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Research Progress on Proprotein Convertase Subtilisin/Kexin Type 9-mediated Atherosclerotic Inflammatory Response and Intervention of Traditional Chinese Medicine

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Abstract:

The "cholesterol theory" has laid the foundation for the treatment of atherosclerotic cardiovascular diseases, but research has proven that the "inflammatory response theory" is another research hotspot related to atherosclerosis (AS) and a potential target for AS intervention. Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) has pleiotropic effects mediated by lipid regulation and inflammatory response. It can drive inflammatory responses through lipids and is also an independent inflammatory mediator involved in the occurrence of AS. The inflammatory response effect of PCSK9 may be one of the important targets of traditional Chinese medicine for the treatment of AS. Traditional Chinese medicines and their extracts (quercetin, berberine hydrochloride, *gynostemma pentaphyllum*, curcumin, 10-dehydrogingerdione and sugarcane element, ginkgolide B, naringin, and hesperidin, etc.), and traditional Chinese medicine compounds (Shoushen granules, Qizhi Tongmai granules, etc.) have inhibitory effects on Pcsk9, which is an important direction for PCSK9 drug research and discovery.

Keywords:

Proprotein convertase subtilisin/kexin type 9
Atherosclerosis
Inflammatory response
Cell adhesion
Interleukin
Toll-like receptor 4
Nuclear factor KB
Traditional Chinese medicine

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1. Introduction

Atherosclerotic Cardiovascular Disease (ASCVD) remains the leading cause of death and rising medical costs globally [1]. It mainly includes coronary heart disease, cerebral infarction, and peripheral artery disease, with atherosclerosis (AS) as their common pathological basis [2]. The "cholesterol theory" has laid the foundation for ASCVD treatment. Although it is clinically believed that lower levels of Low-Density Lipoprotein Cholesterol (LDL-C) are better, there is still a prevalent residual risk of ASCVD in individuals with low or target LDL-C levels [3]. Therefore, intervention in other pathogenic risks of AS is necessary. The "inflammatory response theory" is another research hotspot related to AS and a potential target for AS intervention. In 1999, Ross (1999) [4] proposed that "AS is an inflammatory disease." However, it was only until large randomized controlled clinical trials such as CANTOS, COLCOT, and LoDoCo2 confirmed that canakinumab and colchicine can improve the prognosis of ASCVD that the "inflammatory response theory" gained clinical evidence [5–7].

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) is currently a focal point in lipid research and was discovered in 2003. The PCSK9 gene is the third autosomal dominant hypercholesterolemia-related gene after the Apolipoprotein B (ApoB) gene and the Low-Density Lipoprotein Receptor (LDLR) gene [8]. It can bind to the LDLR binding domain in the liver, accelerating LDLR degradation in lysosomes and reducing LDLR levels in circulation. This decreases the ability of LDLR to clear LDL-C, leading to an increase in LDL-C concentration and ultimately resulting in AS [9]. Populations with PCSK9 loss-of-function mutations have reduced risks of LDL-C and coronary heart disease [10,11]. Studies have confirmed that PCSK9 inhibitors can significantly reduce LDL-C and increase the benefits of ASCVD [12–14]. However, the role of PCSK9 in AS is not limited to regulating LDL-C, as it also exhibits important inflammatory response effects [15]. This may be another pathway for the clinical benefits of PCSK9 inhibitors. Therefore, intervening in the inflammatory response mediated by PCSK9 is one of the potential mechanisms of traditional Chinese medicine for treating AS. This article reviews the research progress on PCSK9-mediated inflammatory response in AS and the intervention of traditional Chinese medicine.

2. Mediation of PCSK9 in the inflammatory response of atherosclerosis (AS)

2.1. PCSK9 mediates cellular inflammatory response via lipid pathway

AS is a lipid-driven inflammatory disease [16]. It initiates the differentiation of inflammatory cells and inflammatory damage mediated by the lipid pathway by promoting the occurrence of hyperlipidemia and the increase of monocytes and neutrophils [17,18]. Oxidized Low-Density Lipoprotein (ox-LDL) can induce the differentiation of monocytes in the blood into macrophages under the intima through damaged endothelial gaps. In this process, PCSK9 regulates the chemokine C-C motif receptor 2 (CCR2) on monocytes, enabling their migration towards vascular smooth muscle cells and further differentiation into macrophages [19]. During the lipid uptake by monocytes differentiating into macrophages, PCSK9 also promotes the inflammatory response of lipid internalization, leading to intracellular lipid accumulation and the formation of foam cells [20]. Elevated cholesterol can activate neutrophil inflammasome components such as Nucleotide Oligomerization Domain-Like Receptor Protein 3 (NLRP3), releasing Interleukin-1β (IL-1β) and IL-8 from the Interleukin (IL) family. This results in the formation of Neutrophil Extracellular Traps (NETs), which cause vascular smooth muscle cell apoptosis and vascular damage by attacking their cells, and participate in AS plaque rupture and thrombosis [21,22].

