MEDS Chinese Medicine (2024)
Clausius Scientific Press, Canada

DOI: 10.23977/medcm.2024.060106
ISSN 2616-1753 Vol. 6 Num. 1

Research Progress on the Mechanism of Radix Salviae Miltiorrhizae on Atherosclerosis

Bingyu Yang[1], Zhen Ma[2,*]

[1]Shaanxi University of Traditional Chinese Medicine, Xianyang, Shaanxi, 712046, China
[2]Xi'an Traditional Chinese Medicine Hospital, Xi'an, Shaanxi, 710021, China
[*]Corresponding author

Keywords: Salvia Miltiorrhiza, Atherosclerosis, Platelet Aggregation, Inflammation, Oxidative Stress, Iron Death

Abstract: Predecessors said that "blindly Danshen Yin, Gongtong Siwu decoction", that is, the effect of promoting blood circulation of Salvia miltiorrhiza can be comparable to that of Angelica sinensis, Radix Rehmanniae, Radix Paeoniae Alba and Ligusticum chuanxiong. Modern Salvia miltiorrhiza is commonly used in the treatment of cerebrovascular and cardiovascular diseases, especially in anti-atherosclerosis, and the curative effect is remarkable, but the specific mechanism of its effect is not clear. Atherosclerosis refers to vascular endothelial injury, fibrous tissue hyperplasia and calcareous deposition, which accumulate in the intima, resulting in vascular wall thickening and hardening, vascular lumen stenosis, so it is important to intervene in the formation of atherosclerosis for clinical prevention and treatment of acute coronary syndrome. It's important to reduce mortality. This article focuses on the possible mechanism of Salvia miltiorrhiza in anti-atherosclerosis and provides new ideas for the treatment of atherosclerosis in the future.

1. Introduction

Statistics show that nearly 8 million people die of acute coronary syndrome (ACS) every year, which has become the clinical type with the highest mortality rate of coronary heart disease.[1] A large number of studies have shown that the key factor for the occurrence of ACS is the formation of atherosclerosis. Atherosclerosis refers to vascular endothelial injury, fibrous tissue hyperplasia and calcareous deposition, which accumulate in the intima, resulting in vascular wall thickening and vascular lumen stenosis. Therefore, intervention in the formation of atherosclerosis is very important for clinical prevention and treatment of ACS and reducing mortality. At present, statins in the routine treatment of atherosclerosis in western medicine have limitations in clinical application because of their high cost, affecting liver function, muscle enzymes, increasing the risk of diabetes and other factors. Therefore, looking for new drugs to interfere with unstable plaque is a problem to be solved in clinical prevention and treatment of coronary heart disease.

"Acute coronary syndrome" belongs to the category of "chest arthralgia and heartache" in traditional Chinese medicine. Due to deficiency of vital qi, diet, emotion, cold evil and so on, blood stasis is blocked by blood stasis and precordial pain as the main clinical manifestation. Activating

blood circulation and removing blood stasis is a common treatment of chest pain. Predecessors said that "blindly Danshen Yin, merit and Siwu decoction" What is said is that the effect of promoting blood circulation of Radix Salviae Miltiorrhizae can be comparable to that of Angelica sinensis, Radix Paeoniae Alba and Ligusticum chuanxiong. Salvia miltiorrhiza is often effective when used alone. Modern medical research has found that the effective components of Salvia miltiorrhiza can be divided into two kinds: water-soluble components and fat-soluble components. The main water-soluble components are Danshensu, Salvia miltiorrhiza polyphenolic acid, rosmarinic acid, shikoric acid and so on. The fat-soluble components are mainly tanshinone diterpenes, such as tanshinone I and tanshinone II A. Its main components have strong inhibitory effects on inflammatory reaction, anti-platelet aggregation, protection of vascular endothelial function, antioxidant stress, improvement of myocardial ischemia-reperfusion injury and protection of cardiovascular function, etc., and are often used in the treatment of cardiovascular diseases. However, the specific mechanism of Salvia miltiorrhiza in the treatment of cardiovascular disease still needs to be further explored.

