

Exploring the Clinical Application of Danshen Injection Combined with Acupuncture Based on Modern Pharmacology

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Abstract: Danshen contains salvianolic acid, tanshinone, volatile oil and inorganic elements, which are widely used in the treatment of cardiovascular diseases in modern clinical practice. The main water-soluble component of Danshen has various pharmacological effects, including anti-inflammatory, anti-tumor, neuroprotection, myocardial protection and immunity enhancement. The purpose of this paper is to explore the current status of pharmacological research on Danshen, discuss the clinical efficacy of Danshen injection combined with acupuncture in the treatment of hypertension, coronary angina and rheumatoid arthritis, combine traditional Chinese medicine acupuncture therapy with the pharmacological mechanism of Danshen, and provide a new direction for the treatment of clinical diseases.

Keywords: Danshen; Danshen injection; Pharmacological effects; Acupuncture; Treatment

1. Introduction

Danshen (*salviae miltiorrhizae radix et rhizoma*), the dried stems and roots of *Salvia miltiorrhiza* Bge, is a member of the Labiatae family and was first published in Shen Nong's Herbal Classi and was classified as a top grade. It has been included in the Materia Medica for many generations, and is a common herb in the pharmacopoeia of China. Danshen tastes bitter, slightly cold, and enters the heart and liver meridians, with the effects of promoting menstruation and relieving pain, activating blood circulation and eliminating blood stasis, clearing heat from the heart and removing irritation, cooling the blood and relieving pain, and is mainly used for various pains caused by blood stasis, such as chest paralysis and cardiac pain, hypochondriac and hypochondriac pain, obstruction of the mass, heat paralysis and pain, dysmenorrhea, sores and swelling pain^[1]. Contemporary research has demonstrated that Danshen primarily contains chemical components like salvianolic acids, tanshinones, volatile oils, and inorganic elements, among which phenolic acids and tanshinones are the main material basis for the pharmacological properties of Danshen, and these two substances play a major part in the management of cerebrovascular and heart system diseases. Moreover, investigations have revealed that Danshen also has antibacterial and anti-inflammatory, antitumor, and organ-protective pharmacological effects^[2], with a wide range of clinical efficacy.

The Global Burden of Disease assessment report published by the World Health Organization shows that cardiovascular conditions such coronary heart disease, angina pectoris, and myocardial infarction are now the main cause of premature death in both men and women, accounting for around one-third and one-quarter of all deaths. The effective avoidance and therapy of cardiovascular illnesses, also known as circulatory system illnesses, has emerged as one of the important challenges in the area of medicine because they are the most common cause of death worldwide and are typically linked to atherosclerosis^[3]. Danshen can be used clinically to treat coronary artery disease, myocardial infarction, blood circulation disorders, and other cardiovascular diseases because it activates blood circulation and removes blood stasis, cools the blood and clears heat from the heart, nourishes the blood, and calms the mind^[4].

2. Progress of research on chemical composition and pharmacological status of Danshen

The makeup of is complicated, and more than one hundred chemical constituents have been extracted and recognized, mainly including diterpenoids, triterpenoids, phenolic acids, flavonoids, and nitrogenous compounds, lactones, polysaccharides, etc.

The primary active ingredients of Danshen are diterpenoids and phenolic acids, the latter of which being a class of organic acids with phenolic rings^[5]. Nowadays, Danshen has been used to isolate more than 100 lipid-soluble components and water-soluble components, and the lipid-soluble components include tanshinones, tanshinolactones, and tanshinols, while the water-soluble components mainly include tannic acid etc. Since the water-soluble components are mainly distributed in the extracellular fluid after entering the blood circulation, they exert their pharmacological effects mainly by affecting the vascular activity^[6].

Tanshinones are one of the characteristic active ingredients in Danshen, and recent studies have revealed that these compounds have significant cardio-protective and anti-tumor effects, as well as anti-bacterial and anti-inflammatory pharmacological effects, especially in anti-tumor activity^[7]. In addition, tanshinone as a natural pigment, is effective and safe to be used in various cosmetic products to eliminate acne, and it is also widely used in dermatological diseases, therefore, the development of cosmetic products containing tanshinone as topical application or disinfection water also has broad application prospects^[8].

