui Sini decoction is traditionally used to warm the meridians, dispel cold, and promote blood circulation, and is widely prescribed in China for diabetic peripheral vascular complications. Recent studies indicate that Danggui Sini Decoction restores hindlimb perfusion and functional recovery in diabetic ischemic mice largely independent of glucose-lowering effects (*53*). Its protective actions are partially attributed to VEGF-PI3K-Akt-driven angiogenesis and rebalancing of the ET-1/eNOS vasomotor axis.

At the level of individual herbal components, several bioactive constituents derived from TCM have demonstrated potent microcirculation-improving and pro-angiogenic activities relevant to diabetic LEAD. Tu *et al.* reported that APS, a major active constituent of *Astragali Radix*, when combined with endothelial progenitor cells, enhanced angiogenesis in diabetic rats with hindlimb ischemia, and the combined treatment produced superior effects at least in part through VEGF/VEGFR and Ang-1/Tie-2 signaling pathways (*54*). Similarly, Pan *et al.* demonstrated that Resveratrol protects vascular endothelial cells from high-glucose-induced ferroptosis by activating the PI3K-AKT-Nrf2 signaling pathway, thereby promoting angiogenesis and accelerating diabetic wound healing (*55*). Heterophyllin B, a cyclopeptide derived from Pseudostellaria heterophylla, markedly improves hindlimb blood flow recovery and promotes angiogenesis in ischaemic muscle, accompanied by elevated CD31, α-SMA, VEGF and endothelial nitric oxide synthase (eNOS) abundance (*56*). Meanwhile, Heterophyllin B dampens local inflammation by lowering TNF-α, IL-6, IL-1β and TGF-β levels. Mechanistically, Heterophyllin B inhibits spermine oxidase (SMOX) to reinforce Nrf2-dependent antioxidant defense and restrain pro-inflammatory signalling, thereby rescuing high-glucose-induced endothelial dysfunction.

In summary, dysregulated angiogenic and vasomotor signaling impairs microcirculation and angiogenesis, which is central to onset and progression of diabetic LEAD, leading to tissue hypoxia, collateral circulation insufficiency, and limb-threatening ischemia. Some TCM bioactive constituents, classical formulas, and patent medicines exert notable effects on improving lower-limb microcirculation and stimulating angiogenesis *via* multi-target modulation of angiogenic and vasomotor signaling cascades, including the HIF-1α/VEGF, VEGF-A/VEGFR-2, PI3K-AKT, Ang-1/Tie-2 axes, as well as Nrf2-mediated antioxidant defense. Such multi-target pro-angiogenic and vasoregulatory features render TCM a promising adjunctive therapy to restore microvascular homeostasis and mitigate limb ischemia in diabetic LEAD. Further well-designed clinical trials and mechanistic studies are therefore warranted.

3. Clinical applications of TCM in diabetic LEAD

In recent years, accumulating clinical studies and evidence-based analyses have continuously validated the unique advantages of traditional Chinese medicine in comprehensive management of diabetic LEAD. Current clinical applications of TCM for diabetic LEAD cover multiple therapeutic dimensions, including perioperative adjuvant medication for endovascular intervention, topical wound rehabilitation for refractory diabetic foot ulcers, and non-pharmacological rehabilitation combined with lifestyle modification (Figure 3). A growing number of systematic reviews and meta-analyses have synthesized empirical clinical data and confirmed that multi-modal TCM interventions can effectively improve lower-limb hemodynamic perfusion, suppress postoperative restenosis, alleviate intractable wound inflammation, delay atherosclerotic progression, and ameliorate long-term clinical prognosis, providing high-level evidence supporting standardized and integrated application of TCM in diabetic LEAD treatment (Table 3).