2.2. PCSK9 as an independent inflammatory mediator

PCSK9 can function as an inflammatory mediator by promoting cell adhesion and mediating the expression of inflammatory molecules. Cell adhesion is involved in AS formation by facilitating the recruitment, migration, and differentiation of inflammatory cells. The cell adhesion molecule family, including Intercellular Adhesion Molecule-1 (ICAM1), Vascular Cell Adhesion Molecule-1 (VCAM1), E-selectin, and P-selectin, has been shown to play a crucial role in this process. In animal models of AS, PCSK9 gene deletion or knockout reduces AS occurrence through a mechanism independent of LDLR, leading to decreased expression of ICAM1 and VCAM1 in endothelial cells [23,24]. Experimental studies

have demonstrated that PCSK9 can increase the release of P-selectin from platelets [25], and there is a strong positive correlation between PCSK9 levels and E-selectin levels in patients with coronary heart disease [26].

PCSK9 can activate the Toll-like Receptor 4 (TLR4)/Nuclear Factor-kappaB pathway, inducing the transcription of many pro-inflammatory genes. Nuclear Factor-kappaB is a key factor in the inflammatory axis of AS, involved in AS injury by mediating the transcriptional regulation of various inflammatory mediators, including Tumor Necrosis Factor-alpha (TNF-α), the IL family, Monocyte Chemotactic Protein-1 (MCP-1), and Lectin-like Oxidized Low-Density Lipoprotein Receptor-1 (LOX-1) [24–28]. Cellular experiments have shown that after incubation with PCSK9 for 24 hours, the messenger ribonucleic acid (mRNA) of IL-1β, TNF-α, and MCP-1 in macrophages and vascular smooth muscle cells is significantly induced [29]. Animal experiments indicate that PCSK9 overexpression can be detected in AS plaques of Apolipoprotein E (ApoE) gene knockout mice. This overexpression upregulates TLR4 expression, leading to the activation of the TLR4 signaling pathway. Silencing the PCSK9 gene can inhibit the transcription of TNF-α, IL-1β, and MCP-1 genes in the TLR4/Nuclear Factor-kappaB signaling pathway, reducing vascular inflammation and directly inhibiting AS without affecting plasma cholesterol levels in ApoE gene knockout mice fed a high-fat diet [30].

In addition, PCSK9 induces the expression of Tissue Factor (TF) by activating the TLR4/Nuclear Factor-kappaB signaling pathway, thereby participating in the process of coagulation and inflammatory response. TF is a transmembrane glycoprotein that serves as the initiator of the coagulation reaction and is associated with the thrombotic state of AS. *In vitro* cellular experiments have confirmed this correlation, where PCSK9 increases the procoagulant activity, mRNA, and protein expression of TF in peripheral blood monocytes and human monocytic leukemia cells (Tohoku Hospital Pediatrics-1, THP-1). Pretreatment with TLR4/Nuclear Factor-kappaB signaling inhibitors can downregulate the level of TF induced by PCSK9 [31].

LOX-1 is a specific receptor for ox-LDL that can internalize, phagocytize, and degrade ox-LDL to form foam cells. There is a positive feedback loop between LOX-1 and PCSK9, and the deletion of the LOX-1 gene significantly inhibits the expression of PCSK9 [24]. Furthermore, the activation of Nuclear Factor-kappaB plays a bridging role in the expression of LOX-1 induced by ox-LDL and lipopolysaccharide [32].

2.3. PCSK9 is a new target for anti-inflammatory therapy in AS

The inflammatory response effects of PCSK9 in AS suggest that it is a new target for anti-inflammatory therapy in AS. PCSK9 inhibitors have been shown to have anti-inflammatory effects. In cellular experiments, PCSK9 siRNA drugs inhibit the activation of the Nuclear Factor-kappaB pathway in THP-1-derived macrophages, reducing the transcription of IL-1a, IL-6, and TNF-a [33]. In animal experiments, anti-PCSK9 vaccines have reduced the expression of ICAM1 in mouse endothelium, subsequently decreasing the adhesion of monocytes to vascular endothelium [34,35]. In clinical studies, patients with familial hypercholesterolemia treated with PCSK9 inhibitors have shown a decrease in monocyte count, CCR2 expression, and levels of TNF-a, IL6, IL8, IL-10, and P-selectin [36–39].

3. Intervention of traditional Chinese medicine

Numerous studies have demonstrated that traditional Chinese medicines and their extracts have inhibitory effects on PCSK9, representing an important direction for PCSK9 drug research and discovery. In addition to the lipid-lowering effects obtained through direct inhibition of PCSK9 in related studies, mediating the inflammatory response of PCSK9 is also a research hotspot in this field and one of the important mechanisms of the anti-inflammatory effects of traditional Chinese medicine in treating AS.

3.1. Traditional Chinese medicine and its extracts

3.1.1. Quercetin

Quercetin, a type of flavonoid widely found in plants and traditional Chinese medicines such as Chaihu and Huaimi, possesses anti-inflammatory, antioxidant, and lipid metabolism effects. In an ApoE gene knockout mouse

model with a high-fat diet, quercetin was able to reduce the size of atherosclerotic plaques while significantly lowering the levels of PCSK9, TNF-a, and IL-6 [40,41].

