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Review Article

Novel insights on the vascular protective effects of tanshinone

Zhe An[1*], Guang Yang[2*], Guohui Liu[1], Haikuo Zheng[1], Chunjie Li[3], Wenqi Zhang[1]

[1]Department of Cardiology, China-Japan Union Hospital of Jilin University, Changchun, China; [2]Department of Molecular Biology, College of Basic Medical Science, Jilin University, Changchun, China; [3]Tianjin Chest Hospital, Tianjin, China. [*]Equal contributors.

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Abstract: Tanshinone (TS) is a traditional Chinese medicine that is derived from phenanthrenequinone isolated from the root of *Salvia miltiorrhiza*. In China, TS is widely used to improve cardiovascular function, relieve angina, and lower blood lipids as well as blood viscosity in clinical treatments for cardiovascular and cerebrovascular disorders. In recent years, cardiovascular and structural protection research has focused on the role of TS in cardiovascular protection. TS is involved in regulating multiple drug targets and exhibits potent pharmaceutical effects on blood vessel dilation, vascular endothelial cell protection, anti-oxidation, anti-angiogenesis, smooth muscle proliferation inhibition, and anti-inflammation. Current studies on the pharmacological mechanisms that are involved in vascular protection are discussed in this review to improve the current understanding of the protective effects of TS and to provide a novel perspective on its clinical use.

Keywords: Tanshinone, traditional Chinese medicine, cardiovascular

Introduction

In China, Danshen has been used for several years to treat various cardiovascular diseases. Two different subtypes of Danshen are available, *Salvia miltiorrhiza and Salvia przewalskii*; *S. miltiorrhiza* is the traditional Danshen, whereas *S. przewalskii* is widely used in the Western areas of mainland China [1]. Danshen, a widely used medicinal plant in China and a complementary medicine in the West, has been indexed in the 2010 *Chinese Pharmacopoeia*; more than 35 formulations and concoctions containing Danshen water extracts, ethanolic extracts, or their combination that are rich in both phenolic acids and different levels of tanshinone (TS) have been included in this issue [2].

TS derivatives, such as TS IIA, cryptotanshinone, and TS I, which are the major bioactive constituents of Danshen, are abietane diterpenes [3, 4]. TS IIA is one of the most pharmacologically active components of Danshen that have been isolated. In Asian countries, TS IIA is used as a component (For example, Qi-Shen-Yi-Qi Dripping Pills) of therapeutic remedies for myocardial infarction (MI), angina pectoris, stroke, atherosclerosis, cancer, neonatal hypoxic ischemic encephalopathy, hepatic fibrosis, and neurodegenerative diseases [5-8].

TS in combination with classic lipid-lowering drugs are clinically used in China to treat atherosclerosis and other cardiovascular diseases. Conventional therapy that is co-administered with sodium TS IIA sulfonate (STS) injections significantly improves the clinical symptoms of patients with acute coronary syndrome [9]. We provide an overview of the recent studies on the cardiovascular effects and the underlying mechanisms of TS, as observed in experimental and clinical studies. This review presents the pharmacological and therapeutic profiles of TS as regards with cardiovascular system, particularly the vascular system.

Vasodilator effect of TS

The initiation of atherosclerosis is closely related with the senescence of endothelial cells [10]. Endothelial cells are located at the inner