2. Anti-platelet Aggregation

Atherosclerosis is due to a variety of factors leading to vascular endothelial cell damage, accelerated platelet accumulation and thrombus formation in the blood vessel wall, resulting in the potential risk of dangerous events. Modern studies have found that anti-platelet aggregation can make platelets cannot connect, do not aggregate, do not form lumps, do not form thrombosis or embolism, and reduce the probability of ACS. We know that platelet contractile activity is related to platelet aggregation and adhesion, and the molecules that control platelet contractile activity are mainly myosin and actin. When platelet contractile activity is activated, it is the actin activating Mg2+-ATP enzyme that provides energy. Zhang H M and other studies have found [2], Tanshinone IIA, the main component of Salvia miltiorrhiza, can inhibit the activity of actin-activated Mg2+-ATP enzyme, that is, the energy of supply and demand of platelet contraction decreases, thus the activity of platelet contraction decreases, which can inhibit platelet aggregation, effectively prevent atherosclerosis and delay or even prevent the occurrence of cardiovascular risk events. Some studies have found that tanshinone IIA can significantly improve blood viscosity, reduce platelet aggregation, reduce the expression of platelet activation markers CD62p, CD63p and PAC, and increase the expression of CD42b in patients with coronary heart disease.[3] It is revealed that tanshinone IIA can achieve the effect of anti-atherosclerosis by improving hemodynamics, reducing platelet aggregation and inhibiting platelet activation. Tanshinone IIA can bind to platelet ADP receptor and achieve the effect of anti-platelet aggregation. The pharmacological mechanism of this effect is consistent with that of clopidogrel, a common antiplatelet drug.[4] This shows that Salvia miltiorrhiza can play an anti-atherosclerotic effect through anti-platelet aggregation, but the specific mechanism of its anti-platelet aggregation is not known.

3. Inhibition of Oxidative Stress

In recent years, more and more studies have shown that oxidative stress caused by excessive production of ROS can lead to endothelial dysfunction and cell damage, and then promote the occurrence of cardiovascular diseases such as atherosclerosis, while traditional Chinese medicine for promoting blood circulation can play a role in antioxidant stress by regulating Nrf2/ROS signal pathway.[5] Oxidative stress means that when the body is subjected to various harmful stimuli, the body produces too many highly active molecules, such as ROS and active nitrogen, the oxidative system and antioxidant system are out of balance, and the degree of oxidation exceeds the scavenging capacity of oxides, resulting in tissue damage.[6] In particular, the injury or necrosis of vascular endothelial cells will further aggravate atherosclerosis. Therefore, the inhibition of

oxidative stress has become another target of anti-atherosclerosis. Looking for effective drugs to inhibit oxidative stress has become an important direction in the prevention and treatment of atherosclerosis [7].

In the early stage of atherosclerosis, macrophages engulfed a large amount of ox-LDL and transformed into vesicular cells. At the same time, vascular smooth muscle cells proliferated excessively and gradually migrated to the subintimal direction, turning into secretory cells, secreting a large number of collagen and other bioactive molecules, resulting in the formation of a large number of connective tissue, increasing the thickness of the injured vascular wall, and finally leading to vascular remodeling. Tanshinone IIA has a good antioxidant effect, which can effectively prevent the production of ox-LDL and inhibit the production of foam cells. After analyzing a large number of literatures, Elabscience found that superoxide dismutase (SOD) and malondialdehyde (MDA) were the two most commonly used indicators in the evaluation of oxidative stress. SOD is an important antioxidant enzyme for scavenging superoxide anion free radicals in organisms, which can protect cells from the damage of oxygen free radicals. MDA is one of the products formed by the reaction of lipids with oxygen free radicals, and its content represents the degree of lipid peroxidation. Kong X L [8] has been found that the active components of Salvia miltiorrhiza can down-regulate the activity of SOD and the content of MDA, play the role of antioxidant stress and protect vascular endothelium, and inhibit the formation of atherosclerotic plaque. Studies have shown that Salvianolic acid B (SalB), the active component of Salvia miltiorrhiza, is a natural antioxidant, which can protect human aortic endothelial cells from apoptosis mediated by oxidative damage by inhibiting the production of ROS.[9] Thus it can be seen that Salvia miltiorrhiza can inhibit the injury of vascular endothelial cells through antioxidant stress and achieve the effect of anti-atherosclerosis [10].