3.1. TCM-assisted endovascular intervention for diabetic LEAD

Endovascular interventions, including balloon angioplasty and stent implantation, serve as the first-line strategy to rapidly restore lower-limb perfusion in diabetic LEAD patients. However, postoperative restenosis remains the dominant obstacle limiting long-term therapeutic efficacy and contributes to disease recurrence (*57*). Accumulating clinical evidence has demonstrated that postoperative adjuvant treatment with *Qi*-tonifying and blood-activating TCM formulas effectively reduces rates of vascular restenosis and long-term recurrence, while significantly improving

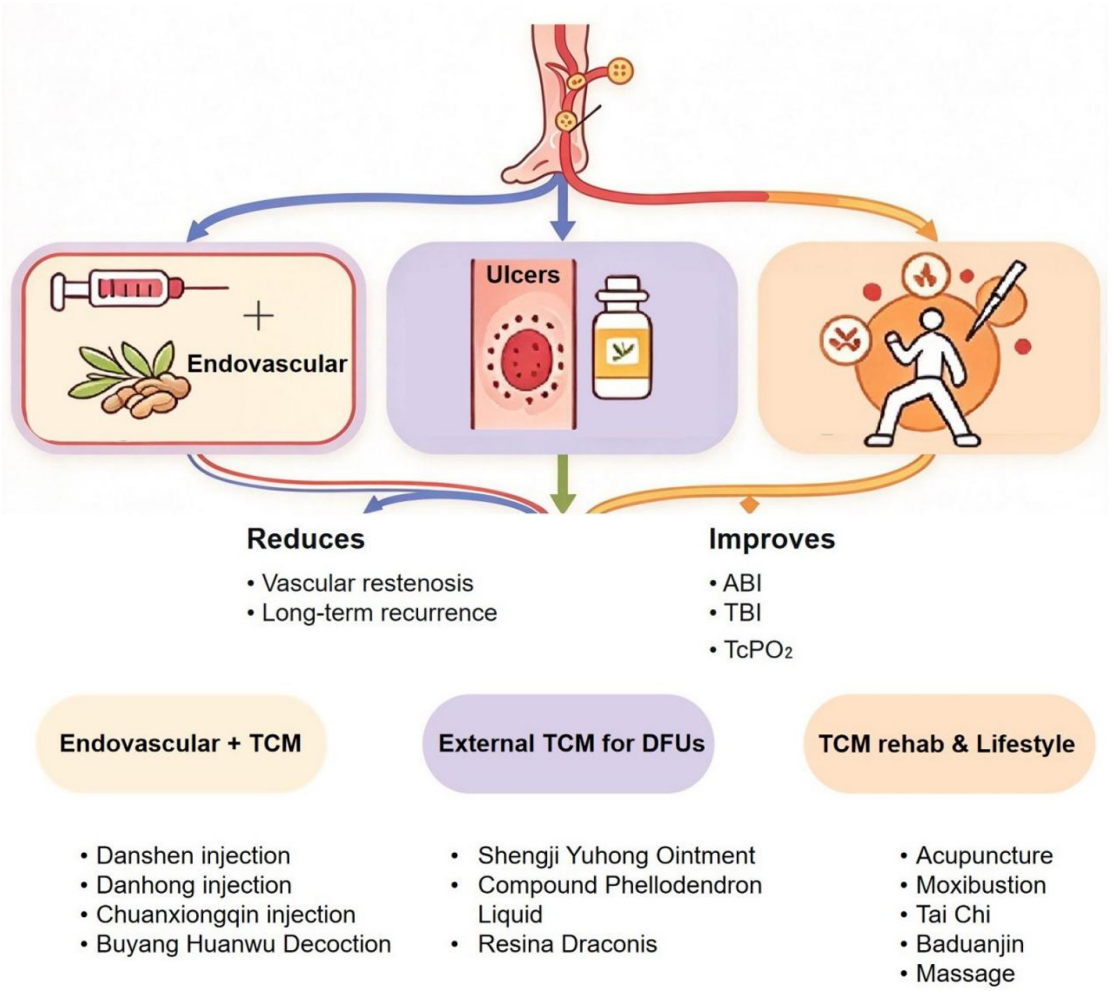


Figure 3. Clinical applications of traditional Chinese medicine (TCM) in diabetic lower-extremity arterial disease (LEAD). Three major TCM-related therapeutic strategies for diabetic LEAD are summarized: perioperative TCM combined with endovascular intervention, topical external TCM therapy for diabetic foot ulcers (DFUs), and nonpharmacological TCM rehabilitation and lifestyle interventions. These multimodal TCM interventions can effectively improve lower-limb hemodynamic perfusion, suppress postoperative restenosis, alleviate intractable wound inflammation, delay atherosclerotic progression, and improve long-term clinical prognosis.

