

Letter to the Editor

Danshen and the Cardiovascular System: New Advances for an Old Remedy

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A recent article published in this journal, entitled “The influence of herbal medicine on platelet function and coagulation: a narrative review,” by McEwen,¹ nicely reviewed how herbal medicines can play a role in modifying cardiovascular diseases (CVDs), and also highlighted the interaction of herbal medicines with standard anticoagulant medicinal therapy. Here, we wish to further reflect on the effects of Danshen on the cardiovascular system, and also to report the novel underlying mechanism of its main constituents on platelets function and hemostasis. To our knowledge, these aspects have not been previously fully described.

CVDs are the main causes of morbidity and mortality worldwide.² They include myocardial infarction, stroke, rheumatic heart disease, and also peripheral artery disease and venous thrombosis.³ The underlying mechanisms diverge depending on the disease in question.⁴ Scientists working on CVDs agree that in most cases hyper-platelet aggregation seems to be a crucial step in cardiovascular hemostasis and in the development and progression of CVDs. For these reasons, pharmacological therapies with agents that modulate platelet reactivity have proven to be effective in the treatment and/or in the prevention of CVDs.⁵ Moreover, advancements in technology and better knowledge of both platelet biology and biological functions of natural products have facilitated this process and pushed researchers to search for new and more reliable targets. Finally, but not less important, research into natural compounds founded on their ethnopharmacological information, has provided significant contributions to drug improvement and has paved the way for new pharmacological tools.⁶

Danshen has been widely used in traditional folk medicine in China and, to a lesser extent, within the United States and several European countries to treat CVDs and cerebrovascular diseases.⁷ Its cardiovascular beneficial actions are attributable to “thinning” the blood and reducing blood clotting, as well as to “invigorate” the blood or improve circulation. Although Danshen is officially listed in the Chinese Pharmacopeia, the cardiovascu-

lar pharmacology of its active constituents has not yet been fully described. To date, more than 40 lipophilic tanshinones and 50 hydrophilic phenolics-like compounds have been isolated from Danshen root and extensively investigated for their cardiovascular activities.⁸

If we had to promote an “ideal candidate” from one of these lipophilic/phenolics-like compounds in the context of CVDs, this would be without any doubt tanshinone IIA (TIIA) and cryptotanshinone (CRY). Indeed, the discovery of these derivatives of phenanthrene-quinone isolated from Danshen have completely changed the way we look at many Danshen-mediated pharmacological properties.⁹ Recently, the pharmacological properties of TIIA and CRY in the cardiovascular system have attracted great interest. Emerging experimental studies and clinical trials have demonstrated that both the compounds prevent atherosclerosis and atherogenesis, as well as cardiac injury due the pleiotropic inhibition of low-density lipoprotein oxidation, monocyte adhesion to endothelium, smooth muscle cell migration and proliferation, macrophage cholesterol accumulation, and proinflammatory cytokine production.^{10,11} Moreover, few but representative studies have reported the effects of Danshen and TIIA on human blood platelets, human cardiomyocytes and vascular endothelial cells.^{12–14} However, no preclinical studies and clinical evidences have as yet underlined the key role of TIIA and CRY on platelet biology.

A recent article¹⁵ has changed this scenario showing that TIIA in vitro selectively inhibited rat platelet aggregation induced by reversible adenosine diphosphate (ADP) stimuli (3 μ M) in a concentration-dependent manner (0.5–50 μ M). Nevertheless, TIIA was less active against the irreversible stimuli induced by ADP (10 μ M) and collagen (10 μ g/mL). Moreover, experiments performed on platelet lysates collected at different time-point after the addition of the stimuli shown that TIIA modulated tubulin acetylation and inhibited Erk-2 phosphorylation. Concomitantly, TIIA administered intraperitoneally at 10 mg/kg significantly prolonged the

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mouse bleeding time. These evidences were also supported by a related original research published in 2015.¹⁶ In this study, CRY *in vitro* was able to inhibit in a concentration dependent manner (0.5–50 μ M) the rat platelet aggregation and *in silico* was able to establish interactions with P2Y₁₂R receptor. This computational method was also performed for TIIA demonstrating even for this diterpenoid an interaction with the same receptor. Additionally, to give a more complete picture of the antiaggregative properties of TIIA and CRY, in more detailed *in silico* studies the interaction of these compounds on Gi-coupled P2Y₁₂ receptor was also compared with AZD1283, a standard receptor antagonist. Even if TIIA and CRY show a relatively simple skeleton structure in comparison to AZD1283, the docking results suggested that their established interactions with P2Y₁₂R were sufficient to support the P2Y₁₂R antagonist activity of these two diterpenoids.

Although these preclinical evidences don't provide direct information on the effect of TIIA and CRY on human platelets, from our point of view, these findings enable a better understanding of TIIA and CRY biological properties in the context of platelet functionality and hyperactivity, which could ultimately lead to the development of novel pharmaceutical strategies for the treatment and/or prevention of some CVDs. More importantly, one aspect that we believe is fundamental for pharmacologists is to determine how and if all these evidences could be converted into clinical practice.

Conflict of Interest

Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' Contributions

M. F. and M. N. equally drafted the article and revised it critically for intellectual content. All authors checked the accuracy or integrity of any part of the work and approved the final version of the article.

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