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Review

Cardiovascular actions and therapeutic potential of tanshinone IIA

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ABSTRACT

Tanshinone IIA (TS), a pharmacologically active component isolated from the rhizome of the Chinese herb *Salvia miltiorrhiza* Bunge (Danshen), has been clinically used in Asian countries for the prevention and treatment of coronary heart disease. Recently, the pharmacological properties of TS in the cardiovascular system have attracted great interest. Emerging experimental studies and clinical trials have demonstrated that TS prevents atherogenesis as well as cardiac injury and hypertrophy. In atherosclerosis, TS acts by inhibiting LDL oxidation, monocyte adhesion to endothelium, smooth muscle cell migration and proliferation, macrophage cholesterol accumulation, proinflammatory cytokine expression and platelet aggregation. TS has some activity and potential to stabilize atherosclerotic plaques. The cardioprotective effects of TS are mainly related to its anti-oxidant and anti-inflammatory actions. In this review, we focus on the protective effects and the mechanism of action of TS in the cardiovascular system, and provide a novel perspective on clinical use of TS.

Contents

Abbreviations: Ang-II, angiotensin II; AP-1, activator protein-1; ApoE$^{-/-}$, ApoE deficient; AT$_1$R, type 1 Ang-II receptor; $[Ca^{2+}]_i$, intracellular calcium; CVD, cardiovascular diseases; CYP, cytochrome P450s; DOX, doxorubicin; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinases; I-κB, inhibitory kappa B; IKK, IκBα kinase; IL, interleukin; I/R, ischemic/reperfusion; JAK, janus activated kinase; LDL, low-density lipoprotein; LOX-1, lectin-like oxidized LDL receptor-1; MEK, mitogen activated protein kinase kinase; MI, myocardial infarction; MMP, matrix metalloproteinase; NADPH, nicotinamide adenosine dinucleotide phosphate; NF-κB, nuclear factor kappa B; NIK, NF-κB-inducing kinase; Nox, NADPH oxidase; NO, nitric oxide; Nrf-2, nuclear factor E2-related factor; oxLDL, oxidized LDL; PKC, protein kinase C; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SOD, superoxide dismutase; SR-A, scavenger receptor-A; STAT, signal transducer and activator of transcription; STS, sodium tanshinone IIA sulfate; TGF-β1, transforming growth factor-β1; TNF-α, tumor necrosis factor-α; TS, tanshinone IIA.

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1. Introduction

Danshen, a crude herbal drug isolated from the dried root or rhizome of *Salvia miltiorrhiza* Bunge (Fig. 1A), has long been used in Asian countries for multiple therapeutic remedies including myocardial infarction (MI), angina pectoris, stroke and atherosclerosis [1,2]. The beneficial actions are attributable to improved microcirculatory, vasodilatory, anti-coagulant, anti-thrombotic, anti-inflammatory, free radical scavenging, and mitochondria-protective effects [1,3,4]. The protective effects of Danshen in cardiovascular system have been reviewed by Cheng [5] and Zhou et al. [6]. Although Danshen is officially listed in the Chinese Pharmacopeia, the exact mechanism(s) for its therapeutic use and the characterization of its active constituents is not fully described at this time [7].

Tanshinone IIA (TS) is one of the most pharmacologically active components isolated from Danshen. Many experimental and clinical investigations have reported that TS can prevent or slow the progression of a wide spectrum of diseases, including cardiovascular diseases (CVD), cancer, neonatal hypoxic ischemic encephalopathy, hepatic fibrosis as well as neurodegenerative diseases [1,2,7–9]. In China, it is used either alone (sodium tanshinone IIA sulfate, STS) or in a composite formula (Fufang Danshen Dripping Pill®, Fig. 1B) for the prevention and management of CVD. The Fufang Danshen Dripping Pill® has completed Phase II clinical trials in US involving the evaluation of its efficacy and safety in patients with chronic stable angina pectoris (see http://clinicaltrials.gov/, No. NCT00797953).

In view of the pharmacological and therapeutic profile of TS in the cardiovascular system especially in atherosclerosis, MI and cardiac hypertrophy we provide an overview of recent research on the cardiovascular effects of TS observed in experimental and clinical studies and the underlying mechanisms. The pharmacokinetic properties of TS are also discussed.