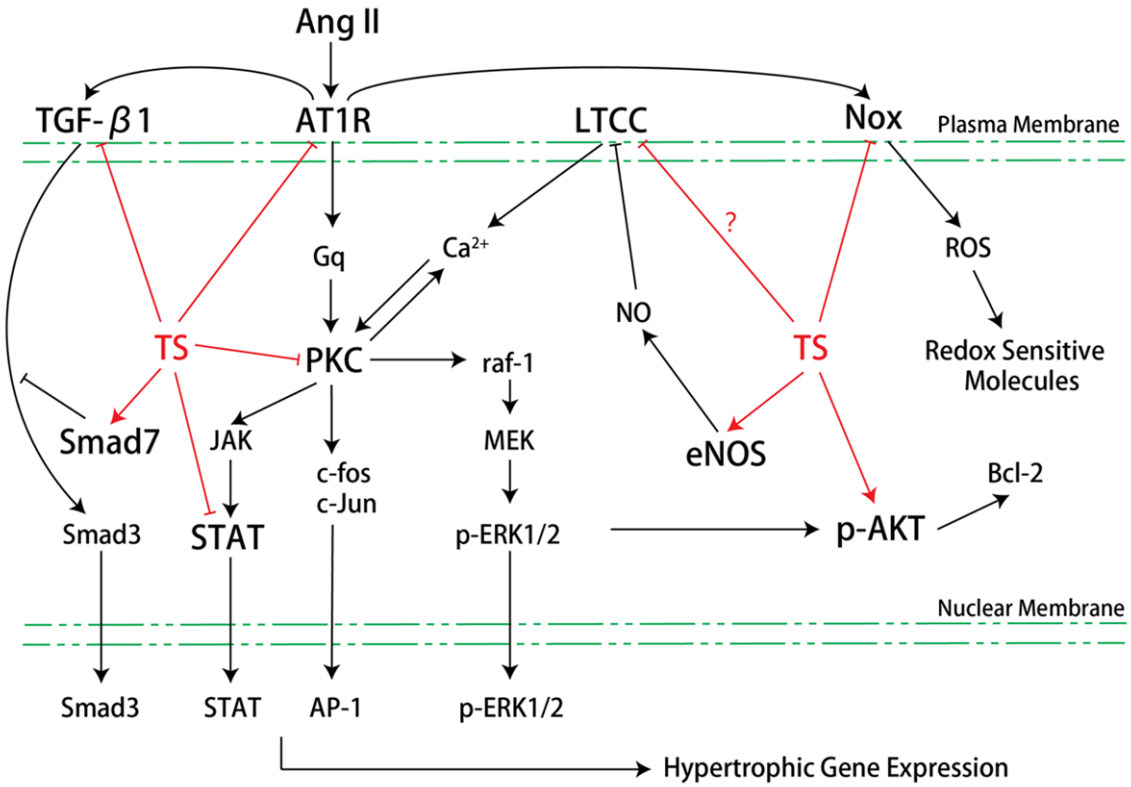

Figure 1. Schematic of the role of TS in cardiac hypertrophy prevention. Legend: AP-1, activator protein-1; Ang-II, angiotensin II; AT1R, type 1 Ang-II receptor; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal regulated kinases; JAK, janus activated kinase; LTCC, L-type calcium channels; MEK, mitogen activated protein kinase kinase; NADPH, nicotinamide adenosine dinucleotide phosphate; Nox, NADPH oxidase; NO, nitric oxide; PKC, protein kinase C; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; TGF-1, transforming growth factor-1; TS, Tanshinone.

vessel wall and they comprise a physiological barrier between the blood and the vascular smooth muscle. They hinder cholesterol, lipids, and macrophages from passing through, thereby resulting in the formation of lipid deposits in the arterial intima and the development of atherosclerotic plaques. Vascular endothelial cells have crucial physiological functions such as maintaining the normal circulation of blood. They can synthesize and release several active substances, such as nitric oxide, prostacyclin, and endothelin (ET), to adjust the size of lumen and maintain their environmental stability [11]. Cytokine secretion significantly changes during the senescence process of vascular endothelial cells. The synthesis of inflammatory cytokines and the expression of adhesion molecules both increase with the decrease in the synthesis of endothelium-dependent vasodilation factor. Gao et al. [12] have shown that TS can modulate multiple signaling pathways in both cardiomyocytes and fibroblasts. The mechanisms of TS are summarized in **Figure 1**.