3.1.2. Berberine hydrochloride

Clinical research has shown that oral administration of berberine hydrochloride, an extract from the traditional Chinese medicine Huanglian, can reduce the levels of IL-6, TNF-a, ICAM1, and VCAM1 [42,43]. However, its correlation with PCSK9 in terms of inflammatory response has not been explored. *In vitro* experiments have demonstrated that berberine hydrochloride can down-regulate the expression of PCSK9 through the MAPK/ERK1/2 signaling pathway, which promotes the transcription and expression of nuclear factor kappa B genes, as well as cell proliferation and differentiation, involved in the inflammatory response of atherosclerosis [44]. Therefore, it is speculated that berberine hydrochloride can interfere with the inflammatory response mediated by PCSK9. Another animal experiment confirmed that oral administration of berberine hydrochloride at 10 mg/kg or 30 mg/kg can reduce the levels of TNF-a and IL-1a by inhibiting lipopolysaccharide, thereby regulating the expression of PCSK9 in a dose-dependent manner [45].

3.1.3. Gypenoside

In a rat model of atherosclerosis induced by vitamin D3 combined with a high-fat diet, gypenoside was able to inhibit the secretion of ICAM1, VCAM1, and MCP-1 in aortic tissue. It is speculated that this effect is mainly achieved by inhibiting the PCSK9/LOX-1 signaling pathway in atherosclerotic rats, thereby reducing endothelial dysfunction and delaying atherosclerotic lesions. Similar results were obtained in experiments on human vascular endothelial cells [46].

3.1.4. Curcumin, 10-dehydrogingerdione, and sugarcane extract

Continuous administration of curcumin, an extract from ginger, for 12 weeks significantly reduced the levels of PCSK9, ICAM1, and VCAM1 in rabbits with hyperlipidemia, thereby reducing atherosclerotic lesions by decreasing the inflammatory response [47]. Another ginger extract, 10-dehydrogingerdione, has a significant inhibitory effect on PCSK9. Compared with atorvastatin treatment, 10-dehydrogingerdione was able to significantly reduce the levels of TNF-α and soluble P-selectin in rabbits, inhibiting macrophage migration and endothelial cell inflammatory infiltration [48–50]. The sugarcane extract, when used alone or in combination with 10-dehydrogingerdione, can also reduce P-selectin levels [51]. These findings suggest that 10-dehydrogingerdione and sugarcane extract can effectively reduce the inflammatory response, platelet activation, and endothelial dysfunction in atherosclerosis by inhibiting PCSK9.

3.1.5. Ginkgolide B

Ginkgolide B, a natural platelet-activating factor antagonist extracted from ginkgo leaves, can participate in lipid metabolism by inhibiting PCSK9. Cell experiments have confirmed that ginkgolide B reduces the inflammatory cascade reaction induced by ox-LDL in human vascular endothelial cells by inhibiting PCSK-9, including down-regulating ICAM1 and VCAM1 levels and inhibiting the mRNA and protein expression of IL-a, IL-1β, IL-6, and MCP-1 [52].

3.1.6. Naringin and hesperidin

Naringin and hesperidin are mainly found in the fruits, peels, and pulp of Rutaceae plants, which are often used as traditional Chinese medicines such as Chenpi, Qingpi, Zhishi, and Zhiqiao. A systematic review and meta-analysis showed that naringin can lower blood lipids through PCSK9. Other studies have confirmed its inhibitory effects on nuclear factor kappa B, IL-6, TNF-a, ICAM1, and VCAM1 [53]. However, it remains unclear whether it acts through the inflammatory response pathway of PCSK9. On the other hand, hesperidin can inhibit the activation of PCSK9 and nuclear factor kappa B by binding to their sites, reducing the expression of TNF-a, IL-1B, and IL-10 mRNA, thereby reducing the pro-inflammatory effects of diesel exhaust particles on the blood vessels of Wistar rats [54].

3.1.7. Others

Rhein, an extract from rhubarb, can significantly reduce the expression of PCSK9, IL-1β, and IL6 mRNA, as well as neutrophil migration and recruitment in a zebrafish

model fed with a high-fat diet, thereby improving inflammatory responses [55]. Tanshinone IIA is an active compound isolated from the traditional Chinese medicine Danshen. It has inhibitory effects on markers of inflammatory responses in atherosclerosis, including PCSK9, TLR4, nuclear factor kappa B, TNF-a, IL-1B, IL-6, and MCP-1 [56]. Evodiamine can reduce the expression of PCSK9 [57] and inhibit endothelial inflammatory responses through the TLR4/nuclear factor kappa B pathway [58]. Resveratrol, an extract from *Polygonum cuspidatum*, can inhibit PCSK9 expression in hyperlipidemia mouse and hamster models [59], reduce NLRP3 and IL-1β levels, alleviate pyroptosis of vascular smooth muscle cells, and exert anti-atherosclerotic effects [60]. Similar drugs include Astragalus polysaccharides [61,62] and total flavonoids from hawthorn leaves [63,64]. However, these drugs lack analysis of the relationship between inflammatory responses and effects after PCSK9 inhibition, so whether they exert anti-inflammatory effects through PCSK9 remains to be further confirmed.