2. Tanshinone IIA

2.1. Major Danshen extracts

The chemical constituents and biological activities of Danshen have been extensively studied since the early 1930s. More than 30 lipophilic diterpene compounds and 50 hydrophilic components have been identified and separated from Danshen [2,6]. Both the hydrophilic and the lipophilic components contribute to the biological activities of Danshen. The hydrophilic extract of Danshen contains a mixture of natural phenolic compounds, including lithospermic acid A, lithospermic acid B, rosmarinic acid, protocatechualdehyde, protocatechuic acid, caffeic acid and danshensu. The major lipophilic components include tanshinone I, tanshinone IIA, tanshinone IIB and cryptotanshinone. Among these components, tanshinone IIA is the most abundant derivative and structural

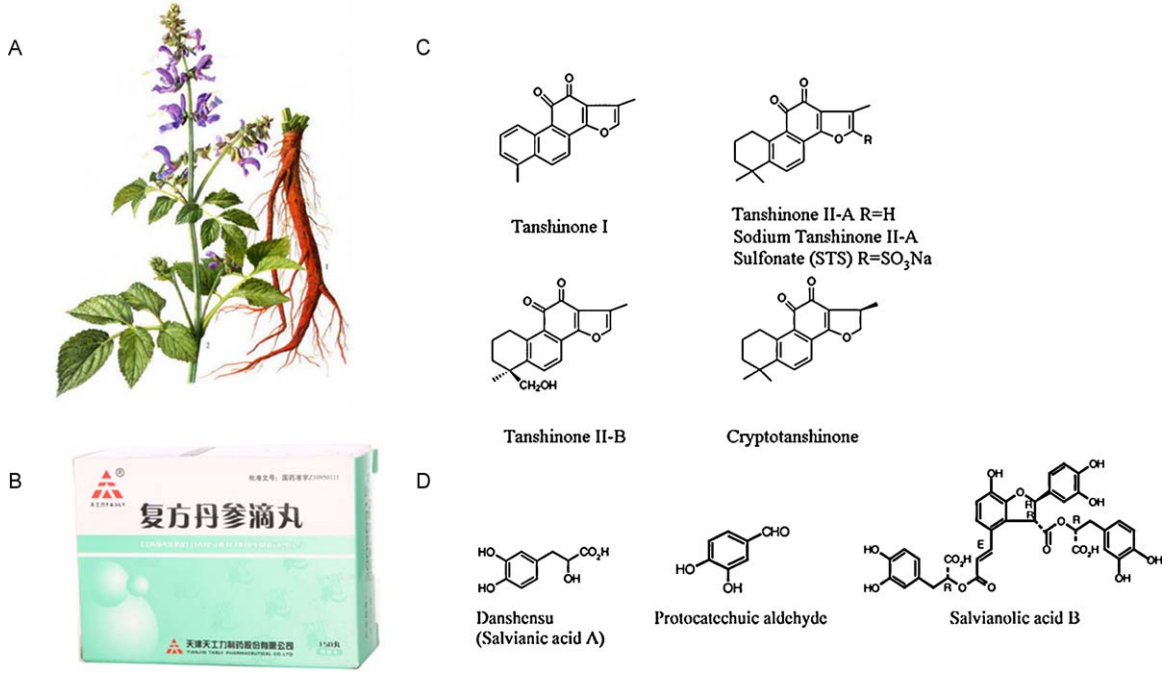

Fig. 1. The plant of Danshen and the chemical structures of its major extracts. Danshen (A) is a crude herbal drug isolated from the dried root or rhizome of *Salvia miltiorrhiza* Bunge (Lamiaceae). The Fufang Danshen Dripping Pill® (B) manufactured by Tasly Pharmaceuticals, Inc. (http://www.tasly.com/) has completed phase II clinical trial in US (No. NCT00797953). The chemical structures of the major lipophilic components (tanshinone I, tanshinone II-A, tanshinone II-B and cryptotanshinone) and the major water-soluble extracts (danshensu, slavianolic acid B and protocatechuic aldehyde) are shown in C and D, respectively.