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Research Progress of traditional Chinese Medicine monomers in Vascular Protection

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Abstract: Cardiovascular disease is seriously harmful to human health, and its mortality and disability rate are increasing, which brings heavy economic pressure to ordinary families. The pathogenesis of most cardiovascular diseases is derived from atherosclerosis, which can cause coronary arteriosclerosis and then cause myocardial infarction. At present, the commonly used anti-atherosclerotic drugs are lipid-lowering drugs, antioxidant drugs and anti-platelet aggregation drugs. Although effective, long-term use of the above drugs will cause adverse reactions such as liver function damage and gastrointestinal bleeding. Some studies have shown that traditional Chinese medicine monomer has a significant effect on atherosclerosis. Because of its many targets, few side effects and economical advantages, it has become a research hotspot in the treatment of cardiovascular diseases. This paper briefly reviews the research progress of anti-AS endothelial cell injury induced by traditional Chinese medicine monomer in four aspects: cell injury caused by antioxidant stress, regulation of vasoactive substances produced by endothelial cells, regulation of adhesion molecules on endothelial cell surface and regulation of lipids.

1. Introduction

As we all know, cardiovascular disease is one of the main diseases that cause human death, and its morbidity and mortality are increasing year by year. Atherosclerosis (AS) is the main cause of cardiovascular disease, it has a complex pathogenesis, and vascular endothelial cell damage is the initial factor of atherosclerosis [1]. Vascular endothelial cells are located on the inner surface of the blood vessels and lymphatic vessels, forming the inner wall of blood vessels and are monolayer flat

epithelial cells. [2]. There are many reasons for vascular endothelial cell injury, such as oxidative stress, abnormal expression of vasoactive substances, overexpressed cytokines and adhesion molecules, overaccumulation of oxidized low density lipoprotein (Oxidizedlowdensitylipoprotein,Ox-LDL) and oxidized cholesterol [1-3]. Cardiovascular disease is mainly treated by anti-platelet aggregation, anticoagulation, lipid regulation, protection of vascular intima and surgery [4]. At present, the main anti-AS drugs are lipid-regulating drugs such as simvastatin and Bezafibrate [4], antioxidant drugs such as vitamin C [1], anti-platelet aggregation drugs such as aspirin [4], antihypertensive drugs such as verapamil and diltiazem [5], but their clinical application is limited because of their side effects. As a treasure of our country, traditional Chinese medicine has been an important treatment of AS because of its "multi-target effect", and the monomer of traditional Chinese medicine which can resist the injury of AS endothelial cells has also become a research hotspot [3]. This paper reviews the research progress in vascular protection in recent years.

2. A traditional Chinese medicine monomer of antioxidant stress

2.1. Dihydromyricetin

Dihydromyricetin (DMY) is a natural flavonoid, which is abundant in rattan tea. It has attracted much attention because of its beneficial effects on inflammation, oxidation, and heart health [6]. Studies have shown that dihydromyricetin may play the role of antioxidant stress by neutralizing free radicals, enhancing antioxidant enzymes activity, and maintaining redox balance and inhibiting oxidative stress-related signal pathways [6,7]. 1) Scavenging free radicals is one of the main causes of oxidative stress. Dihydromyricetin has strong antioxidant ability, which can capture and neutralize the free radicals produced in the body and reduce the damage of cells induced by oxidative stress [7]. 2) Enhance antioxidant enzyme activity: dihydromyricetin may enhance the antioxidant capacity of cells by promoting intracellular antioxidant enzyme activities, including superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) [6]. 3) Regulating redox balance: dihydromyricetin may maintain normal redox state by regulating intracellular redox balance, and it can participate in reduced glutathione (GSH) / oxidized glutathione (GSSG) system to protect cells from oxidative damage [7]. 4) Blocking oxidative stress signaling pathways: dihydromyricetin may regulate the response of cells to oxidative stress by affecting oxidative stress-related signaling pathways, such as NF- κ B, Nrf2/HO-1, etc., and it may alleviate the oxidative stress effects on endothelial cells by inhibiting the activation of these signaling pathways [6].

