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Progress on Preventing Vascular Smooth Muscle Cell Proliferation and Phenotypization based on Traditional Chinese Medicine

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Abstract: Traditional Chinese medicine extracts and preparations have small side effects and targets, many researchers at home and abroad combined with classical prescriptions and drug properties, and different research found to blood activating and stasis removing drugs, drugs for supplementing qi and blood, liver calming and Yang suppressing drugs and antioxidant drugs through different factors can inhibit or reverse vascular smooth muscle cells (vascular smooth muscle cells, VSMCs) proliferation and phenotypization, can be used as the prevention and treatment of hypertension, hyperlipidemia, hyperglycemia, coronary heart disease and angiography vascular wall hardening and plaque formation of hidden drugs.

All tissues and organs of the human body rely on the cultivation of blood. Smooth blood flow is the premise of life and health, so the health of blood vessels and blood circulation are the prerequisite for ensuring life and health. VSMCs proliferation and phenotypization are the main factors in the formation of endovascular plaque. Diabetes, hypertension and angiography can all induce VSMCs proliferation and phenotypization. Studies show that different vascular smooth muscle phenotypization of inducers are also divided into osteogenic type-SMC, inflammatory type SMC and fibroblast type SMC, collectively known as synthetic type [1] The VSMCs of this phenotype have a strong proliferation and migration capacity. Blood rheology and hemodynamic abnormalities caused by VSMCs proliferation and phenotypization are called "blood stasis". Researchers at home and abroad have found that some traditional Chinese medicines can significantly inhibit and reverse VSMCs proliferation and phenotypization and increase the

freshness of blood. Therefore, the use of traditional Chinese medicine is important to control VSMCs proliferation and phenotypization. This paper analyzes and summarizes the research achievements of domestic and foreign scholars in recent years, which is summarized as follows:

1. Stimulation of the Inhibition of the Peroxide Products

Both hyperlipidemia and peroxides produced in diabetes are important factors to inducing VSMCs proliferation to form atherosclerosis [2], many traditional Chinese medicines have the effect of lowering blood lipids, antioxidants, preventing thrombosis and anti-aging, and many researchers at home and abroad have proved the pharmacological mechanism by which some traditional Chinese medicines play a role, See Table 1.

Table 1. Summary of drug functions

Medicine	Effect1.	Effect2.	Effect3.
Saffron	Promoting Blood Circulation	Promoting Menstruation	/
Pueraria Lobata	Lower Blood Pressure	Lower Blood Sugar	Antiinflammatory
Green Tea	Antiinflammatory	Antioxidant	Hypolipidemic
Gynostemma Pentaphyllum	Anti-Aging	Antioxidant	Hypolipidemic
Ginkgo Leaf	Hypolipidemic	/	/
Curcuma Zedoary	Hypolipidemic	Antiinflammatory	/

Saffron has the effect of activating blood circulation and dyspenorrhea, removing blood stasis and relieving pain. It is a common drug of blood stasis block, such as internal, external, and female and injury. The main medicinal effect of saffron is saffron side. Liu Tao[3] Study the pharmacological effect of crocein and found that it has the effect of protecting cardiovascular and cerebrovascular vessels, mainly reflected in crocein can improve the expression level of antioxidant lipoprotein (low density lipoprotein, LDL) to reduce the synthesis of cholesterol to reduce cholesterol ester, inhibit cholesterol into bile acid, reduce the formation of extracellular matrix to protect vascular endothelial cells to prevent VSMCs proliferation and phenotypization, to achieve the effect of inhibiting vascular atherosclerosis. Other studies have shown that crocein can inhibit lipid peroxidation and regulate B axmRNA expression to reduce the abnormal apoptosis of vascular endothelial cells and protect blood vessel [4].

