Research Progresses in Traditional Chinese Medicine in Treating Atherosclerosis

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Keywords: Atherosclerosis, Traditional Chinese Medicine, Endothelial Cells, Immune Cells, Vascular Smooth Muscle Cells.

Abstract: Atherosclerosis (AS) is the major cause of cardiovascular and cerebrovascular diseases, and its formation process mainly involves several stages such as intimal injury, inflammation induction and plaque formation. The cells to play crucial role in the occurrence of AS mainly include endothelial cells, immune cells and vascular smooth muscle cells. Traditional Chinese medicine (TCM) is characterized by multi-components and multi-targets and have significant advantages in the clinical treatment of AS. The paper reviews the regulatory effects of TCM on major cells involved in AS, which provides a reference for future in-depth studies of treating AS by TCM.

1 INTRODUCTION

Atherosclerosis, a chronic vascular inflammatory disease, is the main cause of cardiovascular and cerebrovascular disorders such as coronary heart disease, myocardial infarction and cerebral infarction. Its pathological mechanism is mainly characterized by lipid metabolism, local arterial blood flow disorder, damage to the vascular intima, inflammation induced by lipid deposition, and ischemia or necrosis of arterial blood supply tissue caused by atherosclerotic plaque formation, vascular sclerosis, or lumen narrowing (Ma, 2021). Traditional Chinese medicine (TCM) is characterized by multi-components and multi-targets and has unique advantages in treating AS and relieving various states in the progress of AS. Cells such as endothelial cells, lymphocytes, macrophages and vascular smooth muscle cells are mainly involved in the occurrence of AS (Zhang, 2021). The paper reviews the regulatory effects of TCM on various types of cells in the different stages of AS, providing a reference for the future in-depth study of treating AS by TCM.

2 PROTECTING ENDOTHELIAL CELLS AND REDUCING INTIMAL DAMAGE

In the lipid plaque stage of AS, endothelial cells are damaged, monocytes aggregate and differentiate, and lipid metabolism occurs, while in the fibrous plaque stage, arteries respond to endothelial injury with inflammation-fibroproliferative, and vascular smooth muscle cells (VSMCs) proliferate and migrate. Lots of TCM can prevent and treat AS by protecting endothelial cells and reducing endometrial damage (Fatkhullina, 2016).

Table 1: Therapeutic effects of traditional Chinese medicine in endothelial cells.

Mechanism	Chinese medicine	References
Affecting nitric oxide synthase activity, regulating the expression of nitric oxide and endothelin, improving EC function	Astragalus Polysaccharide; B-Elemene Saikosaponin; Baicalin Puerarin; Tanshinone IIA; Ligusticum Jeholense; PinelliaGinger Jiawei Alisma Decoction; Toona Sinensis Extract Musk Xintongning; Angelica Peony Powder Compound Sanqi Granules; Kangxin Capsules Compound Danshen Dropping Pills;	(Zhu, 2008; Ren, 2017)

Yu, J., Chen, X., Lei, H., Li, L. and Fang, H.
Research Progresses in Traditional Chinese Medicine in Treating Atherosclerosis.
DOI: 10.5220/0012015900003633
In *Proceedings of the 4th International Conference on Biotechnology and Biomedicine (ICBB 2022)*, pages 178-182
ISBN: 978-989-758-637-8

3 IMMUNE SYSTEM AND ATHEROSCLEROSIS

3.1 Regulating Immune Cells to Realize Anti-Inflammatory Effects

3.1.1 Monocytes

In the early stage of AS, the inflammatory process accompanying the formation of AS plaque is mainly related to the recruited monocytes and monocyte-derived macrophages (Liang, 2022). During the formation stage, monocytes are negatively correlated with the thickness of the fibrous cap of AS plaque. Monocytes thereby play a crucial role in the formation and development of AS plaque (Wang, 2022).

Table 2: Therapeutic effects of traditional Chinese medicine on monocytes.