3.2. Compound Chinese medicines

3.2.1. Shoushen granules

Shoushen granules can significantly reduce the levels of PCSK9, TLR4, nuclear factor kappa B in the aorta, and serum levels of TNF-a, IL10, MCP-1, and ICAM1 in ApoE knockout mice fed with a high-fat diet. Compared with atorvastatin, Shoushen granules have a similar lipid-lowering effect, but there are no significant changes in the aforementioned inflammatory markers with atorvastatin. This confirms that Shoushen granules can inhibit the occurrence and development of atherosclerosis by interfering with the PCSK9-mediated TLR4/nuclear factor kappa B inflammatory response pathway [65].

3.2.2. Qizhi Tongmai granules

According to research by Song *et al.* (2021) [66], the empirical prescription Qizhi Tongmai granules (composed of processed Astragalus, leech powder, *Panax notoginseng*, red yeast rice, and *Erigeron breviscapus*) can reduce the levels of PCSK9, VCAM1, and ICAM1 in rats with coronary heart disease, indicating that it may inhibit atherosclerosis by regulating the expression of proteins related to the PCSK9/LDLR and VCAM-1/ICAM-1 signaling pathways.

3.2.3. Blood Vessel Softening Pills

Kong *et al.* (2021) [67] discovered the anti-atherosclerotic effects of Blood Vessel Softening Pills (composed of hawthorn, medicated leaven, pearl, ochre, radish seed, *Poria cocos*, goji berry, dried tangerine peel, forsythia, turmeric, *Panax notoginseng*, and processed pinellia tuber) that compared with the model group, the PCSK9 mRNA and protein expression levels, as well as serum TNF-a and IL-6 levels, were significantly reduced in the Blood Vessel Softening Pill group. This suggests that Blood Vessel Softening Pills may indirectly regulate very low-density lipoprotein receptors by targeting PCSK9, inhibiting vascular inflammatory responses, and reducing smooth muscle cell damage.

3.2.4. Other compound Chinese medicines

Related studies have shown that traditional Chinese medicine compounds such as Diao Xin Xue Kang, Bu Yang Huan Wu Tang, and He Dan Pian, which are used to eliminate phlegm and resolve blood stasis, have inhibitory effects on PCSK9 [68–71]. Theoretically, they can interfere with PCSK9-mediated inflammatory response damage, but relevant studies lack simultaneous detection of inflammatory markers and correlation analysis. Although some studies have shown that the above-mentioned traditional Chinese medicine compounds can exert anti-inflammatory effects by interfering with the TLR4/nuclear factor kappa B pathway or downstream inflammatory response markers [72–74], it is still unclear whether this is mediated by PCSK9. Zhang (2022) [75] found in an experimental study using a PCSK9 inhibitor as a control group that the Huotan Jiedu Tongluo formula (composed of full-grown snakegourd fruit, angelica, rhodiola, nardostachys, figwort, salvia, honeysuckle, leech, and licorice) had similar effects to the control group in reducing NLRP3, IL-1β, and TNF-a levels in mice with atherosclerotic vulnerable plaques. However, PCSK9 levels were not measured in the observation group, so it is unclear whether the effect is mediated by inhibiting CPSK9. Studies have confirmed that Lu Huang granules can reduce PCSK9 and IL-6 levels [76,77], but there is also a lack of correlation analysis.

4. Summary

Basic research has fully confirmed that atherosclerosis (AS) is an inflammatory disease, yet clinical evidence for the anti-inflammatory effects of related drugs remains scarce. PCSK9 exhibits pleiotropic effects, functioning not only in lipid regulation and participating in lipid-driven inflammatory responses but also as an independent inflammatory mediator. These roles often involve cascade reactions, forming an inflammatory network or cascade. Therefore, PCSK9 may represent a novel target for anti-inflammatory therapy.

PCSK9 inhibitors have demonstrated corresponding anti-inflammatory effects and shown benefits independent of blood lipids. However, some studies indicate that their impact on systemic inflammatory markers is not significant, possibly due to the targeted effects of PCSK9 on plaque tissue, monocytes, macrophages, endothelial cells, and vascular smooth muscle cells. More experimental evidence is needed to confirm these findings. On the other hand, while the clinical benefits of PCSK9 inhibitors are relatively clear, clinical research related to their mediation of inflammatory responses remains limited. Obtaining direct evidence in clinical settings may be challenging, particularly due to their local targeting properties.

Traditional Chinese medicine (TCM) represents a natural treasure house for PCSK9 inhibitor discovery. On one hand, there is an expectation to uncover more novel PCSK9 inhibitors from TCM; on the other hand, further exploration of their mechanisms of action is needed. TCM, especially non-monomeric drugs or compound preparations, often exhibit multi-target and multi-site mechanisms. Their role in PCSK9-related inflammatory responses remains unclear. Studies have confirmed their inhibitory effects on both PCSK9 and AS-related inflammatory markers, but research on the correlation between the two is lacking. The mediation of inflammatory responses may occur through several pathways:

(1) Directly inhibiting inflammatory responses via non-PCSK9 and non-lipid pathways;

(2) Inhibiting lipid metabolism-related inflammatory responses independent of PCSK9;

(3) Intervening in lipid metabolism-related inflammatory responses through the PCSK9 pathway without mediating PCSK9's independent inflammatory pathway;

(4) Mediating direct inhibition of both PCSK9 and inflammatory responses, either separately or together.