Puerarin is the main active ingredient extracted from pueraria, which has the effects of lowering blood pressure, hypoglycemia, antioxidant and anti-inflammation. It is widely used in the treatment of cardiovascular and cerebrovascular diseases. Cheng-mei zhang[5] In anti-atherosclerosis, it was found that puerarin can reduce the synthesis and secretion of intracellular cholesterol and lipoproteins, reduce LDL, induce THP-1 cells and inhibit the expression of inflammatory factors, reduce vascular inflammatory response to protect vascular endothelial cells to increase the stability of VSMCs. Some scholars have found that puerarin has both pro-proliferation and phenotypic VSMCs, apoptosis, and is also one of the mechanisms for the treatment of atherosclerosis[6]. Green tea is the most common drink in our daily life. The main ingredients of green tea polyphenols which have antioxidant and anti-inflammatory effects, Ouyang Ping [7] The effect of green tea polyphenols on VSMCs proliferation was studied and found that it could inhibit the VSMCs proliferation caused by the imbalance of inflammatory factors and effects caused by late glycosylation end products. Other studies have shown that the cell cycle of VSMCs cultured with green tea polyphenols has stagnated in the G (0) / G (1) phase, thus inhibiting the proliferation and

phenotypization of VSMCs, which may be related to the fact of green tea polyphenols blocking a certain signaling pathway in VSNCs[8].

Gynostima is one of the common drugs for the prevention and treatment of cardiovascular and cerebrovascular diseases. It has the effects of lowering blood lipid, antioxidant and anti-aging, among which gynosima is the main role. It was found to reduce the damage of lipid and lipid peroxide products to inhibit the proliferation and phenotypization of VSMCs, while inhibiting the expression of MCPIPI induced by inflammatory factors to reduce the degree of VSMCs phenotypization[9].

Ginkgo biloba extract is a common clinical, brain, and peripheral blood circulation improvement agent and can also be used for peripheral circulation disorders. Ginkgo biloba extract by flavonoid side, ginkacide and ginkgo inner fat play a major role [10]. Some scholars have found that ginkgo biloba extract can inhibit the VSMCs proliferation and phenotypization induced by LDL. The mechanism of action may be by inhibiting the activity of AMPK / KLF4 pathway, and the action intensity of ginkgo biloba extract increases in a concentration-dependent manner [11].

Zedoary is the dried root of zedoary, Guangxi Zedoary and Wenjin. Zedoary extract is mainly divided into zedoary oil and curcumin, which has more targets [12-13]. The researchers found that curcumin gavage significantly reduced the serum total cholesterol and LDL in the serum of high-fat rats, and that the inflammatory factors in the vascular tissue were significantly reduced and the VSMCs stability was significantly improved compared with the control group [14]. The efficacy of curcumin in inhibiting the inflammatory response and lowering blood lipid is very good, and the complete pathway that plays its role needs to be further studied.

2. Protection of the Vascular Endothelial Cells

Astragalus is a commonly used tonify energy and enrich the blood medicine in the treatment of qi deficiency and blood stasis, and is also used as a treatment of hypertension. On the basis of known astragalus to reduce swelling to reduce blood pressure, Gu Jing[15]The researchers also found that the astragalus injection and the astragalus methyl side extract can regulate the tension of vascular endothelium and the ER stress response to achieve the effect of lowering blood pressure, improve the plasma NO concentration to reduce the damage of inflammatory factors to vascular endothelial cells, and increase the stability of VSMCs to avoid the improvement of vascular remodeling. It was also shown that astragalus injection solution to some extent can promote proliferative and differentiated VSMCs apoptosis, thus reversing the vascular intimal thickening caused by hypertension [16].

Angelica sinensis also serves as a clinical blood tonic medicine, but also has a strong effect of activating blood circulation and removing blood stasis, and the clinical treatment of astragalus to treat hypertension and its complications are often associated with Angelica. The main active ingredient of Angelica sinensis is Angelica polysaccharide, high and bright[17]Researchers have made a series of studies to explore the effect of Angelica polysaccharide on the tissue structure of blood vessel wall. The study found that Angelica polysaccharide can effectively inhibit the VSMCs proliferation induced by angiotensin II and heparin-bound epidermal growth factor (HB-ECG), and proved that the action mechanism of Angelica polysaccharide is to inhibit the PI 3K / AKT signaling pathway, and it does not affect the activity of VSMCs. Some researchers are comparing the effects of Astragalus and Angelica in inhibiting VSMCs proliferation and phenotypization under the same environmental factors, and have confirmed that Angelica compared with Astragalus has a better effect in this respect[18].

Astragalus and Angelica are closely related to each other, and they are widely used.,See Table 2. In clinical practice, they are often used together in order to give better play to their effects.