Immune Cells	Mechanism	Chinese medicine	References
Monocytes	Preventing monocyte from adhesion, aggregation, infiltration, and differentiation Inhibit inflammatory factors and adhesion molecules release, improving the inflammatory response	Burdock Root Extract Ginsenoside F1; Breviscapine Naringin Scrophoside B; Scrotaloside B Salvianolic Acid B; Puerarin Tanshinone IIA; Catalpol Paeonol; Ligustrazine Musk Ketone; Musk Baoxin Pills	(Zhang, 2021; Ye, 2018; Liu, 2011) (Zhang, 2021; Ye, 2018; Liu, 2011; Li, 2019; Zhou, 2017)

3.1.2 Lymphocytes

Lymphocytes are derived from bone marrow hematopoietic stem cells. The deficiency of total lymphocytes attenuates the occurrence and development of AS. In the pathological process of AS, T and (or) B lymphocytes can identify the presented antigens and then release antibodies, leading to the occurrence of adaptive immune responses.

Table 3: Therapeutic effects of traditional Chinese medicine on lymphocytes.

Immune Cells	Induction factors	Secreted factors and antibodies	Mechanism	Chinese medicine	References
T cell Th1	IL-12	IL-6, IFN-γ, IL-1β, and TNF-α	reducing the expression of adhesion molecules, activating related immune cells, and preventing the polarization of M1 macrophages	Shikonin Sinomenine Huanglian Jiedu Decoction Tongxinluo	(Zhang, 2021; Li, 2019; Ye, 2018; Liu, 2015)
Th17	IL-6 IL-21 TGFβ	IL-17	Mediating immune responses and suppressing inflammatory responses	Total Flavonoids Glycyrrhizinate Angong Bezoar Pills Qishen Yiqi Pills	(Zhang, 2021; Ji, 2019)
Th2	IL-4, IL-5, and IL-13	IL-4, IL-5, IL-10, and TGF-β	activating B cells, and preventing M2 macrophage polarization	Curcumin Huanglian Jiedu Decoction	(Li, 2019; Liu, 2015)
B cell B1	Endogenous substances alarmin	IgM Secretion of natural antibody IgM	Adjusting the proportion of lymphocytes, increasing the proportion of Treg cells and B1 cells, restoring immune balance, identifying antigens, and slowing down the formation of foam cells	Amygdalin Triterpenoid Saponins Huanglian Jiedu Decoction Buyang Huanwu Soup Si Miao Yong An Soup	(Zhang, 2021, Ji, 2019; Tin, 2020)
B2	Endogenous substances alarmin	oxLDL specificity IgG;HSP60 specificity IgG;IgE	Activating macrophages, mast cells, and macrophages, and identifying stressed ECs	Triptolide Dihydroartemisinin Phenethylchromone Derivatives	(Zhang, 2021, Liu, 2015, Tin, 2020, Sage, 2019)

3.1.3 Macrophages and AS

In the early stage of AS, if macrophages take up excessive oxLDL, their ability to reverse cholesterol transport in plaques would be weakened after the activation of cell surface scavenger receptors, resulting in 'fatty streaks' formed by the accumulation of a large number of intracellular lipids, which finally becomes the pathological basis for the occurrence and development of AS (Hansson, 2011). In addition, monocytes also differentiate into various macrophages in the development of AS (Li, 2019). Macrophages are characterized by huge numbers. Besides, their traits such as plasticity and heterogeneity make them play an important role in the physiology and pathology of AS (Zhang, 2021).

Table 4: Therapeutic effects of traditional Chinese medicine on macrophages.