In conclusion, PCSK9-mediated inflammatory responses play a crucial role in the development and progression of AS, potentially opening up a new field of AS inflammatory response therapy. Simultaneously, it represents a novel target for researching the mechanistic action of TCM in the treatment of AS.

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References

[1] Vos T, Lim S, Abbafati C, et al., 2020, Global Burden of 369 Diseases and Injuries in 204 Countries and Territories, 1990–2019: A Systematic Analysis for the Global Burden of Disease Study 2019. Lancet, 396(10258): 1204–1222.

[2] Grundy SM, Stone NJ, Bailey AL, et al., 2019, 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/

American Heart Association Task Force on Clinical Practice Guidelines. Circulation, 139(25): e1082–e1143.

[3] Matsuura Y, Kanter JE, Bornfeldt KE, 2019, Highlighting Residual Atherosclerotic Cardiovascular Disease Risk. Arteriosclerosis, Thrombosis, and Vascular Biology, 39(1): e1–e9.

[4] Ross R, 1999, Atherosclerosis – An Inflammatory Disease. The New England Journal of Medicine, 340(2): 115–126.

[5] Ridker PM, Everett BM, Thuren T, et al., 2017, Anti-inflammatory Therapy with Canakinumab for Atherosclerotic Disease. The New England Journal of Medicine, 377(12): 1119–1131.

[6] Tardif JC, Kouz S, Waters DD, et al., 2019, Efficacy and Safety of Low-dose Colchicine after Myocardial Infarction. The New England Journal of Medicine, 381(26): 2497–2505.

[7] Nidorf SM, Fiolet ATL, Mosterd A, et al., 2020, Colchicine in Patients with Chronic Coronary Disease. The New England Journal of Medicine, 383(19): 1838–1847.

[8] Abifadel M, Varret M, Rabès JP, et al., 2003, Mutations in PCSK9 Cause Autosomal Dominant Hypercholesterolemia. Nature Genetics, 34(2): 154–156.

[9] Piper DE, Jackson S, Liu Q, et al., 2007, The Crystal Structure of PCSK9: A Regulator of Plasma LDL-Cholesterol. Structure, 15(5): 545–552.

[10] Cohen J, Pertsemlidis A, Kotowski IK, et al., 2005, Low LDL Cholesterol in Individuals of African Descent Resulting from Frequent Nonsense Mutations in PCSK9. Nature Genetics, 37(2): 161–165.

[11] Cohen JC, Boerwinkle E, Mosley TH, et al., 2006, Sequence Variations in PCSK9, Low LDL, and Protection against Coronary Heart Disease. The New England Journal of Medicine, 354(12): 1264–1272.

[12] Sabatine MS, Giugliano RP, Keecha C, et al., 2017, Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. The New England Journal of Medicine, 376(18): 1713–1722.

[13] Ray KK, Wright RS, Kallend D, et al., 2020, Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. The New England Journal of Medicine, 382(16): 1507–1519.

[14] Schwartz GG, Steg PG, Szarek M, et al., 2018, Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. The New England Journal of Medicine, 379(22): 2097–2107.

[15] Luquero A, Badimon L, Borrell-Pages M, 2021, PCSK9 Functions in Atherosclerosis Are Not Limited to Plasmatic LDL-Cholesterol Regulation. Frontiers in Cardiovascular Medicine, 8: 639727.

[16] Yurtseven E, Ural D, Baysal K, et al., 2020, An Update on the Role of PCSK9 in Atherosclerosis. Journal of Atherosclerosis and Thrombosis, 27(9): 909–918.

[17] Drechsler M, Megens RT, Van ZM, et al., 2010, Hyperlipidemia-Triggered Neutrophilia Promotes Early Atherosclerosis. Circulation, 122(18): 1837–1845.

[18] Louloudis G, Ambrosini S, Paneni F, et al., 2021, Adeno-Associated Virus-Mediated Gain-of-Function mPCSK9 Expression in the Mouse Induces Hypercholesterolemia, Monocytosis, Neutrophilia, and a Hypercoagulative State. Frontiers in Cardiovascular Medicine, 8: 718741.

[19] Grune J, Meyborg H, Bezhaeva T, et al., 2017, PCSK9 Regulates the Chemokine Receptor CCR2 on Monocytes. Biochemical and Biophysical Research Communications, 485(2): 312–318.

[20] Badimon L, Luquero A, Crespo J, et al., 2021, PCSK9 and LRP5 in Macrophage Lipid Internalization and Inflammation. Cardiovascular Research, 117(9): 2054–2068.

[21] Chistiakov DA, Bobryshev YV, Orekhov AN, 2015, Neutrophil's Weapons in Atherosclerosis. Experimental and Molecular Pathology, 99(3): 663–671.

[22] Tall AR, Westerterp M, 2019, Inflammasomes, Neutrophil Extracellular Traps, and Cholesterol. Journal of Lipid Research, 60(4): 721–727.

[23] Sun H, Krauss RM, Chang JT, et al., 2018, PCSK9 Deficiency Reduces Atherosclerosis, Apolipoprotein B Secretion, and

Endothelial Dysfunction. Journal of Lipid Research, 59(2): 207–223.