2.1.1. Resveratrol

Resveratrol is a natural non-flavonoid polyphenolic plant antitoxin with anti-inflammatory, anticancer and antioxidant properties [8]. Resveratrol has strong free radical scavenging ability, which can neutralize oxygen free radicals (such as hydroxyl free radicals, superoxide free radicals, etc.) and nitrogen free radicals (such as nitric oxide, etc.) produced in the body, thereby reducing the damage of oxidative stress on cells [9]. Resveratrol can induce the expression of various antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), and further enhance the antioxidant capacity of cells [8].Resveratrol can participate in the REDOX reaction in cells and maintain the normal REDOX balance. It can reduce the synthesis of glutathione (GSH) and reduce the accumulation of oxidized glutathione (GSSG), thus protecting cells from oxidative damage [10]. Resveratrol may affect cell response to oxidative stress by regulating multiple oxidative stress-related signaling pathways, including NF-κB, Nrf2-ARE, etc. It

may reduce the effects of oxidative stress on cells by inhibiting the activation of these signaling pathways [10.11]. In addition, resveratrol can directly inhibit lipid peroxidation and prevent oxidative damage of lipid molecules, thus protecting the integrity and function of cell membranes [12]. In summary, resveratrol exerts its powerful antioxidant effect and protects endothelial cells from oxidative damage by neutralizing free radicals, boosting antioxidant enzyme activity, and balancing redox, inhibiting oxidative stress-related signaling pathways and inhibiting lipid peroxidation and other mechanisms.

2.1.2. Astragaloside

Astragaloside is a key active compound of the traditional Chinese medicine plant Astragaloside, which exhibits diverse biological and pharmacological properties, such as anti-inflammatory, antioxidant and anti-apoptosis [13]. In terms of anti-oxidative stress of endothelial cells, Astragaloside may play a role through the following mechanisms: 1) Antioxidant effect: Astragaloside has obvious antioxidant activity, which can remove free radicals in the body and mitigate the damage of endothelial cells induced by oxidative stress. It may play an antioxidant role by directly removing reactive oxygen species or enhancing the activity of endogenous antioxidant systems, including SOD, CAT, etc. [13]. 2) Blocking oxidative stress signaling pathways: Astragaloside may regulate the response of endothelial cells to oxidative stress by affecting oxidative stress-related signaling pathways, including NF-κB and Nrf2-ARE.It may reduce the effect of oxidative stress on endothelial cells by inhibiting the activation of these signaling pathways [14]. 3) Protect endothelial cell membrane integrity: Astragaloside may prevent oxidative stress from damaging the cell membrane by enhancing the membrane integrity of endothelial cells.This may be achieved through regulating the composition of membrane lipids and enhancing the function of membrane proteins [15]. 4) Inhibiting inflammatory response: Oxidative stress is closely related to inflammatory response, while astragaloside has anti-inflammatory effects.It may reduce the damage of endothelial cells caused by oxidative stress by inhibiting inflammatory response and reducing the release of inflammatory cytokines [14]. 5) Regulation of blood vessel function: Astragaloside may improve the physiological function of endothelial cells and enhance their antioxidant capacity by regulating blood vessel function, including dilating blood vessels and regulating blood flow [16].

In summary, astragaloside may play a role in anti-oxidative stress of endothelial cells through various mechanisms, such as antioxidant effect, inhibition of oxidative stress-related signaling pathways, protection of endothelial cell membrane integrity, inhibition of inflammatory and modulation of vascular function.

2.1.3. Astragalus polysaccharide

Astragalus polysaccharide (APS) is a biological macromolecule extracted from Astragalus, which can promote Cu/Zn-SOD expression in endothelial cells, thus enhancing the antioxidant capacity of endothelial cells [17]. Research suggested that Astragalus polysaccharide (APS) shielded against oxidative stress in diabetic cardiomyopathy (DCM) [18]. In an experiment to explore the effects of APS on hyperglycemia-induced oxidative stress in rat H9C2 cells, Sun et al observed APS treatment preserving H9C2 cell ultrastructure, reduced the apoptosis level of H9C2 cells induced by high sugar or silenced by SOD2, and inhibited the production of ROS in cells. The levels of oxidative stress damage markers 8-OH-dG and nitrotyrosine were decreased. It also altered mRNA and protein levels of genes associated with oxidative stress [18]. The results showed that APS could enhance the H9C2 cells' antioxidant capacity against high sugar-induced oxidative stress, reducing damage.

