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•Review•

The mechanisms of traditional Chinese medicine underlying the prevention and treatment of atherosclerosis

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[ABSTRACT] Atherosclerosis (AS) is a chronic inflammatory disease associated with high morbidity and mortality. The incidence of AS is increasing in the last decades. So development of safe and effective therapeutics for treating AS has become prominently important. Although there are numerous chemical drugs available for treating AS, some drugs are not effective and some have serious side effects. Traditional Chinese medicine (TCM) has a long history for the prevention and treatment of AS due to its less side effects and superior efficacy. This paper describes the effectiveness and underlying mechanisms for prevention and treatment of AS by TCM or its active components. Some TCM, e.g. *XuemaiNing*, *Tongxinluo* and *Salvia miltiorrhiza* have been reported to have cardio-protective effect. Some active components of TCM, e.g. saikosaponin-A, kuwanon G, luteolin and *β*-elemene have been isolated from various TCM and demonstrated to have beneficial effects on prevention and treatment of AS.

[KEY WORDS] Atherosclerosis; Traditional Chinese medicine; Mechanism

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Introduction

Atherosclerosis (AS) is a chronic inflammatory disease associated with high morbidity and mortality [1]. It is well-known that AS is the main pathologic basis of cerebral- cardiovascular diseases, such as myocardial infarction, stroke and acute coronary syndrome [2]. With the aging process, the incidence of these diseases has increased year by year, so it is urgent to strengthen the research for the drug discovery for treatment of AS. It is well known that AS often appears in coronary arteries, brain arteries, and carotid arteries [3]. Some risk factors can lead to AS, which including hypertension, diabetes, hyperlipidemia, hyperhomocysteinemia, obesity and smoking [4]. Atherosclerotic plaque rupture is a main etiology of AS [5]. Thus, stabilizing unstable atherosclerotic plaques is clinically significant for the treatment and prevention of AS [6]. The unstable plaques rupture is pathologically characterized by large thrombogenic necrotic cores with lipids, intraplaque hemorrhage, a thinner fibrous cap and inflammatory cells infiltration, and these pathological features eventually result in platelet aggregation and thrombus formation. The long-term accumulation of thrombi results in vascular remodeling and stenosis of the lumen, which obstructs the blood flow, causing infarction in relevant tissues [7-8]. Several factors contribute to unstable plaques rupture, including vascular wall thickening [9-10], foam cell formation [11], inflammation [12-13], angiogenesis [14], oxidative stress [15], extracellular matrix (ECM) degradation [16] and decreased collagen content [17].

Clinically, the AS patients are usually treated with statins, aspirin, nitroglycerin and other types of drugs [18]. The molecular mechanisms of AS are still not clear, the efficacy of these drugs is imperfect and long-term administration often results in myocardial infarction and stroke, these diseases would seriously affect the quality of life of the patients [3].

Given side effects of chemical drugs, many researchers are searching for a more safe and alternative treatment for AS. TCM has been used to treat AS for many years in China. So far, TCM is still very effective in the prevention and treatment of AS [3]. Researcher have found some TCM and their active components from appear as important sources for treatment of AS [19]. It is still urgent to develop safe and effective drugs in the treatment of AS. This review attempts to summarize and analyze the mechanisms of TCM for treatment of AS, TCM

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includes Chinese herbal compounds, herbal formulations and their active components or chemicals in regard to the treatment of AS.

The Mechanisms of Traditional Chinese Medicine against AS

Regulation of inflammatory responses

When atherosclerotic plaques transform into an unstable state, the immune system is activated [20]. At atherosclerotic lesions, activated macrophages, T lymphocytes, B lymphocytes, dendritic cells (DCs), endothelial cells (ECs) and resident immune cells can produce chemokines and inflammatory cytokines that induce inflammatory effects and progression of atherosclerotic lesions [21]. Th1 cells can recognize low density lipoprotein (LDL) then secrete various molecules, including IFN-γ, TNF-α, IL-6 and IL-1β. These multifunctional inflammatory factors affect the progression of AS. Th2 cells secrete anti-inflammatory cytokines that may regulate inflammation such as IL-4, IL-10 and transforming growth factor-β (TGF-β). Th1 and Th2 cytokines influence the formation of macrophages of different phenotypes [22]. For example, Th1 cytokines such as IFN-γ and IL-1β, can selectively activate M1 macrophages, pro-inflammatory cells that selectively secrete the inflammatory factors TNF-α, IL-6, and IL-12 and the chemokines chemokine C-X-C motif ligand CXCL9, CXCL10, and CXCL11. Some chemokine-receptors, including C-C motif chemokine receptor (CCR)1, CCR5, and CXC3 receptor 1 can affect monocyte recruitment and inflammatory macrophages formation in atherosclerotic plaques [23].