TS has a pharmacological effect that is similar to that of type 1 Ang-II receptors (AT1R); Ang-II plays a key role in mediating cardiomyocyte hypertrophy and interstitial fibrosis, mainly by binding with AT1R to suppress its expression [13, 14]. The downregulation of both the protein kinase C (PKC) and the NO/NOS system expression, which has a close relationship with the pathological process of myocardial hypertrophy, is also affected by the expression of eNOS and the production of endogenous NO in the local myocardium [15]. NO is a potent vasodilator that plays an important role in regulating vascular tones [16]. Hong et al. demonstrated that TS IIA inhibits strain-induced ET-1 expression. However, the production of NO, phosphorylation of eNOS, and activation of transcription factor 3 (ATF3) expressions in the human umbil-

ical vein endothelial cells (HUVEC) are enhanced by TS IIA [17, 18]. TS IIA also inhibits Ang II-induced cell proliferation, reactive oxygen species (ROS) formation, and extracellular signal regulated kinases (ERK) phosphorylation; thus, TS IIA prevents cardiac fibroblast proliferation by interfering with the generation of ROS [18]. TS may also activate eNOS, which leads to vasodilation and reduction of blood pressure [18-21]. Pan et al. demonstrated that TS IIA and salvianolic acid have certain levels of cardioprotective functions, such as eNOS phosphorylation, L-arginine uptake, and CAT expression, through multiple targets that are related with NO production [20]. The level of circulation and the amount of local Ang-II are both elevated during cardiac hypertrophy, which elicit and promote the disease by activating AT1R. TS acts as an AT1R antagonist by negatively regulating AT1R and its downstream pathways, including PKC, MEK/ERK1/2, TGF-β1/Smad, JAK/STAT, and NADPH oxidase pathways [12]. TS selectively increases mesenteric perfusion in a dose-dependent manner, possibly by endothelium-derived hyperpolarizing factor vasodilating pathway in newborn piglets [22].

TS can repress the vasorelaxant effect by inhibiting the role of calcium ions. TS IIA initiates vasodilation through the ATP-sensitive K^+ channel to lower $[Ca^{2+}]$. TS IIA has endows a relaxing effect on the tonic contraction of phenylephrine in isolated aortic rings with no endothelial cell [23]. TS IIA has a biphasic effect on a rat's isolated pulmonary arteries. The mild constrictive effect that is induced by TS IIA is affected by the integrity of the endothelium and the production of NO. Meanwhile, the potent dilative effect is endothelium-independent, which is primarily the result of the inhibition of extracellular Ca^{2+} influx, whereas a partial result of the inhibition of intracellular Ca^{2+} release and activation of Ca^{2+}-activated K^+ channels [24, 25].

Dihydrotanshinone is a lipophilic component of the medicinal herb *Salvia miltiorrhiza* (Danshen); it also inhibits the influx of Ca^{2+} in the vascular smooth muscle cells and is independent from the pathways involving the endothelium, muscarinic receptors, beta-adrenoceptors, adenylyl cyclase, and guanylyl cyclase [26]. TS also acts as a calcium antagonist by minimizing the increase of $[Ca^{2+}]$ in cardiac cytoplasm and by blocking L-type calcium channels (LTCC). However, whether TS indirectly reduces calcium influx through its effects on PKC and eNOS/NO or through direct combination with LTCC remains unclear.

Anti-oxidant activity of TS

Endothelial cell injury is a critical part of vascular disease. Oxidative stress among endothelial cells is critical to pathogenic factors on both endothelial cell injury and apoptosis. Chan et al. showed that TS IIA can inhibit H_2O_2-induced injury of HUVECs. The pretreatment with TS IIA decreases the activity of caspase-3 and the expression of p53, but it induces the expression of ATF3 [27]. TS IIA significantly decreases the expression of pro-apoptotic proteins (Bax and caspase-3), but significantly increases the expression of anti-apoptotic protein Bcl-2, which is mainly associated with ROS generation, followed by an imbalance in Bax/Bcl-2 ratio and caspase-3 activation that leads to apoptosis [28]. TS prevents endothelial dysfunction by protecting HUVEC from H_2O_2-induced injury by decreasing CD40 expression and enhancing NO production through the PI3K-Akt-AMPK-eNOS pathway [20, 29, 30]. Moreover, TS initiates Ang-II-induced cardiomyocyte apoptosis by increasing the phosphorylation of Akt and the Bcl-2/Bax ratio [31, 32].