core perfusion indicators including ABI, toe-brachial index (TBI) and transcutaneous oxygen partial pressure ($TcPO_2$).

Buyang Huanwu Decoction, a classic traditional Chinese medicine formula, is composed of seven herbs: *Astragali Radix* (Huangqi), *Angelicae Sinensis Radix* (Danggui), *Paeoniae Radix Rubra* (Chishao), *Chuanxiong Rhizoma* (Chuanxiong), *Persicae Semen* (Taoren), *Carthami Flos* (Honghua), and *Pheretima* (Dilong). The formula is traditionally used for treating blood stasis secondary to *Qi*-deficiency. Clinical studies have reported that adjunctive Buyang Huanwu Decoction treatment after balloon angioplasty significantly improved ABI, TBI, and blood flow velocity of the dorsal pedis and posterior tibial arteries in type 2 diabetic LEAD patients. This combination therapy also reduced the 6-month and 12-month restenosis rates and improved VAS scores and claudication distance (*58*). In addition, a Bayesian network meta-analysis compared efficacy of blood-activating Chinese herbal injections for diabetic LEAD. The results demonstrated that adjuvant use of herbal injections including Danshen injection, Danhong injection, and Chuanxiongqin injection combined with conventional Western therapy significantly improved the ankle-brachial index (ABI), dorsalis pedis artery blood flow velocity, and hemorheological parameters. These findings support that blood-activating Chinese herbal injections represent a valuable adjunctive therapeutic option for patients with diabetic LEAD (*10*).

In summary, TCM adjuvant therapy, represented by *Qi*-tonifying and blood-activating formulas and herbal injections, optimizes lower-limb hemodynamics, improves peripheral perfusion, and reduces postoperative vascular restenosis, thereby enhancing long-term efficacy of endovascular revascularization for diabetic LEAD.

3.2. Application of external TCM therapy in wound management of LEAD-related diabetic foot ulcers

Diabetic foot ulceration and gangrene secondary to

Table 3. Clinical Application of traditional Chinese medicine (TCM) in the treatment of diabetic lower-extremity arterial disease (LEAD)

Therapeutic approach	Specific interventions	Treatment phase	Therapeutic efficacy	Outcome measures	*Ref.*
TCM-assisted endovascular intervention	Adjunctive Buyang Huanwu Decoction after balloon angioplasty	Post-interventional phase	Improving hemodynamics and reducing restenosis	ABI, TBI, blood flow velocity, restenosis rate, VAS score, claudication distance	(*58*)
	Blood-activating herbal injections (Danshen, Danhong, Chuanxiongqin) + conventional Western therapy	Post-interventional phase	Improving hemodynamics and hemorheology	ABI, dorsalis pedis artery blood flow velocity, hemorheological parameters	(*10*)
External TCM therapy for diabetic foot ulcers	Shengji Yuhong Ointment; Compound Phellodendron Liquid	Wound management phase	Eliminating necrotic tissue, controlling infection, and promoting wound healing	Ulcer healing, complete healing rate, healing duration, ulcer size	(*60-63*)
	Resina Draconis	Wound management phase	Improving healing efficiency, diminishing wound area, and downgrading Wagner grades	Healing efficiency, wound area, Wagner grade	(*64*)
TCM-based rehabilitation	Acupuncture	Rehabilitation phase	Improving microvascular perfusion	Microcirculatory parameters, lower-extremity blood flow	(*65*)
	Moxibustion	Rehabilitation phase	Elevating transcutaneous oxygen tension and relieving ischemic manifestations	Transcutaneous oxygen tension, exercise tolerance	(*66*)
	Tai Chi/Baduanjin	Rehabilitation phase	Stabilizing glycemic/lipid profiles and slowing atherosclerotic progression	Glycemic and lipid profiles, vascular function	(*67*)
	Local foot acupoint massage	Rehabilitation phase	Enhancing lower-limb blood perfusion and alleviating numbness/coldness	Lower-limb blood perfusion, clinical symptoms	(*68*)