2.1.4. TanshinoneIIA

TanshinoneIIA is an active component of Salvia miltiorrhiza, which has various biological activities, such as antioxidant, anti-inflammatory and anticoagulant effects [19]. Yang et al. established a H_2O_2 injury model with H9C2 cells to investigate tanshinone IIA's protective effect against H_2O_2-induced oxidative stress injury in rat cardiomyocytes and its potential mechanism [20]. The results showed that Tanshinone IIA could promote the proliferation of rat cardiomyocytes induced by H_2O_2, reduce apoptosis and oxygen species (ROS), increase the activities of CAT , SOD and GSH-Px, and decrease the activities of LDH and MDA. In addition, the expression of HO-1, Nrf2 and NQO1 proteins in tanshinone IIA group was significantly up-regulated, and the expression of Keap1 protein was significantly down-regulated.Further research showed that silent Nrf2 had the exact opposite result.All these results suggest that tanshinone IIA can activate the Nrf2 pathway to protect rat cardiomyocytes from oxidative stress induced by H_2O_2 [20].

2.1.5. Pecan leaves total flavonoids

Total flavonoids from pecan leaves are an important active component in pecan leaves and have significant antioxidant activity [3,21]. H_2O_2 can induce cell apoptosis via reactive ROS and active nitrogen (RN) release, leading to mitochondrial damage [21]. An experimental study investigated the effect of total flavonoids (TFS) from hickory walnut leaves on oxidative damage and apoptosis caused by hydrogen peroxide in vitro. In the experiment, oxidative damage model of rat aortic endothelial cells (RAECs) induced by hydrogen peroxide was constructed, and oxidative superoxide dismutase, ROS and others were used to evaluate their antioxidant activities [21]. The results show that TFS can inhibit H_2O_2-induced cytotoxicity and apoptosis of vascular endothelial cells, in addition, they also regulate oxidase levels and suppress ROS production [21]. In summary, TFS extracted from pecan leaves could become a viable option for preventing oxidative stress in the future. In addition, they may provide directions for the study of antioxidant activity prevention through the ROS pathway.

2.1.6. Ginkgolide B

Ginkgolide B is an important active ingredient in ginkgo biloba leaves, which is used in treating cardiovascular and cerebrovascular diseases with some antioxidant effects [22,23]. Studies have shown that ginkgolide B (GB) has a certain resistance to oxidative stress caused by transient focal cerebral ischemia in vitro and in vivo through the Akt/Nrf2 pathway activation[22]. After the hypoxia model was constructed in vitro and in vitro, GB was applied. In vitro experimental data showed that compared with GA and GK groups, GB could significantly reduce ROS, increase SOD activity, significantly up-regulate p-Nrf2 protein levels in ginkgolide B. In vivo experiment results showed that GB significantly up-regulated the protein levels of SOD, p-Nrf2 and Nrf2 [22]. In summary, GB can significantly inhibit oxidative stress damage from cerebral ischemia-reperfusion, and GB has the strongest anti-oxidative stress effect on ischemic stroke. In addition, GB protects neurons from oxidative stress by mediating the Akt/Nrf2 signaling pathway to up-regulate antioxidant protein levels. In another study to investigate the angiogenesis mechanism of GB in perforator flap, 72 rats were divided into 3 groups and treated with normal saline, GB, or GB combined with itamycin for 7 days, respectively. The results showed that GB decreased endoplasmic reticulum stress-related protein levels, lowered flap MDA levels, and boosted SOD activity and Nrf2 mRNA levels. In addition, GB induced vascular regeneration compared to normal saline or GB+TM. It was concluded that GB enhanced angiogenesis and reduced oxidative stress by inhibiting ER stress, improving the survival rate of perforator flaps [23].

2.1.7. Ginsenoside

Ginsenoside is a kind of active ingredient extracted from ginseng, which has various drug therapeutic effects, including anti-oxidation, vascular easing, anti-allergy, anti-inflammation and anti-cancer [24,25]. It has been reported that various ginsenoside monomers can play an antioxidant role through these signaling pathways, which has a good application prospect. It provides a theoretical foundation for experimental research and clinical treatment involving ginsenosides [25]. Studies have shown that [25] ginsenosides can play an antioxidant role through Keap1/Nrf2/ARE signaling pathway. Ginsenosides can exert anti-oxidative stress through PI3K/Akt signaling pathway. Also, ginsenosides can exert anti-oxidative stress through Wnt/ β-catenin signaling pathway.Ginsenosides can play an antioxidant role through NF-κB signaling pathway. Apart from the mentioned pathways, ginsenosides can also trigger antioxidant effects through various signaling pathways. For example, ginsenosides can activate MAPK signaling pathway to reduce oxidative stress in kidneys; Ginsenoside Rb1 inhibits TNF-α-induced ROS and MDA production, increases SOD and GSH-Px activity, and safeguard endothelial cells against TNF-α-induced oxidative stress and inflammation by restraining NF-κB. In addition, ginsenoside Rd reduced the expression of MDA and boosted the expression of GSH and SOD in SCI rat models, thus playing a role in nerve protection. In summary, ginsenosides shield endothelial cells via diverse signaling pathways. In addition, animal experiments have confirmed that ginsenosides can inhibit oxidative damage mainly by clearing ROS and anti-oxidation [24].