Anti-inflammatory effect of TS

Inflammatory damage plays an important role in cerebral ischemic pathogenesis. TS IIA elicits a series of biologic effects in cerebral ischemia through its anti-inflammatory properties [33, 34]. The HMGB1-induced NF-κB activation pathway has gained recognition as a key contributor to proinflammatory response. TS IIA protects the brain from damage caused by pMCAO through downregulating HMGB1, RAGE, TLR4, and NF-κB and upregulating claudin-5 expression [35]. TS IIA decreases the levels of MMP-9, TNF-α, IL-1α, IL-2, IFN-γ, and ROS in leukocytes. TS IIA can also protect the blood-brain barrier (BBB) against leukocyte-associated hypoxia-reoxygenation injury by minimizing the activation of leukocytes and inhibiting the destructive effects of leukocytic products [36].

Moreover, TS IIA inhibits ET-1 production in TNF-α-induced BMVEC by suppressing the endothelin-converting enzyme-1 synthesis [37]. Tang et al. demonstrated that TS IIA significant-

Table 1. The multiple signaling molecules that are involved in atherosclerosis and are regulated by TS IIA, effects on myocardial cell protection

Effect on myocardial cells	Active site			
Clinical indicators	MDA↓	LDH↓	CK↓	ST segment↓
Vasorelaxation	NO↑			
Increased membrane stability	Ca2+ entry into cell↓			
Suppressed apoptosis of cardiac myocytes	Bax/bcl-2↓	P53↓	Casepase-3↓	
Inhibition of inflammatory repose in myocardial impairment	IL-1β, IL-6↓	IL-10↑	VEGF↓	

Malondialdehyde (MDA); lactate dehydrogenase (LDH); creatine kinase (CK); interleukin (IL); vascular endothelial growth factor (VEGF). ↑represents an increase in either mRNA or protein level, or the activation of the target molecule; ↓represents a decrease in either the mRNA or protein level, or the inhibition of activity.

ly inhibits the TNF-α-induced production of ROS, accompanied by decreased malondialdehyde levels. It regulates the TNF-α-induced expression of VCAM-1 and ICAM-1 by inhibiting the activation of NF-κB and the generation of ROS in BMVECs [38]. TSB has limited brain penetration through the BBB because of the contribution of P-glycoprotein, and to a lesser extent, of multidrug resistance-associated protein in rodents. Further studies are needed to confirm the involvement and clinical relevance of the corresponding transporters in humans in limiting the penetration of TSB across the BBB [39, 40].

Atherosclerosis is a well-recognized inflammatory disease that is triggered by lipid and oxLDL accumulation in arterial wall [41]. TS inhibits the production of inflammatory mediators, such as IL-1, IL-6, TNF-α, iNOS, cyclooxygenase-2, and NO in RAW264.7 cells [42-45]. TS IIA performs its anti-inflammatory effect by modulating the TNF-α-induced expression of VCAM-1, ICAM-1, and fractalkine, or by inhibiting the TNF-α-induced activation of the IKK/NF-κB signaling pathway in human vascular endothelial cells [46]. Most recently, TS IIA was reported to anti-inflammatory in ovariectomized ApoE mice by activating the estrogen receptor through the extracellular signal-regulated kinase (ERK) signaling pathway [47]. The representative target molecules that are involved in the pathogenesis of AS and regulated by TS IIA are summarized in **Table 1** [48].

TS I and dexamethasone exhibit anticancer effects on the cancer cell expressions of intercellular adhesion molecule-1 (ICAM-1) and on vascular cell adhesion molecule-1 (VCAM-1) in the TNF-α-stimulated endothelial cells [49]. These molecules, such as E-selectin and ICAM-1, are critical components of both carcinogenesis and cancer metastasis [50].