Note: Abbreviations: ABI, ankle-brachial index; TBI, toe-brachial index; VAS, visual analogue scale.

severe lower-limb ischemia represent the most disabling complications of diabetic LEAD. Conventional debridement and antibiotic treatment often yield unsatisfactory outcomes for refractory ulcers complicated with drug-resistant bacterial infection, especially *Pseudomonas aeruginosa* (*59*). External TCM therapies directly act on local wounds, exerting multiple effects including heat-clearing and detoxifying, necrotic tissue removal, blood circulation activation and granulation promotion. Classic external preparations, such as Shengji Yuhong Ointment and Compound Phellodendron Liquid, are widely applied to eliminate necrotic tissue, control local infection and accelerate wound repair (*60,61*).

A systematic review covering 49 randomized controlled trials (RCTs) demonstrated that adjuvant TCM treatment significantly elevated the complete healing rate of diabetic foot ulcers (RR 1.42-1.76), shortened healing duration by 4-23 days, and reduced ulcer size (*62*). Consistently, another recent meta-analysis of 34 RCTs further validated clinical benefits of topical TCM preparations, confirming that commonly used external TCM patent medicines including Compound Phellodendron Liquid and Shengji Yuhong Ointment substantially improved overall therapeutic efficacy of conventional wound care for diabetic foot ulcers (*63*). Additionally, *Resina Draconis*, a well-known blood-activating TCM resin derived from *Dracaena cochinchinensis*, exerts wound-clearing, detumescent and tissue-regenerating pharmacological properties for cutaneous ulcer management. A systematic review and meta-analysis of RCTs focusing on this agent demonstrated that topical application of *Resina Draconis* extract significantly improved ulcer healing efficiency, diminished wound area, and downgraded Wagner ulcer grades among patients with diabetic foot ulcers (*64*).

In summary, external TCM treatments inhibit local drug-resistant bacterial growth, alleviate intractable wound inflammation and facilitate tissue regeneration, constituting an indispensable component of comprehensive management for LEAD-related diabetic foot ulcers.

3.3. TCM-based rehabilitation and lifestyle modification for diabetic LEAD

Beyond pharmacotherapy and endovascular adjuvant therapy, TCM-based rehabilitation and lifestyle modification constitute critical non-pharmacological components for comprehensive management of diabetic LEAD. These non-pharmacological approaches ameliorate lower-limb microcirculation, stabilize glycolipid homeostasis, and retard atherosclerotic progression.

Acupuncture regulates *Qi*-blood circulation *via* targeted acupoint stimulation and improves peripheral microvascular perfusion. Clinical evidence demonstrates that acupoint-based acupuncture optimizes microcirculatory parameters and augments lower-extremity blood flow in patients with diabetic peripheral arterial disease, which may further facilitate chronic wound repair (*65*). Moxibustion applied at Zusanli (ST36), Sanyinjiao (SP6), and Yongquan (KI1) elevates transcutaneous oxygen tension, improves exercise tolerance, and relieves ischemic manifestations among PAD patients (*66*). Furthermore, traditional Chinese mind-body exercises including Tai Chi and Baduanjin, when combined with treadmill training and dietary regulation, help stabilize glycemic and lipid profiles, preserve vascular function, and slow atherosclerotic progression (*67*). Local foot acupoint massage enhances lower-limb blood perfusion through neuro-reflex modulation and alleviates clinical symptoms such as limb numbness and coldness; notably, massage should be cautiously performed in patients with severe arterial stenosis or skin ulceration to avoid tissue injury (*68*).