2.2. Traditional Chinese medicine monomers that regulate vasoactive substances

2.2.1. Tanshosu sodium

Danshensu sodium, as the main active component of salvia miltiorrhiza, is a phenolic aromatic acid compound [3].The mechanism of Tanshosu sodium participating in the regulation of vasoactive substances mainly includes the following aspects: 1) inhibition of endothelin: Tanshosu sodium can inhibit the synthesis and release of endothelin, thus reducing the vasoconstriction and blood pressure increase caused by endothelin [3]. 2) Promote nitric oxide (NO) production: Danshensu sodium can stimulate endothelial cells to release nitric oxide, which is a potent vasodilator that can relax vascular smooth muscle and lower blood pressure [26]. 3) Anti-platelet aggregation: Danshosin sodium can inhibit platelet aggregation and agglutination, reduce thrombosis, improve blood flow, and help maintain vascular patency [26]. 4) Reduce vasoconstrictor factors: Danshensu sodium may regulate the release of angiotensin and other vasoconstrictor factors, reduce their contractile effect on blood vessels, and help maintain vasodilation [27]. In summary, Danshensu sodium regulates the balance of vasoactive substances by inhibiting endothelin, promoting the production of nitric oxide, inhibiting platelet aggregation and reducing vasoconstrictor factors, which helps to maintain the normal state of vascular function.

2.2.2. Resveratrol

Resveratrol is a polyphenol plant antitoxin that is present in various plant species [28]. In animal models of cardiovascular disease, resveratrol has been demonstrated to enhance blood vessel function as well as prevent atherosclerosis. The vascular protective effect of resveratrol can arise from enhanced nitric oxide (NO) production by endothelial NO synthase (eNOS) [28]. Resveratrol boosts NO production in endothelial cells by upregulating eNOS expression, enhancing eNOS enzyme activity, and averting eNOS uncoupling [29]. Simultaneously, resveratrol inhibits endothelin-1 synthesis and reduces oxidative stress in both endothelial and smooth muscle cells[29].

These mechanisms collectively contribute to resveratrol's protective effects on blood vessel function and blood pressure regulation in the body.

2.2.3. Astragalus Polysaccharide

Astragalus Polysaccharide (APS), a key bioactive compound in Astragalus, is extensively used in treating cardiovascular diseases [30]. Han et al. [30] studied the effect of Astragalus polysaccharide on H_2O_2-induced injury in human umbilical vein endothelial cells (HUVEC) and found that 400 μM H_2O_2 treated for 24h could decrease cell survival rate and increase cell apoptosis rate. Pretreatment with APS for 1h could significantly reduce H_2O_2-induced HUVEC injury. Additionally, compared with the model group, APS decreased intracellular ROS levels and boosted the protein expression of endothelial nitric oxide synthase and Cu-Zn superoxide dismutase, increased the level of cycloguanosine monophosphoric acid, an active marker of NO, and restored mitochondrial membrane potential. Overall, these findings implied that Astragalus polysaccharides may protect HUVEC from H_2O_2 damage by improving the antioxidant capacity of cells and the bioavailability of NO, which may help to ameliorate the imbalance between ROS and NO levels. Chen et al. [31] found through the diabetic hamster model that APS treatment significantly decreased myocardial AngII levels compared to insulin treatment, expression of myocardial chylase and p-ERK1/2 kinase. However, in diabetic hamsters, plasma AngII levels did not change as a result of APS treatment. These findings indicate that APS treatment in diabetic hamsters suppresses the local chymase-ANGII system and enhances indicators of diabetic cardiomyopathy[31].