[24] Zufeng D, Shijie L, Xianwei W, et al., 2015, Cross-Talk Between LOX-1 and PCSK9 in Vascular Tissues. Cardiovascular Research, 107(4): 556–567.

[25] Zhiyong Q, Liang H, Jianjun Z, et al., 2021, PCSK9 (Proprotein Convertase Subtilisin/Kexin 9) Enhances Platelet Activation, Thrombosis, and Myocardial Infarct Expansion by Binding to Platelet CD36. Circulation, 143(1): 45–61.

[26] Qiang W, Bo Z, Peng C, et al., 2022, Leptin and PCSK9 Concentrations Are Associated with Vascular Endothelial Cytokines in Patients with Stable Coronary Heart Disease. Open Medicine (Wars), 17(1): 185–190.

[27] Roshan MH, Tambo A, Pace NP, 2016, The Role of TLR2, TLR4, and TLR9 in the Pathogenesis of Atherosclerosis. International Journal of Inflammation, 2016: 1532832.

[28] De Winther MP, Kanters E, Kraal G, et al., 2005, Nuclear Factor Kappa B Signaling in Atherogenesis. Arteriosclerosis, Thrombosis, and Vascular Biology, 25(5): 904–914.

[29] Ricci C, Ruscica M, Camera M, et al., 2018, PCSK9 Induces a Pro-Inflammatory Response in Macrophages. Scientific Reports, 8(1): 2267.

[30] Zhihan T, Juan P, Zhong R, et al., 2017, New Role of PCSK9 in Atherosclerotic Inflammation Promotion Involving the TLR4/NF-kB Pathway. Atherosclerosis, 262: 113–122.

[31] Scalise V, Sanguinetti C, Neri T, et al., 2021, PCSK9 Induces Tissue Factor Expression by Activation of TLR4/NF-kB Signaling. International Journal of Molecular Sciences, 22(23): 12640.

[32] Zufeng D, Shijie L, Xianwei W, et al., 2015, Hemodynamic Shear Stress via ROS Modulates PCSK9 Expression in Human Vascular Endothelial and Smooth Muscle Cells and Along the Mouse Aorta. Antioxidants & Redox Signaling, 22(9): 760–771.

[33] Zhihan T, Lu J, Juan P, et al., 2012, PCSK9 siRNA Suppresses the Inflammatory Response Induced by OxLDL Through Inhibition of NF-kB Activation in THP-1-Derived Macrophages. International Journal of Molecular Medicine, 30(4): 931–938.

[34] Kühnast S, Hoorn JWV, Pieterman EJ, et al., 2014, Alirocumab Inhibits Atherosclerosis, Improves Plaque Morphology, and Enhances the Effects of a Statin. Journal of Lipid Research, 55(10): 2103–2112.

[35] Landlinger C, Pouwer MG, Juno C, et al., 2017, The ATO4A Vaccine Against Proprotein Convertase Subtilisin/Kexin Type 9 Reduces Total Cholesterol, Vascular Inflammation, and Atherosclerosis in APOE 3Leiden.CETP Mice. European Heart Journal, 38(32): 2499–2507.

[36] Scicali R, Pino AD, Ferrara V, et al., 2021, Effect of PCSK9 Inhibitors on Pulse Wave Velocity and Monocyte-to-HDL Cholesterol Ratio in Familial Hypercholesterolemia Subjects: Results From a Single Lipid Unit Real-Life Setting. Acta Diabetologica, 58(7): 949–957.

[37] Bernelot Moens SJ, Neele AE, et al., (2017), PCSK9 Monoclonal Antibodies Reverse the Pro-Inflammatory Profile of Monocytes in Familial Hypercholesterolaemia. European Heart Journal, 38(20): 1584–1593.

[38] Barale C, Bonomo K, Frascaroli C, et al., 2020, Platelet Function and Activation Markers in Primary Hypercholesterolemia Treated with Anti-PCSK9 Monoclonal Antibody: A 12-Month Follow-Up. Nutritional Metabolism and Cardiovascular Diseases, 30(2): 282–291.

[39] Basiak M, Kosowski M, Hachula M, et al., 2022, Impact of PCSK9 Inhibition on Pro-Inflammatory Cytokines and Matrix Metalloproteinases Release in Patients with Mixed Hyperlipidemia and Vulnerable Atherosclerotic Plaque. Pharmaceuticals (Basel), 15(7): 802.

[40] Li SS, Cao H, Shen DZ, et al., 2020, Effect of Quercetin on Atherosclerosis Based on Expressions of ABCA1, LXR-a, and PCSK9 in ApoE -/- Mice. Chinese Journal of Integrative Medicine, 26(2): 114–121.

[41] Jia Q, Cao H, Shen D, et al., 2019, Quercetin Protects Against Atherosclerosis by Regulating the Expression of PCSK9,

CD36, PPARγ, LXRα, and ABCAI. International Journal of Molecular Medicine, 44(3): 893–902.

[42] Cao C, Su M, 2019, Effects of Berberine on Glucose-Lipid Metabolism, Inflammatory Factors and Insulin Resistance in Patients With Metabolic Syndrome. Experimental and Therapeutic Medicine, 17(4): 3009–3014.