Immune cells	Mechanism	Chinese medicine	References
Macrophages	Activate PPARγ, inducing M2-type differentiation of macrophages	Emodin; Huperzine A Curcumin; Magnolol Ginsenoside Rb1	(Zhang, 2021; Liu, 2011; Zhou, 2017)
	Regulating lipid metabolism and reducing oxidative factors	Soybean Extract; Quercetin Licorice Flavonoids; Astragalus Polysaccharides Ginkgolide B; Ferulic AcidSoy;	(Zhang, 2021; Liu, 2015; Meng, 2017; Guo, 2021)
	Activating the LXRαABCA1/ABCG1 pathway, promoting cholesterol efflux, and inhibiting the formation of macrophage cells	Phellinone G; Salvianol C Saponin a; Ligustrazine Arctigenin; Quercetin Ginsenoside Rd; Salvia North Bupleurum; Chuanxiong Burdock; Bupleurum Ginseng;	(Li, 2019; Liu, 2015; Meng, 2017)
	Mediating the expression of CD36 and ABCA1 and reducing the volume of oxLDL-induced lipid deposition in cells	Danshensu Salidroside; Turmeric Butter Icariin; Puerarin Salvia	(Zhang, 2021; Liu, 2015)
	Enhancing macrophage autophagy and inhibiting macrophage apoptosis to resist AS	Green Glucoside; Olean Nuts Araya; Calamus; Sanqi	(Liu, 2015)
	Reducing the expression of SRA1, and inhibiting the uptake of oxLDL by macrophages to treat AS	Dihydrotanshinone I Formononetin Astragaloside IV Luteolin	(Liu, 2015)

4 INHIBITING PROLIFERATION AND MIGRATION OF VASCULAR SMOOTH MUSCLE CELLS

Activation, proliferation and migration of vascular smooth muscle cells (VSMCs) are essential for the development of atherosclerotic lesions. In the early stage of AS, the damaged vascular endothelium would cause abnormal proliferation of VSMCs, and migration from the medial to the intima would promote the formation of atherosclerotic plaques. Whereas, in the advanced stage of AS, VSMCs would further proliferate and aggregate, forming fibrous caps to stabilize fragile plaques (Chen, 2018). Therefore, inhibiting the proliferation and migration of VSMCs or promoting VSMCs proliferation in different stages has dual actions in the prevention and treatment of AS (Zhao, 2019).

Table 5: Therapeutic effects of traditional Chinese medicine on vascular smooth muscle cells.

Mechanism	Chinese medicine	References
Inhibiting VSMCs proliferation and migration, yet not inducing VSMCs apoptosis	Triptolide; Baicalin Luteolin; Resveratrol Hyperoside; Yew Panax;	(Zhou, 2017; Zhao, 2019; Liu, 2021; Wei, 2019)
Inhibiting VSMCs migration, yet not affecting cell proliferation and FAK phosphorylation	Geranin Geranium	(Zhao, 2019; Liu, 2021)
Inhibiting oxidative stress and apoptosis in VSMCs	Dihydromyricetin Bayberry	(Zhou, 2017; Zhao, 2019; Liu, 2021; Wei, 2019)
Significantly inhibiting VEGF-induced phosphorylation of VEGFR2	Resveratrol Glycosides Knotweed	(Zhou, 2017; Zhao, 2019; Liu, 2021; Wei, 2019)
Inhibiting VSMCs proliferation and antigen expression by regulating the ERS pathway to increase SMC apoptosis	Emodin; Crocoside; Curcumin Icariin; Tanshinone IIA; Thapsigargin Rhubarb; Safflower; Ginger Epimedium; Radish	(Zhou, 2017; Zhao, 2019; Liu, 2021; Wei, 2019)

5 CONCLUSION

The drugs currently treated AS such as statins, aspirin, nitroglycerin which have effective in lowering cholesterol and preventing and treating AS, but it often cause adverse reactions such as liver damage and myalgia [6]. Besides, there is a higher residual risk after intensive lipid-lowering therapy, without significant improvement in stabilizing advanced plaques. To get rid of this dilemma, more and more people are pinning their hopes on the research of TCM to treat AS. Clearing away heat and detoxification, promoting blood circulation and removing blood stasis are the theoretical basis of TCM for treating AS [23]. We need to conduct more detailed research on various Chinese medicines and their components, so that TCM can become the gospel of AS patients in the near future.

ACKNOWLEDGMENT

This work was supported by the 2021 Graduate Innovation Special Fund Project (No. YC2021-X21) and Education Reform Project of Jiangxi Science &Technology Normal University (JGYB-20-61-24).

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