2.2.4. Allicin

Allicin, a sulfur compound from garlic, exhibits positive effects on various cardiovascular risk factors by regulating cellular mechanisms and signaling pathways [32,33]. Studies have shown that allicin can can dose-dependently inhibit intracellular ROS production, safeguarding cardiomyocytes and endothelial cells from apoptosis. It also decreases malondialdehyde (MDA) levels and boosts NO release and eNOS expression in both cell types [33]. In addition, it regulates the activity of NADPH oxidase (NOX), and phase II detoxification antioxidant enzymes, and prevents apoptosis by regulating BCL2-associated apoptosis regulators (Bax) [33]. Studies in healthy subjects reported an rise in GSH concentration in circulating red blood cells after taking garlic powder tablets (900mg with 0.6% allicin) for two months [33]. In summary, allicin regulates the balance of vasoactive substances by promoting the release of NO, antioxidant and other mechanisms, which is conducive to maintaining a stable state of blood vessels.

2.2.5. Total flavonoids from Dingxin Rattan

Total flavonoids from Dingxin Rattan, a flavonoid extracted from Dingxin Rattan, have been found to boost NO production in endothelial cells of mice on a high-fat diet [34]. At the same time, it can also enhance SOD expression, serving an antioxidative role[34].

2.2.6. Tanshinone IIA

Tanshinone IIA (TanIIA), the primary lipophilic component of salvia miltiorrhiza, induces coronary artery vasodilation [35]. Fan et al. [35] studied TanIIA's impact on blood vessels via vascular ring measurement of rat aorta with intact endothelium and endothelial denaturation, and the results showed that endothalium-dependent relaxation induced by TanIIA could be blocked by ER antagonist ICI182,780. In addition, Fan et al. [35] used primary cardiac microvascular

endothelial cells as a model and confirmed that TanIIA can activate the estrogen receptor signaling pathway, resulting in enhanced endothelial NO synthase gene expression and NO production. Overall, direct vasodilation of TanIIA is activated by estrogen receptors via endothelial nitric oxide synthase.

2.2.7. Ginsenoside Rb1

Ginsenoside Rb1 is a prevalent active compound in ginseng. Previous studies have indicated that Rb1 played a beneficial role in the treatment of atherosclerosis [36]. It helps to improve the elasticity of blood vessel wall, reduce the inflammatory response of endothelial cells, and stabilize arterial plaque and slow down the formation of plaque [36]. Xu et al. [37] found that in the Hcy-induced endothelial injury model, auxin releasing peptide could prevent Hcy-induced vascular endothelial dysfunction and structural damage, while ginsenoside Rb1 could significantly stimulate auxin releasing peptide endocrine and inhibit endothelial damage. In addition, Ginsenosides also up-regulate NO signaling pathway of Hcy reduction through molecular mechanism of auxin releasing peptide [37]. These results suggest that both ginsenoside Rb1 and auxin releasing peptide can prevent Hcy-induced endothelial dysfunction through eNOS / NO mechanism.

2.3. Chinese herbal monomer that inhibits the expression of adhesion molecules

2.3.1 Resveratrol

Resveratrol (RSV) exhibits anti-inflammatory properties and protects against atherosclerosis [38]. Studies have shown that RSV can inhibit NF-κB pathway activation, reducing ICAM-1 and VCAM-1 expression in endothelial cells [38]. Kaplan et al. found that resveratrol reduced the increase in adhesion molecules on human saphenous vein graft endothelial cells, as well as neutrophil adhesion to these cells [39]. In addition, resveratrol also increased the expression of inducible NOS-2 and raised cyclic guanosine phosphate levels [39]. These findings indicated resveratrol may enhance vascular balance and lessen endothelial damage during hypoxic storage of saphenous vein grafts post-coronary artery bypass grafting.

2.3.2 Taurine

Taurine, as an innate antioxidant, it offers endothelial protection in vitro. LOX-1, an endothelial receptor for oxidized low-density lipoprotein (oxLDL), potentially mediates endothelial dysfunction and atherosclerosis formation [40]. Wang et al. [40] used streptozotocin-induced rats as a type 1 diabetes model to assess taurine's protective effect on vascular endothelial dysfunction and related molecular mechanisms. After 6 weeks of taurine treatment, endothelium-dependent vasodilation, serum oxLDL and aorta LOX-1 and intercellular adhesion molecule-1 (ICAM-1) expression were assessed. The results indicated taurine treatment reduced acetylcholine-induced vasodilation, elevated serum oxLDL levels, and lowered LOX-1 and ICAM-1 overexpression. In another experiment, taurine was found to have a protective effect against hyperglycemia-induced endothelial dysfunction by down-regulating apoptosis and adhesion molecules [41]. In summary, taurine can improve vascular endothelial dysfunction, and this mechanism of action may involve reduced expression of LOX-1 and ICAM-1 on the vascular endothelium.