Anti-angiogenic effect of TS IIA

Ischemia and reperfusion (I/R) exert multiple insults in microcirculation, which is frequently accompanied by endothelial cell injury, enhanced leukocyte adhesion, macromolecular efflux, oxygen free radical production, and mast cell degranulation. The protection of organs after I/R is important in clinical practice, given that microcirculatory disturbances result in an injury of the organ involved. TS IIA promotes angiogenesis and upregulates VEGF expression in MI rats by enhancing the expression of hypoxia-inducible factor 1 alpha mRNA; moreover, TS IIA provides a novel target for TS IIA in the prevention and treatment of myocardial ischemia injury [51]. TS IIA inhibits in vivo angiogenesis by chorioallantoic membrane assay and exhibits in vitro anti-angiogenic effects by modulating the secretion of MMP-2 and TIMP-2 in an opposite manner, resulting in decreased MMP-2 activity of vascular endothelial cells [52]. Recently, in vitro experiments results indicated that TS IIA inhibits angiogenesis by downregulation of the VEGF/VEGFR2 pathway [53]. Liu et al. demonstrated that TS IIA elicits its effects by stimulating the production of endothelial microparticle and the eicosanoid metabolism pathway [54].

Inhibitory effect of TS IIA on smooth muscle proliferation

Vascular smooth muscle cell (VSMC) proliferation plays a central role in the development of intimal hyperplasia on pathological artery healing. Oral administration of TA can significantly decrease the intimal thickening of injured vessels and can trigger the proliferation of cell

nuclear antigen-positive VSMC in the intimal area of a rat's carotid artery that is injured by complete cessation of blood flow [55]. TS IIA can significantly decrease intimal thickening, cell proliferation, and bromodeoxyuridine incorporation into DNA, as well as block cell cycles in the G(0)/G(1) phase and inhibit both ERK1/2 phosphorylation and c-fos expression. TA abolishes VSMC proliferation and reduces intimal hyperplasia by inhibiting the mitogen-activated protein kinase signaling pathway and by down-regulating c-fos expression [56, 57]. TS IIA elicits human endothelial cell death by activating quinone oxidoreductase, which induces a calcium imbalance and mitochondrial dysfunction, given that anti-neovascularization is an effective strategy for anti-cancer therapy; as such, the activity of caspase is stimulated [58]. SMC migration plays an important role in normal angiogenesis and is relevant to disease-related vascular remodeling under certain conditions such as brain arteriovenous malformations, pulmonary hypertension, arteriosclerosis, and restenosis after angioplasty. TS inhibits both the human aortic smooth muscle cell migration and MMP-9 activity through the AKT signaling pathway [59, 60]. TS IIA also inhibits SMC migration by decreasing osteopontin expression [61]. TS IIA prevents rat basilar artery SMCs proliferation by inactivation of PDK1 during the development of hypertension [62]. TS IIA inhibits high glucose-induced VSMCs proliferation and migration through activation of AMPK/NF-κB signaling axis [63].

Conclusion and perspective

Various challenges on vascular diseases, such as cardiovascular and cerebrovascular diseases, have emerged in the beginning of the 21st century. The number of deaths that are caused by cardiovascular diseases has been reduced because of medical development. However, vascular diseases remain as the most common cause of death. Chinese medicine has made significant contributions as complementary and alternative medicine that goes back thousands of years. The application of traditional Chinese medicine in improving the function of blood circulation has been widely recognized. TS research has achieved remarkable results in recent years. The current worldwide research on TS may broaden its potential clinical uses under various formulations. New formulations and synthetic analogs with enhanced bioavailability and reduced risk of side effects are also being developed. TS demonstrates various pharmacological effects, such vasodilation and anti-thrombotic, anti-inflammatory, antioxidant, anti-arrhythmic, and anti-fibrosis effects; thus, TS is a promising cardioprotective agent. However, many of the cardiovascular protective mechanisms of TS remain unclear, and thus, further studies are necessary.

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Disclosure of conflict of interest

None.

Address correspondence to: Wenqi Zhang, Department of Cardiology, China-Japan Union Hospital of Jilin University, Changchun 130033, China. Tel: +86-431-84995259; Fax: +86-431-84995091; E-mail: Adler1980@gmail.com

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