Studies have shown that salvianolic acid compounds have effects of cooling blood and resolving carbuncle, clearing heat from the heart and removing the annoyance, anti-inflammatory and antioxidant effects. Volatile oil and polysaccharide components have anti-inflammatory, antioxidant and organ protective effects^[9]. According to contemporary pharmacological investigations, Danshen plays a significant function in the protection of the cardiovascular system by widening coronary arteries, preventing myocardial ischemia and myocardial infarction, promoting microcirculation, and lowering myocardial oxygen consumption^[10]. Nowadays, is primarily used for the treatment of cardiovascular disorders, cancer adjuvant therapy, diseases of the sluggish digestive system, diabetes, and skin conditions, among other conditions. Danshen is mostly utilized in the treatment of cardiovascular diseases due to its extraordinary effectiveness in reducing blood stasis, easing pain, and accelerating blood circulation^[5], such as compound Danshen dripping pills have become a good medicine for cardiovascular diseases.

2.1. Mitigation of cardiomyocyte injury

Cellular experiments demonstrated that Danshen extract, which is based on tanshinone IIA, has some estrogen-like effects, and it can activate protein kinase B through estrogen receptor-mediated activation and inhibit Leu27IGF-II-induced apoptosis activated by insulin-like growth factor II (IGF-II) receptor signaling in cardiomyocytes, demonstrating that this extract has the potential to be exploited as an estrogen receptor modulator for the treatment of cardiovascular disorders and the prevention of cardiomyocyte death^[11]. In addition, moreover, studies on animals showed that salvianolic acid A could prevent apoptosis during cardiac ischemia-reperfusion by triggering extracellular signal-regulated kinase 1/2 and blocking Jun kinase, preliminarily elucidating its myocardial protective mechanism of action^[12].

Liu Chang^[13] established a rat cardiomyocyte H9C2 oxidative injury model and found that tanshinone IIA significantly increased the survival rate of cardiomyocytes, reduced LDH and MDA levels, and reversed the H₂O₂-induced decrease in SOD levels, which indicated that tanshinone IIA could maintain SOD levels, reduce the production of lipid peroxidation products such as MDA, further inhibit the damage to biofilm structure and function by lipid peroxidation reactions, and reduce the oxidative damage to cardiomyocytes. Wu Xiaoqian^[14] also found that Tanshinone IIA pretreatment played a significant protective role against functional and structural disorders in rat hearts after ischemia-reperfusion injury, suggesting that Tanshinone IIA has an anti-myocardial ischemia-reperfusion injury effect.

2.2. Anti-atherosclerosis

Atherosclerosis (AS) causes narrowing of blood vessels, tissue ischemia, and even blood clots. Wan Qiang^[15] demonstrated that tanshinone IIA could reduce inflammation response by reducing the expression of TNF- α -induced VCAM-1, ICAM-1 and chemokine CX3CL1 in vascular endothelial cells, and one of the mechanisms of the anti-AS effect of tanshinone IIA may be achieved by inhibiting the

extracellular signal-regulated protein kinase 1/2 signaling pathway and attenuating the LCN-2-induced injury in human umbilical vein endothelial cells. Yang Ping^[16] similarly confirmed that in AS mice, tanshinone IIA regulates lipid metabolism, which may prevent the expression of certain inflammatory cytokines, thereby inhibiting the formation and development of AS lesions. It was found that in the early stages of AS, macrophage autophagy can promote cholesterol reversal transport, reduce the accumulation of foam cells and inhibit the development of AS plaque formation, which has a positive effect on the treatment of AS.

Tanshinol attenuated the accumulation of foam cells due to methionine-rich diet, downregulated the expression of pro-inflammatory factor TNF- α in aortic endothelial cells and intercellular adhesion molecule ICAM-1, and reduced the expression of platelet-derived growth factor genes thereby inhibiting oxidized low-density lipoprotein-induced VSMC proliferation and reducing the risk of AS. It is suggested that salvininol exerts its AS effects mainly by inhibiting monocyte activation and foam cell formation, lowering the production of mediators of inflammation and inhibiting vascular smooth muscle cell growth^[3].