2.3.3 Tanshinone IIA

Studies [42,43] have found that tanshinone IIA (TanIIA) can effectively treat inflammation and

atherosclerosis. Cell surface adhesion molecule expression is crucial in endothelial cell injury, contributing to vascular inflammation and various cerebrovascular diseases. Therefore, anti-inflammatory agents targeting these adhesion molecules could be potential drugs for cerebrovascular disease treatment. In an experiment to investigate the expression of tanshinone IIA (TanIIA) on cell adhesion molecules in TNF-α-stimulated brain microvascular endothelial cells (BMVECs). TanIIA treatment was found to inhibit VCAM-1 and ICAM-1 expression,it was also found to suppress VCAM-1 and ICAM-1 expression, thereby inhibiting TNF-α (tumor necrosis factor--α) induced adhesion of neutrophils to BMVECs [42]. In addition [42], TanIIA can also significantly inhibit the production of TNF-α-induced reactive oxygen species (ROS) and is associated with a decrease in the level of malondialdehyde (MDA). These findings suggest TanIIA regulates TNF-α-induced VCAM-1 and ICAM-1 expression by inhibiting NF-κB activation and ROS production in BMVECs. Another experiment to explore the TNF-α-induced expression of adhesion molecules in endothelial progenitor cells (EPC) showed that [43] TanIIA decreased the adhesion of TNF-α-induced EPCs and VCAM-1/ICAM-1 expression in EPCs. It also reduced the amount of NF-κBp65 phosphorylation in the nucleus.This study suggests that a novel mechanism of TanIIA's anti-inflammatory/antiatherogenic activity may involve the downregulation of VCAM-1 and ICAM-1 by blocking TNF-α triggers NF-κB activation and IκB-α phosphorylation by suppressing a segment of the IKKα / β pathway in EPCs

2.3.4 Astragaloside

The regulation and expression of endothelial cell surface adhesion molecules is a pivotal step in inflammation development. The saponin Astragaloside IV (AS-IV) is a primary compound extracted from the Chinese herb Astragalus, known for its demonstrated in vivo anti-inflammatory properties [44]. In an experimental study, Zhang et al. investigated the effects of AS-IV on the adhesion expression of cytokines and LPS-stimulated adhesion molecules in endothelial cells and leukocyte adhesion. Results showed that AS-IV markedly decreased LPS-induced adhesion activity in HUVEC to polykaryotic leukocyte (PMN) and monocyte line THP-1, and decreased the expression of e-selectin and VCAM-1 on the surface of LPS-induced HUVECs [44]. In addition, AS-IV significantly inhibited LPS-induced and TNF-β-induced E-selectin and VCAM-1 specific mRNA levels [44]. It is concluded that AS-IV may inhibit inflammation in vivo by supressing the NF-κB pathway.

2.3.5 Curcumin

Kim et al. [45] found that curcumin treatment significantly reduced TNF-α-induced mRNA expression of ICAM-1 and VCAM-1 in endometrial stromal cells. Additionally, curcumin treatment reduced TNF-α-induced protein expression of ICAM-1 and VCAM-1 in both cell surface and total protein levels, in a dose-dependent manner. In addition, curcumin treatment in endometrial stromal cells notably inhibited TNF-α-induced secretion of IL-6, IL-8, and MCP-1, and it also suppresses NF-κB activation, a crucial inflammation regulator [45]. These findings suggest that curcumin inhibits a variety of mediators, pro-inflammatory cytokines, and chemokines. In another study, Zhang et al. confirmed that curcumin can prevent platelet adhesion to cultured brain microvascular endothelial cells (BMEC) [46]. Studies have shown that curcumin (30-240μmol/L) can inhibit the adhesion of TNF-α-activated brain microvascular endothelial cells (BMEC) to normal platelets in a concentration-dependent manner, and in addition, curcumin can inhibit the increased expression of GPIIb / GPIIIa in thrombin-activated platelets in a concentration-dependent manner [46]. In summary, curcumin can inhibit platelet adhesion to BMEC, which may be related to the decreased expression of P-selectin, E-selectin and GPIIb / GPIIIa on platelets and BMEC.

