Review Article

Novel insights on the vascular protective effects of tanshinone

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Received January 12, 2016; Accepted May 2, 2016; Epub November 15, 2016; Published November 30, 2016

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
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 umbl-
Vascular protective effects of tanshinone

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$_2$O$_2$-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$_2$O$_2$-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-
Vascular protective effects of tanshinone

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

<table>
<thead>
<tr>
<th>Effect on myocardial cells</th>
<th>Clinical indicators</th>
<th>Vasorelaxation</th>
<th>Increased membrane stability</th>
<th>Suppressed apoptosis of cardiac myocytes</th>
<th>Inhibition of inflammatory repose in myocardial impairment</th>
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<tr>
<td></td>
<td></td>
<td>MDA↓</td>
<td>LDH↑</td>
<td>NO↑</td>
<td>Ca2+ entry into cell↓</td>
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<td></td>
<td></td>
<td>Bax/bcl-2↓</td>
<td>P53↑ Casepase-3↓</td>
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<td></td>
<td></td>
<td></td>
<td>IL-1β, IL-6↑</td>
<td>IL-10↑ VEGF↑</td>
</tr>
</tbody>
</table>

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.

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 as 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.

Acknowledgements

The present study was supported by the Ministry of Education’s “Innovative Research Team Development Plan” (No. IRT1276).

Disclosure of conflict of interest

None.

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Vascular protective effects of tanshinone


Vascular protective effects of tanshinone