2.3. Anti-inflammatory effect

Prostaglandin F_{2a} and prostaglandin E levels in blood can be decreased by tanshinone IIA, which can also prevent the release of lysozyme and the generation of inflammatory molecules like IL-1 and TNF- α . Lymphocytes are activated during the inflammatory response by inflammatory substances including IL-1 and TNF- α , promote the expression of adhesion molecules by inflammatory cells such as neutrophils, promote the release of cytokines and chemokines, aggravate the inflammatory response, and cause damage to vascular endothelial function^[10]. Zhang Kun^[17] examined the expression of TNF- α in cultured cells in vitro from the mRNA level and protein level using real-time fluorescence quantitative PCR and enzyme-linked immunoassay, and found that both the level of TNF- α mRNA expression and compared to the control group, the group's TNF- levels were much lower. It was shown that tanshinol has an inhibitory effect on the inflammatory factor TNF- α . Jang^[18] found that tanshinone IIA acts as a Ca²⁺ blocker, reduces calcium inward flow, prevents intracellular calcium overload-induced cell damage, and inhibits the production of inflammatory cytokines IL-1 β and TNF- α . The mechanism by which tanshinone inhibits the activation of inflammatory cells and the expression of chemokines and inflammatory cytokines may be related to the signaling pathway of pattern recognition receptors, i.e. Toll-like receptors, expressed by natural immune cells, such as macrophages and dendritic cells^[19].

3. Clinical effect of Danshen injection combined with acupuncture in the treatment of cardiovascular diseases

3.1. Danshen injection combined with acupuncture for hypertension

The pathogenesis of hypertension is linked to the mechanisms of immune damage, and studies have shown that immune dysfunction exists in patients with hypertension, and T cells play a significant role in the onset and progression of hypertension^[20]. In Chinese medicine, hypertension is mainly caused by phlegm and dampness blocking the Middle-jiao, liver and kidney Yin deficiency, and Yin and Yang imbalance, and treatment is based on harmonizing Qi and blood, calming the liver and suppressing the hyperactive Yang. The acupuncture points of Hegu (LI4) and Taichong (LR3) on both sides of the body are called Siguan points, and acupuncture at the Hegu (LI4) point can clear the meridians and open the orifices; the Taichong (LR3) point can calm the liver to stop the wind and regulate the liver and Qi; the Baihui (DU20) point is the meeting point of the Three Hand and Foot Yang meridians, the Du meridian, and the Liver Meridian of Foot-Jueyin, and acupuncture at Baihui (DU20) can relieve patients' dizziness and headache caused by hypertension^[21]. Yang Wanyong^[22] used acupuncture with Danshen injection to treat and intervene in hypertensive patients, and the outcomes demonstrated that patients receiving acupuncture with Danshen injection had considerably greater levels of different CD cells in cellular immunity when compared to the control group, and the cellular immunity of hypertensive patients showed different degrees of decrease in CD4 and CD8 cells compared with normal subjects, and the CD4⁺/CD8⁺ ratio was increased. The level of peripheral blood immunoglobulin decreased significantly in the patients treated with acupuncture and injection compared with the control group, suggesting that acupuncture and Danshen injection drip could play an anti-inflammatory role; CIC and PIP decreased significantly in the patients treated with acupuncture and Danshen injection, demonstrating that the interventional treatment of traditional Chinese medicine could reduce the synthesis of CIIC and PIIP, thus protecting vascular endothelial cells and reducing vascular damage.

3.2. Danshen injection combined with acupuncture for the treatment of angina pectoris in coronary artery disease

Angina pectoris in coronary artery disease belongs to the category of Thoracic Obstruction and heart pain in traditional Chinese medicine, which is characterized by the devitalization of heart Yang, cold-stagnate in the meridians and stasis blocking the heart veins. It can also be seen in the evidence of Qi and blood deficiency or liver Qi discomfort. Acupuncture therapy mostly takes the method of warming the meridians and dispersing cold, opening the veins and relieving pain. Acupuncture points are mainly selected from the pericardium meridian and heart meridian points. In Chinese medical ancient books and records, it is said that "when the five zang-organs have diseases, the twelve Yuan-primary points should be taken" and "the twelve Back-Shu points are all connected to the five zang-organs ", so the Yuan-primary points and the Back-Shu points are mostly taken, and points such as Daling (PC7), Neiguan (PC6), Xinshu (BL15), Jueyinshu (BL14), and Danzhong (RN17) are commonly used^[23].

Zhan Yan^[24]found that clinical application of Danshen injection combined with acupuncture had better efficacy in the treatment of coronary artery disease. Danshen has been shown through pharmacological tests to have a protective impact on cardiomyocytes. In addition, Danshen injection can considerably lower plasma viscosity and enhance the deformability of red blood cells, which helps to improve microcirculatory disorders and prevent microthrombosis^[25]. Danshen injections are thus used to treat coronary heart disease. The acupuncture points are selected from the pericardium meridian point Neiguan (PC6), the Yuan-primary point Shenmen, the Back-Shu point Xinshu (BL15), and the meridian-Qi intersection point Danzhong (RN17), which can tonic the heart Qi, help the heart Yang and relieve pain, tranquilizing the heart and calming the palpitations, and the points work together to invigorate the blood and remove blood stasis, regulate the Qi and resolve phlegm, and tonic the heart Qi.