2.3.6 Ginsenosides

Ginsenosides, vital components of ginseng, are triterpenoid glycosides [47]. VCAM-1 and ICAM-1 play key roles in the occurrence and development of atherosclerosis. Zhao et al found in a study [47] that ginsenoside Rg2 inhibited the expression of VCAM-1 and ICAM-1 induced by LPS in HUVEC. Moreover, it decreased LPS-induced THP-1 monocyte adhesion to HUVEC in a dose-dependent manner [47]. These data suggest that Ginsenoside Rg2 may directly benefit blood vessels by preventing white blood cells from sticking to vessel walls, thus protecting against vascular inflammatory diseases. Ginsenosides Rg3 (Rg3) is one of the most potent ginsenosides, with anti-inflammatory and anticancer effects [48]. Studies have investigated how Rg3 affects the expression of adhesion molecules induced by cytokines, a crucial early event in atherosclerosis development [48]. The results showed that Rg3 treatment suppressed TNF-α-induced protein and mRNA expression of two cell adhesion molecules, VCAM-1 and ICAM-1, in ECV304 human endothelial cells. Additionally, Rg3 inhibited two types of pro-inflammatory cells by reducing TNF-α-induced interleukin-1β (IL-1β) expression [48]. Taken together, these findings indicated that Rg3 might possess anti-inflammatory and anti-atherosclerotic properties in the vasculature, possibly by reducing the expression of cell adhesion molecules and pro-inflammatory cytokines in endothelial cells.

2.4. Herbal monomer that regulates lipids

2.4.1 Panax notoginseng total saponins

Previous research reported the anti-atherosclerotic effect of panax notoginseng total saponins (PNS) and its mechanism in inflammation. 30 rats were randomly assigned to three groups: a control group, a group with enzyme-induced inflammation, and a group treated with PNS [49]. The rats in the three groups were given liquid paraffin, zymosanA or zymosanA and PNS, respectively, and all the animals were fed high-fat diet [49]. Experimental results indicated that PNS treatment mitigated the typical pathological changes of atherosclerosis in rats induced by zymosanA, significantly lowering serum total cholesterol, triglycerides, and blood viscosity [49]. Additionally, PNS treatment notably decreased the gene expression of inflammatory factors including integrin, interleukin (IL)-18, IL-1β, and matrix metalloproteinases 2 and 9. Following PNS treatment, there was a decrease in the expression of NF-κB/p65, accompanied by a significant increase in the expression of IκBα [49]. It is concluded that PNS may play a therapeutic role in atherosclerosis through anti-inflammatory effects and regulation of lipid profiles, and involve the NF-κB signaling pathway. PNS has been categorized as a component in functional foods for treating various ailments. However, its mild effect has limited its clinical application in diseases [50]. Wang et al. developed a "steaming" simulation in which PNS was steamed to treat hyperlipidemia and obesity, and found that steamed PNS exhibited promising effects in improving hyperlipidemia and reducing body weight and white adipose tissue weight, as well as inhibiting lipogenesis in obese mice. It may implicate the adenosine monophosphate (AMP) activated protein kinase (AMPK) signaling pathway via T172 phosphorylation, promoting the down-regulation of its downstream factors [50]. In summary, steamed PNS exhibits potential in improving hyperlipidemia and obesity, laying a foundation for future research and applications in atherosclerosis treatment.

2.4.2 Resveratrol

In one study, Zhao et al. performed the first meta-analysis on the effects of resveratrol on lipid levels in type 2 diabetes patients, analyzing 10 randomized controlled trials with 363 participants

[51]. Results showed that ≥6 months of resveratrol intervention reduced TG levels and increased LDL levels in obese type 2 diabetes patients and patients taking lipid-lowering drugs [51]. The conclusion drawn is that resveratrol can enhance triglyceride levels in patients with type 2 diabetes.

2.4.3 Grape seed proanthocyanidins

Grape seed proanthocyanidins are among the most abundant polyphenols in the human diet, which can regulate lipid metabolism and and serve as effective lipid-lowering agents [52]. Non-coding RNAmiR-33 and miR-122 are genes involved in lipid metabolism regulation [52]. The results showed that grape seed proanthocyanidins inhibited miR-33 and miR-122 expression in rat hepatocytes both in vivo and in vitro. Proanthocyanidins treatment boosted hepatic cholesterol efflux, generating new HDL particles by suppressing miR-33, and decreased lipogenesis by inhibiting miR-122 [52]. These results suggest that grape seed proanthocyanidins reduce blood lipids through their effects on miRNA regulators of lipid metabolism.