At the site of atherosclerotic lesions, recruited monocytes can differentiate into different phenotypic macrophages according to microenvironmental cues such as exposure to elevated levels of lipids, cholesterol or inflammatory stimuli or activation of specific intracellular signaling pathways, such as the nuclear factor (NF-κB), Toll-like receptor (TLR)4, signal transducer and activator of transcription(STAT)3, and peroxisome proliferator-activated receptor (PPAR)γ signaling pathways [24-25], which play vital roles at all stages of progression of atherosclerotic lesions [20]. Upregulation of cellular adhesion molecules, including VCAM-1, ICAM-1 and endothelial-selectin (*E*-selectin) are essential for recruitment of monocytes from the circulation and adherence to ECs. The imbalance of M1 and M2 phenotypic macrophages can destabilize atherosclerotic plaques, which affect the progression of AS [26].

Crocin is an active compound extracted from *Crocus sativus* L.. It is well-known that crocin has anti-oxidant, anti-cancer and anti-inflammatory pharmacological effects. Studies have reported that crocin has the effect of anti-AS. Compared with VD3-induced rat coronary atherosclerosis model group, crocin could significantly decrease the expressions of IL-6, iNOS and TNF-α, then enhance the expressions of IL-10, IL-4 and TGF-β. NF-κB has been served as a pro-atherogenic signaling pathway, and promotes the macrophages polarized towards M1 phenotype [27]. Crocin significantly decreased the expression of the subunit of NF-κB, and inhibited the macrophages polarized towards M1 phenotype. Crocin markedly up-regulated the levels of M2 macrophage biomarkers CD68 and CD206, then down-regulated the levels of M1 macrophage biomarker CD11c and CD40. These results suggested that crocin promoted the macrophages polarized towards M2 phenotype, and alleviated coronary atherosclerosis [28]. Activated CD40 and CD11con macrophages promote the macrophages polarization towards M1 phenotype. Activated CD68 and CD206 on macrophages can promote the macrophages polarized towards M2 phenotype [29]. Brassinin is an active phytoalexin extracted from *Brassica rapa*, and has antiproliferative and antioxidant effects. In TNF-α-induced human umbilical vein endothelial cells (HUVECs), the expressions of ICAM-1, VCAM-1, E-selectin, and IL-8 were down-regulated under the administrate of brassinin. Brassinin significantly inhibited U937 cells adhesion to TNF-α-induced HUVECs. Brassinin has beneficial effects on prevention of AS through inhibiting inflammation [30]. Notoginsenoside R1, a unique compound from the *Panax notoginseng* root, possesses anti-inflammatory and anti-oxidative properties. The study showed that compared with ApoE$^{-/-}$ blank group, isoproterenol (ISO) might significantly aggravate the destruction of endothelial structure and function in ApoE$^{-/-}$ mice. Notoginsenoside R1 remarkedly inhibited this process in ISO-induced ApoE$^{-/-}$ mice. Notoginsenoside R1 treatment significantly restrained the expressions of TNF-α, MCP-1, ICAM-1, CCR2, IL-1β and IL-6 in ISO-induced ApoE$^{-/-}$ mice. In addition, notoginsenoside R1-treated ApoE$^{-/-}$ mice received CCR2 lentivirus, and the process inhibited the accumulation of inflammatory cytokines and promoted Ly6C^{high} monocytes recruitment to the myocardium. These results suggested that notoginsenoside R1 supressed atherosclerotic lesions and reduced the accumulation of inflammatory cytokines in the myocardium. However, these results could be partially reversed by CCR2 lentivirus [31]. CCL2 is also known as MCP-1 and affects monocytes recruitment *via* modulating CCR2 activation [32].

In summary, inflammation plays a crucial role in the progression of AS. From the above experiments, we can see that some TCM or their active components can reduce the inflammatory effect by reducing the expression level of inflammatory factor and modulating the balance of M1/M2 macrophage. Many TCM or their active components may serve as anti-inflammatory drugs.

Improvement of macrophage metabolismis

Disruption of macrophage metabolism is also an important cause of AS, as depicted in Fig. 1. LDL and modified LDL serve as the primary source of lipid deposition in atherosclerotic lesions. Several studies have indicated that intracellular cholesterol accumulation is caused by pro-atherogenic modified LDL [33]. Moreover, elevated levels of LDL cholesterol (LDL-C), triglyceride (TG), and total cholesterol (TC) and