[43] Meng S, Wang LS, Huang ZQ, et al., 2012, Berberine Ameliorates Inflammation in Patients With Acute Coronary Syndrome Following Percutaneous Coronary Intervention. Clinical and Experimental Pharmacology and Physiology, 39(5): 406–411.

[44] Ma CY, Shi XY, Wu YR, et al., 2021, Berberine Attenuates Atherosclerotic Lesions and Hepatic Steatosis in ApoE–/– Mice by Down-Regulating PCSK9 via the ERK1/2 Pathway. Annals of Translational Medicine, 9(20): 1517.

[45] Xiao HB, Sun ZL, Zhang HB, et al., 2012, Berberine Inhibits Dyslipidemia in C57BL/6 Mice With Lipopolysaccharide-Induced Inflammation. Pharmacological Reports, 64(4): 889–895.

[46] Huang YP, Wang YS, Liu YY, et al., 2022, Chemical Characterization and Atherosclerosis Alleviation Effects of Gypenosides From Gynostemma Pentaphyllum Through Ameliorating Endothelial Dysfunction via the PCSK9/LOX1 Pathway. Journal of Agricultural and Food Chemistry, 70(38): 11944–11957.

[47] Majeed ML, Ghafil FA, Fatima G, et al., 2021, Anti-Atherosclerotic and Anti-Inflammatory Effects of Curcumin on Hypercholesterolemic Male Rabbits. Indian Journal of Clinical Biochemistry, 36(1): 74–80.

[48] El-Seweidy MM, Amin Rs, Atteia HH, et al., 2019, Dyslipidemia-Induced Inflammatory Status, Platelet Activation and Endothelial Dysfunction in Rabbits: Protective Role of 10-Dehydrogingerdione. Biomedical Pharmacotherapy, 110: 456–464.

[49] Elseweidy MM, ElSwefy SE, Younis NN, et al., 2020, The Modulation of PCSK9 and GAGs by 10-Dehydrogingerdione and Pentoxifylline in Hyperlipidemic Rabbits. Natural Product Research, 34(16): 2372–2377.

[50] Elseweidy MM, ElSwefy SE, Younis NN, et al., 2019, Contribution of Aorta Glycosaminoglycans and PCSK9 to Hyperlipidemia in Experimental Rabbits: The Role of 10-Dehydrogingerdione as an Effective Modulator. Molecular Biology Reports, 46(4): 3921–3928.

[51] Elseweidy MM, Amin RS, Atteia HH, et al., 2018, New Insight on a Combination of Policosanol and 10-Dehydrogingerdione Phytochemicals as Inhibitors for Platelet Activation Biomarkers and Atherogenicity Risk in Dyslipidemic Rabbits: Role of CETP and PCSK9 Inhibition. Applied Biochemistry and Biotechnology, 186(4): 805–815.

[52] Gang W, Zhenbin L, Menghu L, et al., 2019, Ginkgolide B Mediated Alleviation of Inflammatory Cascades and Altered Lipid Metabolism in HUVECs via Targeting PCSK9 Expression and Functionality. Biomedical Research International, 2019: 7284767.

[53] Viswanatha GL, Shylaja H, Keni R, et al., 2022, A Systematic Review and Meta-Analysis on the Cardioprotective Activity of Naringin Based on Pre-Clinical Evidences. Phytotherapy Research, 36(3): 1064–1092.

[54] Olumegbon LT, Lawal AO, Oluyede DM, et al., 2022, Hesperetin Protects Against Diesel Exhaust Particles-Induced Cardiovascular Oxidative Stress and Inflammation in Wistar Rats. Environmental Science and Pollution Research International, 29(35): 52574–52589.

[55] He LF, Wang C, Zhang YF, et al., 2022, Effect of Emodin on Hyperlipidemia and Hepatic Lipid Metabolism in Zebrafish Larvae Fed a High-Cholesterol Diet. Chemistry and Biodiversity, 19(2): e202100675.

[56] Chenhui Z, Zuan L, Liyuan K, et al., 2021, Recent Research Progress (2015–2021) and Perspectives on the Pharmacological Effects and Mechanisms of Tanshinone I A. Frontiers in Pharmacology, 12: 778847.

[57] Yang Y, Pan C, Zhang M, et al., 2018, Effects of Evodiamine on NARC-1/PCSK9 Expression in Atherosclerotic Rabbits. Pharmacology and Clinics of Chinese Materia Medica, 34(6): 27–30.

[58] Wang Y, Yang W, Peng F, et al., 2019, Evodiamine Inhibits Lipopolysaccharide-Induced Human Umbilical Vein Endothelial Cell Injury Through TLR4/NF-kB Pathway. Journal of Cellular and Molecular Immunology, 35(12): 1088–1093.

[59] Gao N, Yang Q, 2017, Study on the Preventive Effect of Resveratrol on Hyperlipidemia Model Mice and the Improvement Effect on Model Golden Hamsters. China Pharmacy, 28(31): 4393–4397.

[60] Li S, Li Q, Zhou C, et al., 2022, Resveratrol Regulates NLRP3 Inflammasome-Mediated Pyroptosis of Vascular Smooth Muscle Cells to Resist Atherosclerosis. Drug Evaluation Research, 45(10): 1972–1979.