Collectively, these multi-modal rehabilitation interventions exert synergistic effects to attenuate vascular lesion progression, reduce ulcer recurrence risk, and improve long-term quality of life.

4. Limitations and future perspectives

Although accumulating preclinical findings have verified the protective efficacy of TCM and its bioactive components against diabetic LEAD, several notable limitations still restrict its clinical translation and standardized application. Current relevant evidence is predominantly derived from rodent hindlimb ischemia models, while high-quality, large-sample clinical randomized controlled trials in diabetic LEAD patients remain insufficient, lacking robust clinical validation for TCM therapeutic effects. Mechanistically, most existing studies merely focus on single bioactive constituents or individual signaling pathways (*e.g.*, Nrf2-mediated antioxidant pathway and HIF-1α/VEGF angiogenesis axis), ignoring the holistic multi-component and multi-target characteristics of TCM formulas, and synergistic interactions among herbal ingredients remain poorly elucidated. In addition, significant heterogeneity in TCM syndrome differentiation, formula composition, dosage and treatment duration across studies impairs reproducibility and comparability of research data. Furthermore, systematic evaluations on long-term safety, adverse reactions and herb-drug interactions between TCM and conventional anti-platelet or lipid-lowering therapies are still lacking.

To address these deficiencies, future research should focus on standardized, rigorously designed clinical trials with unified syndrome stratification and intervention protocols to consolidate clinical efficacy of TCM for diabetic LEAD. Advanced multi-omics technologies are recommended to explore synergistic mechanisms of integral herbal formulas, instead of limited investigation of single monomers. Key signaling axes including SMOX-Nrf2, HIF-1α/VEGF and PI3K-AKT deserve in-depth exploration, as they are critical targets for improving

endothelial dysfunction and restoring lower-limb microcirculation. Moreover, targeted studies are required to clarify the safety profile and herb-drug interactions of TCM adjuvant therapy, to guide its safe and standardized combination with conventional revascularization and symptomatic treatments. Meanwhile, emerging organoid models and large animal ischemic limb models can be applied to bridge the gap between basic research and clinical practice. Integrated basic and clinical studies will further promote innovative development and clinical popularization of TCM-based combinatory strategies for diabetic LEAD.

5. Conclusion

Diabetic LEAD is a severe macrovascular complication of diabetes driven by endothelial dysfunction, glycolipid metabolic disturbance, persistent vascular inflammation, and defective microcirculatory angiogenesis, ultimately leading to limb ischemia, refractory foot ulcers, and increased risks of amputation and mortality. As a complementary and alternative therapeutic approach, TCM offers unique holistic advantages in comprehensive management of diabetic LEAD through multi-component, multi-pathway, and multi-target regulatory mechanisms. This review systematically summarizes modern pharmacological mechanisms of representative TCM bioactive constituents, classical formulas, and patent medicines, encompassing vascular endothelial protection, glycolipid metabolism regulation, vascular inflammatory inhibition, and microcirculation improvement coupled with pro-angiogenic effects. Clinically, various TCM modalities, including perioperative adjuvant herbal medication, topical wound-healing therapies, and traditional rehabilitation combined with lifestyle modification, have been shown to reduce postoperative restenosis, accelerate ulcer repair, improve lower-limb perfusion, and delay atherosclerotic progression. Collectively, TCM-based interventions represent promising adjunctive strategies for diabetic LEAD, and further high-quality evidence is warranted to support their precise, standardized, and personalized clinical application.

Funding: This study was funded by the Co-construction Science and Technology Project of the Department of Science and Technology, National Administration of Traditional Chinese Medicine (No. GZY-KJS-SD-2023-068).

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received September 9, 2026; Revised October 14, 2026; Accepted October 18, 2026.

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Released online in J-STAGE as advance publication October 20, 2026.