3.3. Danshen injection combined with acupuncture for rheumatoid arthritis (RA)

RA is a common multisystemic non-suppurative inflammatory autoimmune system disease in clinical practice, mainly manifesting as chronic multiple small joint symmetrical lesions, with joint pain, swelling, and morning stiffness as clinical symptoms, and if left untreated, the disease will gradually develop, with joint deformity and ankylosis, affecting joint function and causing disability^[26]. According to Chinese medicine, RA belongs to the category of "arthromyodynia" and "joint disease", which is caused by insufficient Yang Qi, weakness of external defense and invasion of poisonous, resulting in unfavorable joint conditions. Acupuncture is an effective treatment commonly used in Chinese medicine for RA, and taking basic points such as Sanyinjiao (SP6), Yinlingquan (SP9), and Zusanli (ST36) throughout the body can improve the body's positive energy, reinforce the vital essence and strengthen the primordial Qi, and taking local points around the joint lesions mainly at Yang meridian points can make the joint flexible, disperse cold and remove dampness, and activate the meridians, thus improving clinical symptoms such as joint pain, swelling, and morning stiffness^[27].

Studies have shown that Danshen injection combined with acupuncture is effective in the treatment of RA and can jointly promote the improvement of clinical symptoms, which is mainly related to the effects of Danshen injection in improving tissue ischemia and hypoxia, intraosseous microcirculatory disorders and connective tissue metabolism, blocking excessive proliferation of synovial membrane, and reducing cartilage and fiber destruction^[28]. RA develops due to the abnormal expression and interaction of multiple inflammatory factors, among which TNF- α has a regulatory role in inflammatory and immune responses, shows high expression in RA patients and its level decreases with remission of the disease; IL-1 is able to regulate the expression of several inflammatory factors and has an important role in promoting bone erosion and cartilage destruction, accelerating joint destruction in RA^[29]; IL-6 is one of the important mediators of RA and is involved in the process of joint synovial inflammation and damage, and also induces TNF- α production and enhances inflammatory destruction^[30]. Therefore, reducing the inflammatory response of the organism is an important aspect of RA treatment. Ming He^[31]found that the levels of inflammatory factors TNF- α , IL-1 and IL-6 decreased in RA patients after treatment, and the decrease was more obvious when combined with Danshen injection, demonstrating that the compound Danshen injection can successfully lower the level of RA-related inflammatory factors, thus effectively relieving clinical symptoms and delaying the process of joint destruction.

4. Conclusion and outlook Acknowledgements

In summary, Danshen has a wide range of complex pharmacological activities, among which the main

pharmacological activities of the lipid-soluble components of tanshinones are anticoagulation and anti-platelet aggregation, lipid regulation, anti-inflammation and anti-tumor. The water-soluble phenolic acid components primarily have anti-atherosclerotic, hypotensive, and antioxidant properties. The effective combination of Danshen injection and acupuncture has obvious clinical effects on hypertension, coronary angina, cerebral infarction, other cardiovascular system diseases and rheumatoid arthritis. Danshen injection can effectively improve blood rheology, reduce fibrinogen content, and mitigate platelet adhesion^[32]. Combining acupuncture treatment with cerebral infarction can also improve the abnormal state of blood rheology and reduce the risk of thrombus formation, as well as reduce the effect on cardiac drainage, which can significantly contribute to the treatment and recovery of cerebral infarction^[33]. Danshen injection can reduce free radicals, inhibit peroxidation, reduce mitochondrial damage, and with acupuncture can lower blood pressure by inhibiting sympathetic excitation and relieve the symptoms of vertigo and headache caused by hypertension^[22].

As the mechanism of tanshinol is gradually elucidated, its application in the clinical treatment of diseases such as cardiovascular system becomes more widespread. At the same time, we should master the theory and operation of acupuncture therapy, effectively combine traditional Chinese medicine theory and acupuncture therapy with Danshen injection to explore more effective treatment modalities for more diseases and maximize the characteristics and advantages of acupuncture therapy in Chinese medicine.

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