[61] Sun S, Zhang Z, Qiao Y, et al., 2018, Effects of Astragalus Polysaccharides on Inflammatory Factors in Atherosclerosis of ApoE' Mice. Preventive Medicine Forum, 24(6): 407–408.

[62] Zou H, Liu Z, 2017, Effect of Astragalus Polysaccharides on the Expression of Proprotein Convertase Subtilisin/Kexin Type 9 in THP-1 Cells. Chinese Journal of Biologicals, 30(2): 157–162.

[63] Huiming H, Jiajun W, Can C, et al., 2022, The Hypolipidemic Effect of Hawthorn Leaf Flavonoids Through Modulating Lipid Metabolism and Gut Microbiota in Hyperlipidemic Rats. Evidence-Based Complement and Alternative Medicine, 2022: 3033311.

[64] Liu S, 2022, Effects of Total Flavonoids from Crataegus Leaf on Myocardial Lesions and Akt/Nrf2 Pathway in Myocardial Ischemia-Reperfusion Rats. Jilin Journal of Traditional Chinese Medicine, 42(5): 585–590.

[65] Shanshan L, Hui C, Dingzhu S, et al., 2019, Efficacy of Shoushen Granule on Adenosine Triphosphate Binding Cassette Transporter A1, Proprotein Convertase Subtilisin/Kexin Type 9, and Toll-Like Receptor 4/Nuclear Factor Kappa-B Signaling Pathway in ApoE-Knockout Mice. Journal of Traditional Chinese Medicine, 39(4): 524–534.

[66] Song Q, Fan R, Li Y, et al., 2021, Effects of Qizhi Tongmai Granules on PCSK9/LDLR Pathway in Rats with Dyslipidemia and Coronary Heart Disease. Chinese Journal of Emergency in Traditional Chinese Medicine, 30(11): 1920–1923.

[67] Kong Y, Qin H, Wang Y, et al., 2021, Study on the Anti-Atherosclerotic Effect of Xueguan Ruanhua Pill by Regulating miR-17-5p and PCSK9/VLDLR Signaling Pathway. Journal of Anhui University of Chinese Medicine, 40(6): 69–75.

[68] Liping Q, Didi L, Xiaoping G, et al., 2018, Di'ao Xinxuekang Capsule, a Chinese Medicinal Product, Decreases Serum Lipids Levels in High-Fat Diet-Fed ApoE-/- Mice by Downregulating PCSK9. Frontiers in Pharmacology, 9: 1170.

[69] Jiyi L, Wei L, Honglin L, et al., 2022, Di'ao Xinxuekang Capsule Improves the Anti-Atherosclerotic Effect of Atorvastatin by Downregulating the SREBP2/PCSK9 Signaling Pathway. Frontiers in Pharmacology, 13: 857092.

[70] Wang W, Liu L, 2018, Effects of Buyang Huanwu Decoction on Lipid Levels and SREBP-2/Pcsk9 Signaling Pathway in Hyperlipidemia Model Golden Hamsters. Zhejiang Journal of Integrated Traditional Chinese and Western Medicine, 28(12): 1000–1008.

[71] Wu N, Xu R, Li S, et al., 2015, Effects of Hedan Tablets on Lipid Profile, PCSK9 Levels, and High-Density Lipoprotein Particles in Patients with Hyperlipidemia. Chinese Journal of Arteriosclerosis, 23(12): 1277–1280.

[72] Zhang W, Li G, Qi Q, et al., 2020, Regulatory Effect of Di'ao Xinxuekang on TLR4/MyD88/NF-kB Signaling Pathway in Atherosclerotic Rats. China Journal of Chinese Materia Medica, 45(3): 602–608.

[73] Li Y, Lei Z, You Y, et al., 2023, Exploring the Mechanism of Buyang Huanwu Decoction in Regulating Macrophage Polarization Based on the TLR4/NF-kB/NLRP3 Pathway. Chinese Journal of Experimental Traditional Medical Formulas, 29(19): 18–25.

[74] Sun L, Xu F, Ge Z, et al., 2017, Effects of Hedan Tablets on the Expression of IL-1β and TNF-α in Serum of Atherosclerotic ApoE Mice. Chinese Journal of Emergency in Traditional Chinese Medicine, 26(7): 1137–1140.

[75] Zhang M, 2022, Exploring the Role and Mechanism of Huotan Jiedu Tongluo Recipe in Intervening Atherosclerotic Vulnerable Plaques Based on Endoplasmic Reticulum Autophagy-NLRP3 Inflammasome Signaling Pathway, thesis, Changchun University of Chinese Medicine.

[76] Jiang X, Wang Z, 2021, Effects of Luhuang Granules on Serum LDL-C, PCSK9, and Liver Tissue NNMT, Sirt6, PCSK9, LDLR Gene Expression in ApoE' Mice. Lishizhen Medicine and Materia Medica Research, 32(1): 51–53.

[77] Liu C, Tang S, Sun Y, 2005, Effects of Luhuang Granules on C-Reactive Protein and Interleukin-6 Levels in Experimental

Atherosclerotic Rabbits. Chinese Journal of Integrated Traditional and Western Medicine in Intensive and Critical Care, 12(6): 366–368.