Therefore, some scholars set different doses of six chemical components of astragalus angelica, namely stilbene, astragaloside I, astragaloside A, pistil isoflavone, ferulic acid and pistil isoflavone glycoside, to carry out experimental verification, so as to obtain the best drug concentration. The results showed that the six chemical constituents of Astragalus Angelica could inhibit the proliferation of VSMCs in a concentration dependent manner. [19]

Table 2. Summary of drug functions

Medicine	Effect1.	Effect2.	Effect3.
Astragalus membranaceus	Lower blood pressure	Replenish qi	Replenish blood
Chinses angelica	Promoting blood circulation	Promoting removing stasis	Lower blood pressure

3. Suppress Pro-Vascular Smooth Muscle Proliferation Factor Expression

Disease development in the process of many complications, most of the time these complications are the key factors affecting our quality of life, traditional Chinese medicine and symptoms so often will have clinical related Chinese medicine compatibility, can make the drug effect play to larger, more comprehensive so as to achieve the effect of curing, See Table 3. huoluo-xiaoling pellets (from "Medical Ginseng Xi Lu") has the effect of activating blood circulation and removing blood stasis, dredging collaterals and relieving pain, and is commonly used clinically to treat pain caused by blood stasis. Gao Shanshan and other scholars studied the mechanism of action and found that it can reduce the activity of platelet-derived growth factor mRNA in VSMCs and thus inhibit the proliferation and phenotype of VSMCs[20].

Table 3. Summary of drug Functions

Medicine	Effect1.	Effect2.	Effect3.
Tianma Gouteng Drink	Lower blood pressure	Calming the liver and suppressing yang	/
Trichosanthes	Vasodilator	Anti-ulcer	Disaggregation

Gastrodia elata hook vine drink (from "New Medicine of Traditional Chinese Medicine") is a representative prescription of flat liver, and also a specific drug for the clinical treatment of hypertension and other wind disturbance. Zhong guangwei[21]When exploring the mechanism of action, the researchers found that it could inhibit the VSMCs proliferation and phenotylation induced by angiotensin II, and found that the reduced degree of intracellular mRNA expression also led to the reduced total DNA methylation level. Whether the methylation level affects VSMCs proliferation and phenotylation remains to be further explored.

As a commonly used clinical medicine, trichosanthes can clear away heat and phlegm, promote qi and disperse knots. Modern research shows that trichosanthes also has a good therapeutic effect in vasodilation, anti-ulcer, anti-myocardial ischemia and other aspects, and its main role is trichosanthes peel extract (EPT). EPT can promote the expression of Akt, p-Akt (Ser 473) and anti-apoptosis protein Bcl-2, which may improve cardiomyocyte apoptosis induced by hypoxia/reoxygenation injury by activating PI3K/Akt signal pathway[22] .Yang Zheng and other scholars found through experimental research that EPT can inhibit the proliferation of VSMCs by inhibiting the expression of angiotensin II, and its mechanism may be related to reducing the high expression of proto oncogene c-fos mRNA and increasing the expression of nitric oxide synthase mRNA.

4. Summary and Outlook

Table 4. Efficacy intensity grading table

Indirect effect (Small effect)	Astragalus	Gynostemma pentaphyllum	Green tea polyphenols	Saffron	Pueraria lobata
Direct action (Potent)	Angelica sinensis	Ginkgo biloba extract	Gastrodia elata hook vine drink	huoluo-xiaoling pellets	Trichosanthes