4. Inhibit Inflammatory Response

In recent years, a large number of studies have found that inflammation exists in a variety of diseases, accelerating the occurrence and development of diseases and invading human health. Inflammation is a defensive response of the innate immune system to adverse stimuli.[11] When the body suffers from exogenous infection or endogenous cell tissue injury, it will lead to inflammation, and any change in physiological balance parameters in the body balance will lead to local or systemic inflammatory reaction.[13]Changes in tissue injury and homeostasis parameters can induce innate immune cells to activate and release danger signals, which is the danger associated molecular patterns(DAMPs). The body's defense system must recognize DAMPs through pattern recognition receptors (PRRs) before it is activated, and then further activate the inflammatory pathway to cause inflammation [12]. The occurrence or aggravation of vascular inflammation and injury is related to the inflammatory response mediated by cytokines and inflammatory cells. Further deterioration will lead to the occurrence of cardiovascular diseases such as atherosclerosis.[14]

Atherosclerosis as an inflammatory disease, a large number of inflammatory cells and inflammatory mediators can participate in its occurrence and development, including interleukin, cell adhesion molecules and so on. Tanshinone IIA, the main component of Salvia miltiorrhiza, can inhibit the above-mentioned mediators and factors and play an anti-atherosclerotic effect through anti-inflammatory and immunomodulatory effects. Wang Nanding et al established vulnerable plaque model mice by using ApoE gene deficient mice (ApoE-/-mice) and right common carotid artery external catheterization (PCCP) and high fat feeding. It was proved that tanshinone IIA could inhibit the occurrence and development of inflammation and further anti-atherosclerosis by inhibiting TLR4/NF- κ B signal pathway, NLRP3 inflammatory pathway and reducing the levels of TNF- α, IL-6, IL-18, CRP and MMP-9mRNA. A recent clinical study found that the levels of monocyte ROS, plasma MCP-1 and TLR4 in patients with acute myocardial infarction treated with Salvia miltiorrhiza polyphenols were significantly decreased at the end of 7 days after percutaneous

coronary intervention (PCI). It is suggested that Salvia miltiorrhiza polyphenols can reduce the inflammatory injury caused by monocytes after PCI. It can be seen that Salvia miltiorrhiza can resist atherosclerosis by inhibiting inflammatory reaction.

5. Inhibition of Iron Death

The mechanism of occurrence and development of atherosclerosis is complex, but the final result is the injury of vascular endothelial cells. Studies have found that there are various ways of cell death, including apoptosis, autophagy, programmed necrosis, scorch death and iron death. [15] As a newly discovered regulatory cell death, iron death refers to a new form of cell death caused by the increase of iron-dependent lipid peroxides.[16] Iron death is a kind of iron-dependent oxidative cell death, which is characterized by the lethal accumulation of lipid peroxides caused by the increase of intracellular iron and the decrease of antioxidant capacity. Excess iron promotes ROS production and lipid peroxidation through Fenton reaction.[17] GPX4 is the most important pathway against lipid peroxidation in vivo. SLC7A11 is a component of cystine / glutamate reverse transport system. Inhibition of SLC7A11 can inhibit the production of GSH and lead to inactivation of GPX4 [18]. Research shows that [19], There is iron death in the pathogenesis of atherosclerosis. some studies have shown that atherosclerosis in ApoE-/- mice induced by high-fat diet (HFD) and treatment of ApoE-/- mice with Ferrostatin-1, a specific inhibitor of iron death, can slow down atherosclerosis and inhibit lipid peroxidation.[20] Iron death is an important inhibitory factor in the process of atherosclerosis. Ferrous ion accumulation can induce oxidative stress and lipid peroxidation leading to endothelial cell dysfunction, leading to the formation of atherosclerosis. In addition, inhibiting the occurrence of iron death can reduce lipid peroxidation and vascular endothelial function damage, and reduce the process of atherosclerosis.