2.4.4 Gallic acid

Gallic acid (GA), a natural polyphenol, protects against hepatic steatosis in animal models. One study investigated the effects of GA on hepatic lipid accumulation, apoptosis and inflammatory response induced by hepatocellular macrophage crosstalk [53]. It was shown that GA attenuates palmitic acid (PA) -induced fat accumulation by activating AMPK in HepG2 cells [53]. In addition, GA also reduces the expression of inflammatory mediators and induces antioxidant enzymes expression [53]. These results suggest that GA can inhibit hepatic lipid buildup, cell death (apoptosis), and inflammation due to hepatocellular and macrophage interaction.

2.4.5 Compound K

Compound K is the intestinal metabolite of ginsenosides. Recent studies have found that AMPK increases significantly when Compound K is used to treat cells, and Compound K reduces the gene expression of sterol regulatory element binding protein 1c (SREBP1c) responded to time and dosage variations. Fatty acid synthase (FAS) and stearoyl-CoA desaturase 1 (SCD1), both targeted by SREBP1c, were also suppressed [54]. In summary, CompoundK may reduce hepatic lipid accumulation through AMPK activation in human liver cancer cells.

2.4.6 Danshensu

Studies have shown that macrophage foam cells and cholesterol effection defects play a key role in the formation of atherosclerosis [55]. A study reported danshensu's therapeutic effect in reducing intracellular cholesterol levels and unveiled its mechanism in promoting cholesterol efflux. In the experiment, low-density lipoprotein in Raw264.7 cells was induced to oxidize into foam cells, which were treated with Danshensu (DSS) alone or in combination with simvastatin and rosiglitazone [55]. It was found that DSS significantly reduced CD36 and its homolog SR-BI, while also up-regulating cellular cholesterol transporters ABCA1 and ABCG1 to reduce intracellular lipid accumulation [55]. These results suggest that DSS helps balance CD36 and ABCA1 protein expression, reducing lipid buildup in Raw264.7 foam cells.

2.4.7 Puerarin

In order to study the mechanism of Puerarin regulation of lipid metabolism by puerarin extract from Puerarin, Zheng et al randomly divided 50 mice into 5 groups: normal diet, high-fat diet (HFD), and HFD supplemented with 0.2%, 0.4%, or 0.8% puerarin for 12 weeks [56]. Compared to the HFD group, mice fed diets containing 0.4% and 0.8% puerarin exhibited significant reductions in serum and liver total cholesterol, triglyceride, and leptin concentrations, along with inhibited fatty acid synthase activity[56]. These findings imply that puerarin concentrations exceeding 0.4% impact liver lipid metabolism enzymes, leading to decreased serum and liver lipid levels, while also increasing body weight and fat accumulation.

3. Conclusion and prospect

Some progress has been made in the study of vascular protection of TCM monomer.Through in-depth study of TCM monomers, we found that many TCM monomers have various mechanisms of action to protect blood vessels, including anti-oxidative stress induced cell damage, regulation of endothelial cell-derived vasoactive substances, regulation of adhesion molecules on the surface of endothelial cells, regulation of lipids, etc. [3, 57]. These effects help maintain the normal function of blood vessels and prevent and treat diseases related to blood vessels, such as atherosclerosis, hypertension, cardiovascular and cerebrovascular diseases [2, 57]. Among them, some traditional Chinese medicine monomeric, such as total flavonoids of Dingxinteng and ginsenoside Rb1, have shown good vascular protective effect in experimental studies [34, 37].

Future research can be carried out from the following aspects: First, further explore the action mechanism of TCM monomers, especially their signaling pathways and molecular targets in vascular protection, so as to further understand their action principle [3]. Secondly, clinical research on TCM monomer should be strengthened to verify its safety and effectiveness in clinical practice and promote its clinical application [58]. In addition, combined with modern scientific and technological means, such as genomics, proteomics, etc., research on TCM monomer and individualized therapy has been carried out to achieve accurate treatment for patients [58]. Finally, the research on the joint application of TCM monomer and Western medicine should be strengthened to explore its synergistic mechanism and provide more options and programs for clinical treatment [59]. Through continuous and in-depth research, the application prospect of TCM monomer in the field of vascular protection will be broader.

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