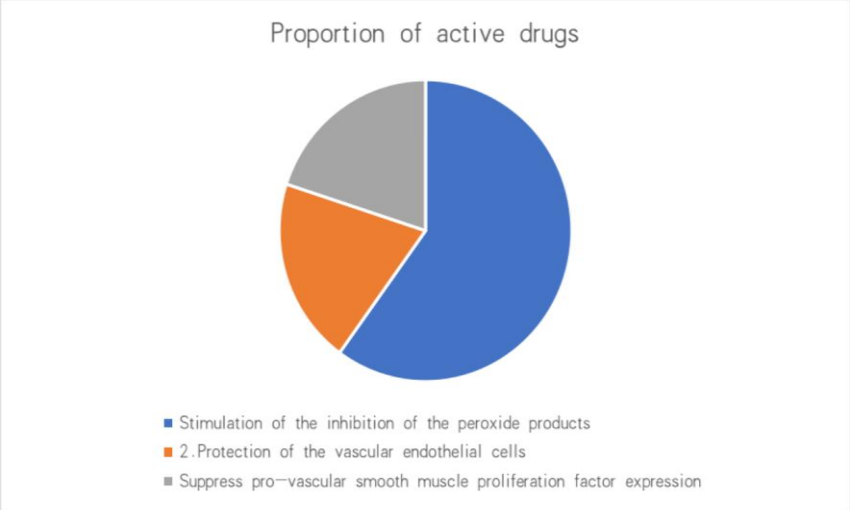

Figure 1. Efficiency ratio chart

Chinese medicine extracts and its preparation and side effects and targets, many researchers at home and abroad combined with classical prescriptions and drug properties different research are found to promote blood stasis, qi nourishing blood, flat liver latent Yang drugs and antioxidant drugs through different factors can directly or indirectly inhibit or reverse VSMCs proliferation and phenotyping, can be used as the prevention and treatment of hypertension, hyperlipidemia, hyperglycemia, coronary heart disease and angiography of vascular wall hardening and plaque formation, See Table 4 and Figure 1. At present, we mostly use in vitro cell culture experiments or animal experiments in our research, and there are relatively few clinical studies. Different delivery routes and drug targets in different bodies will affect the final effect, See picture1. Although some TCM extraction agents have been used in clinical treatment, their limitations are very great. They are mostly used in health care defense treatment, and they will not be our first choice in clinical acute treatment. It is hoped that the majority of scholars can improve the safety of drugs and vigorously carry out clinical research, so as to provide a reference for the wide application of TCM in clinical practice.

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Data Availability

The datasets used during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

The author states that this article has no conflict of interest.

References

[1] Cui, Y.Y., Wang, X. and Zhao, F.H. (2018) Phenotypic Transformation of Vascular Smooth Muscle Cells and the Associated Mechanisms. Cardiovascular disease progression, 39 (06): 900-903.

[2] Souhad, E.A., Isabelle, C. and Jean-Fran ̧ois, T. (2013) Adipocytes Modulate Vascular Smooth Muscle Cells Migration Potential through their Secretions. Journal of Diabetes Mellitus, 3(4).

[3] Liu, T., Chu, X., Han, X., et al. (2016) Progress in the Pharmacology of Crocein. Guangdong Chemical Industry, 17, 77-78.

[4] He, S.Y., Qian, Z.Y. and Xu, G.L. (2004) Effects and Mechanism of Crocein on Smooth Muscle Cell Proliferation. Journal of China Pharmaceutical University, 1, 65-68.

[5] Zhang, C.M. and Wang, H.F. (2019) Effects of Puerarin on the TLR4-NF- K B Signaling Transduction Pathway in the Oxldl-Induced THP-1 Macrophages. Chinese Journal of Immunology, 22, 2705-2710. https://doi.org/10.26549/yzlcyxzz.v3i3.3920

[6] Cao, P., Zhang, Y.S., Wei, X.M. et al. (2021) New Progress in Studying the Pharmacological Effects of Puerarin. Chinese patent medicine, 8, 2130-2134.

[7] Ouyang, P., Peng, W.L., Xu, D.L., et al. (2004) Green Tea Polyphenols Inhibit Rat Vascular Smooth Muscle Cell Proliferation Induced by Late Glycosylation End Products. Journal of the First Military Medical University, 3, 247-251.

[8] Han, D.W., Jung, D.Y., Park, J.C., Cho, H.H., Hyon, S.H. and Han, D.K. (2010) Underlying Mechanism for Suppression of Vascular Smooth Muscle Cells by Green Tea Polyphenol EGCG Released from Biodegradable Polymers for Stent Application. Journal of biomedical materials research. Part A, 95(2). https://doi.org/10.1002/jbm.a.32870

[9] Beam, W., Liu, Z.J. and Qian, M.Z. (2017) Effect of Gynososide on Vascular Smooth Muscle Cell Phenotype in Hyperlipidemic Rats. Natural Products Research and Development, 2, 217-223.