The relationship between iron death and atherosclerosis has received widespread attention. As an iron-dependent mode of cell death, iron death is characterized by oxidative damage of cell membrane, by accelerating endothelial cell injury, inducing macrophage inflammation, participating in foam cell formation and vascular smooth muscle proliferation and migration, and then affecting the formation and rupture of atherosclerotic plaques, but the pathological mechanism of atherosclerosis is not completely clear. In recent years, related studies have reported that traditional Chinese medicine compound, single medicine and active ingredients treat diseases by interfering with the mechanism of cell iron death, indicating that the regulation of iron death may be an important mechanism of traditional Chinese medicine in the treatment of many diseases. Exploring the regulation of traditional Chinese medicine on the mechanism of iron death can provide a new scientific basis for further exploring the mechanism of traditional Chinese medicine in the treatment of atherosclerotic diseases. It was found that tanshinone II A could regulate iron metabolism and up-regulate the expression of ferritin heavy chain protein, increase the synthesis of ferritin and reduce the concentration of unstable iron, while tanshinone II A could also inhibit p53 to increase the level of SLC7A11 protein, increase the activity of GSH and GPX4, effectively reduce the accumulation of ROS and reduce lipid peroxidation in hepatocytes. It is suggested that tanshinone II A can regulate iron death in hepatocytes by interfering with iron metabolism pathway.[21] Effectively improve atherosclerosis. ShenY et al found that Salvianolic acid B (SalB), the active component of Salvia miltiorrhiza, can reduce iron overload and oxidative stress and inhibit iron death induced by myocardial infarction by activating Nrf2 signal pathway.

6. Summary

The process of occurrence and development of atherosclerosis is complex, with the characteristics of acute disease, great harm, serious illness and high mortality. At the same time, it often involves other systemic diseases, which is a common and dangerous disease in clinic. However, statins are routinely used in western medicine. There are many side effects and adverse

reactions, which will increase the psychological burden and economic burden. With the development of basic research and evidence-based medicine, it has been widely proved that Salvia miltiorrhiza and its active ingredients have good therapeutic effects on atherosclerotic diseases.[22] The effects are involved in many ways, such as anti-platelet aggregation, inhibition of oxidative stress, inhibition of inflammation, inhibition of cell iron death and so on. However, at present, most of the studies on Salvia miltiorrhiza and its active components are the separate action mechanism of some of the main active components, and there is a lack of more basic research and evidence-based medicine evidence on the synergism between its components. To sum up, we should speed up the study of Salvia miltiorrhiza and its effective components, explore the specific mechanism of Salvia miltiorrhiza in the treatment of atherosclerotic diseases, and provide more evidence for clinical treatment of atherosclerotic diseases.

References

[1] Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation. 2002; 106(4):68-72

[2] Zhang Huimin, Zhuang Qingqi, Li Chengzhu, etc. Effect of sodium tanshinone II-A sulfonate on Mg2+-ATP activity activated by platelet actin. Journal of Shanghai Medical University, 1988, (04): 289-292.

[3] Yang J, Dong J C, Li D Z, et al. The effect of Tanshinone II-Sodium A sulfonate on platelet functions in patienes with coronary heart disease. Journalof Traditional Chinese Medicine, 2013, 54(15): 1294-1296.

[4] Maione F, Cantone V, Chini M G, et al. Molecular mechanism of tanshinone IIA and crypto tanshinone in platelet antiaggregating effects: an integrted study of pharmacology and computational analysis. Fitoterapia, 2015, 100: 174-178.

[5] Zhang H M, Zhuang Q Q, Li C Z, et al. The effect of tanshinone II-A sulf Onate on actin activated Mg2+-ATP ase activity in platelets. Journal of Shanghai Medical University, 1988, 15(4): 289-292.

[6] Li Z, Li Q, Wang L, et al. Targeting mitochondria-inflammation circle by renal denervation reduces atheroprone endothelial phenotypes and atherosclerosis. Redox Biol. 2021; 47: 102156.

[7] Kong X L, Lyu Q, Zhang Y Q, et al. Effect of astragaloside IV and salvianolic acid B on antioxidant stress and vascular endothelial protection in the treatment of atherosclerosis based on metabonomics. Chin J Nat Med. 2022; 20(8): 601-613.

[8] Zhu Z, Li J, Zhang X. Astragaloside IV Protects Against Oxidized Low-Density Lipoprotein (ox-LDL)-Induced Endothelial Cell Injury by Reducing Oxidative Stress and Inflammation. Med Sci Monit. 2019; 25: 2132-2140.

[9] Zhang J, Wu C, Gao L, Du G, Qin X. Astragaloside IV derived from Astragalus membranaceus: A research review on the pharmacological effects. Adv Pharmacol. 2020; 87: 89-112.

[10] Yang TL, Lin FY, Chen YH, et al. Salvianolic acid B inhibits low-density lipoprotein oxidation and neointimal hyperplasia in endothelium-denuded hypercholesterolaemic rabbits. J Sci Food Agric. 2011; 91(1): 134-141.

[11] Medzhitov R. Origin and physiological roles of inflammation. Nature, 2008, 454(7203): 428-435.

[12] Medzhitov R. Inflammation 2010: new anventures of an old flam. Cell, 2010, 140(6): 771-776.

[13] De Torre-Minguela C, Mesa Del Castillo P, Pelegrin P. The NLRP3 and pyrin inflammasomes: implications in the pathophysiology of autoinflammatory diseases. Front Immunol, 2017, 8: 43.

[14] Wen H, Ting JP, O, Neill LA. Arole for the NLRP3 inflammasome inmetabolic diseses-did Warburg miss inflammation? Nat Immunol, 2012, 13(4):352-357

[15] Bai Y J, Lam H C, Lei X G. Dissecting programmed cell death withsmall molecules. Acc Chem Res, 2020, 53(5): 1034-1045.

[16] Dixon S J, Lemberg K M, Lamprecht M R, et al. Ferroptosis: an irondependent form of nonapoptotic cell death. Cell, 2012, 149(5): 1060-1072.

[17] Wang Y, Zhao Y, Wang H, et al. Histonedemethylase KDM3B protects against ferroptosis by upregulating SLC7A11.FEBS OpenBio, 2020, 10(4):637-643.

[18] Latunde-Dada GO. Ferroptosis: role of lipid peroxidation, iron andferritinophagy, Biochimica et biophysica acta. General Subjects, 2017, 1861(8):1893-1900.

[19] Kobayashi M, Suhara T, Baba Y, et al. Pathological roles of iron incardiovascular disease. Curr Drug Targets, 2018, 19(9):1068-1076.

[20] Kraml P. The role of iron in the pathogenesis of atherosclerosis. Physiol Res, 2017, 66(Suppl 1):s55-s67.

[21] Wu Yao, Song Nan, Jia Lianqun, etc. Effects of tanshinone II An on lipid deposition and expression of iron death related proteins in liver of ApoE-/- mice. Chinese Journal of Pathophysiology, 2020, 36 (7): 1261-1268.

[22] Wang J, Xu J, Gong X, Yang M, Zhang C, Li M. Biosynthesis, Chemistry, and Pharmacology of Polyphenols from Chinese Salvia Species: A Review. Molecules.2019 Jan 2;24(1):155.