[10] Sha, R.N., Tang, L., Du, Y.W., Wu, S.X., Shi, H.W., Zou, H.X., Zhang, X.R., Dong, X.L. and Zhou, L. (2022) Effectiveness and safety of Ginkgo Biloba Extract (GBE50) in the Treatment of Dizziness Caused by Cerebral Arteriosclerosis: A Multi-Center, Double-Blind, Randomized Controlled Trial. Journal of traditional Chinese medicine = Chung i tsa chih ying wen pan, 42(1).

[11] Liang, X.J. and Dong, S.H. (2004) Experimental study on Vsmooth Cell Apoptosis Induced by Ginkgo Biloba Extract. Guangdong Medicine, 6, 640-641.

[12] Mao, H.M., Liu, J.G., Zhao, F.H., Shi, D.Z. and Liu, X.H. (2016) Progress in the Regulation of Restenotic Vascular Smooth Muscle Cell Proliferation after Stents by Zedoary Extracts. China Pharmacology Bulletin, 32 (01): 19-22.

[13] Pan, H.L., He, X.Q., Cheng, Y., Li, D., Qi, Y.J., Yao, L.Y. and Wo, J.S. (2020) Effects of Curcumin on Inflammatory Factors and Blood Lipid in the Blood of Atherosclerotic Rats and its Mechanism of Action. Journal of Precision Medicine, 35 (02): 160-164.

[14] Gu, J., Guo, C., Che, M., Wu, H.Y. and Li, H.L. (2019) Effects of Astragalus Sinensis on the ER Stress Response to Vascular Remodeling in Hypertensive Rats. Chinese Journal of Experimental Animals, 27 (01): 65-71.

[15] Liu, Y., Liu, W.B. and Zhao, Y.X. (2006) Progress in the prevention and treatment of atherosclerosis. Journal of Difficult Diseases, 06, 463-465.

[16] Gao, X.L., Qin, L.P., Li, Y.Z. and Li, A.Y. (2021) Angelica Polysaccharide Inhibiting the PI3K / AKT Pathway Hindering Smooth Muscle Cell Proliferation and Migration. Natural Products Research and Development, 33 (12): 2004-2010.

[17]Li, Q., Wen, J.K. and Han, M. (2004) Effects of Astragalus And Angelica Sinensis On Gene Expression And Cell Proliferation As A Marker Of Vascular Smooth Muscle Cells. The Chinese Journal of Arterial Sclerosis, 2, 147-150.

[18] Gao, S.S., Hao, L.Z., Zhu, J.J., Chai, X.L. and Zhang, Y.S. (2015) Effect of Rdan on Phenotype-Transformed Mirna-24 Expression in Vascular Smooth Muscle Cells of Type 2 Diabetic Rats. Traditional Chinese Medicine Guide, 21 (03): 4-7.

[19] Chen, L.B., Ren, R.B., Yan, H.F. and Deng, C.Q. Effect of Dosage Compatibility of Main Chemical Components of Astragalus and Angelica Sinensis based on Uniform Experimental Design on Proliferation of Vascular Smooth Muscle Cells. Chinese Journal of Experimental Formulas, 1-10

[20] Zhong, G.W., Wan, L., Wang, D.S., Fang, X., Chen, Q., Xie, M.X. and Tang, T. (2016) Effect of Serum-Containing Serum on Proliferation and Migration and DNA Methylation Levels of Vascular Smooth Muscle Cells. Chinese Journal of Integrated Traditional Chinese and Western Medicine, 36 (05): 580-585.

[21] Chu, D.H. and Zhang, Z.Q. (2020) The Role of PI3K/Akt Signaling Pathway in the Protection of Pericarpium Trichosanthis Against Hypoxia/Reoxygenation Injury of Myocardial Cells. Chinese Journal of Traditional Chinese Medicine, 04:220-225.

[22] Yang ,Z., Song, M., Chen, Q., Song, Y.T., Guo, X.H. and Qiu, M. (2018) Effect of Trichosanthes Peel Extract on Ang Ⅱ Induced Proliferation of Vascular Smooth Muscle Cells. Journal of Clinical Rational Drug Use, 01:44-46