decreased levels of high-density lipoprotein cholesterol (HDL-C) are closely associated with atherosclerotic initiation and progression [25]. Endothelial dysfunction has also been shown to cause AS. At the site of atherosclerotic lesions, circulating LDL infiltrates and accumulates into the vascular intima. LDL itself, as well as modified LDL, including oxidized LDL (oxLDL), acetylated LDL (acLDL), malondialdehyde LDL (MDA-LDL) and glycosylated LDL (glyLDL) involve in this process [34]. Pro-inflammatory cytokines, chemokines and adhesion molecules may be produced by modified LDL activated ECs and intimal macrophages at atherosclerotic lesions and by resident arterial wall cells. Additionally, pro-inflammatory monocytes infiltrating into the vascular intima differentiate into macrophages, then leading to the development of atherosclerotic lesions [35]. Monocyte-derived macrophages recognize and ingest modified LDL through TLRs and various receptors, including CD36, scavenger receptor A1 (SR-A1), scavenger receptor B1 (SR-B1), LDL receptor-related protein-1(LRP-1) and lectin-like oxLDL receptor-1 (LOX-1) to generate foam cells [36-37]. Accumulation of foam cells result in cell apoptosis on the vascular intima, eventually forming thrombogenic and full-lipid necrotic cores. Foam cells and necrotic cores in the vascular intima are significant markers of unstable atherosclerotic plaques. Increases in these components result in greater chance of atherosclerotic plaque rupture. Formation of foam cells also involve in modulating the inflammatory effect in AS [38]. Experimental studies in mice with knockout of scavenger receptors, such as CD36, SR-A1, or LOX-1, have decreased cholesterol or lipid accumulation in macrophages and show inhibition of lesional macrophage proliferation, further reducing the formation of foam cells and protecting against atherosclerotic plaque rupture [39].

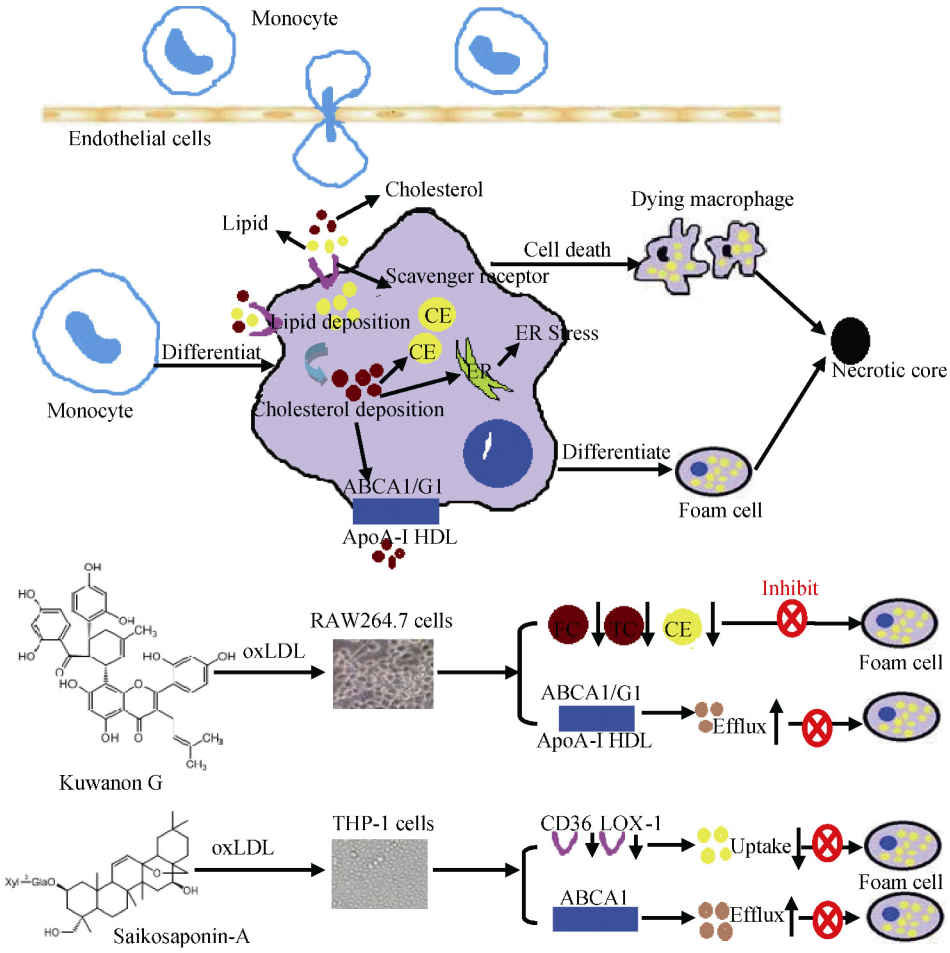

Fig. 1 Active compounds against the formation of foam cells

Recruiting monocytes can differentiate into various phenotypic macrophages, which take up excess cholesterol and gradually form macrophage-foam cells, leading to the generation of necrotic cores [40]. Modified LDL can affect cholesterol accumulation in atherosclerotic plaques, and accumulation of cholesterol, which is converted into cholesterol ester (CE) and deposited on lipid granules, may lead to the formation of foam cells. However, cholesterol is stored in lipid granules in the form of CE, which can reduce the toxic effects of cholesterol accumulation on cells to some extent [41]. Endoplasmic reticulum (ER) stress can contribute to AS, particularly ACS. Accumulation of cholesterol can cause ER

stress, which is associated with multiple mechanisms of AS. Activated ER stress in lesional resident cells may result in macrophage apoptosis and the formation of macrophage-foam cells [42]. HDL functions inreverse transport, which regulates the efflux of excess LDL, TGs and cholesterol. Reverse cholesterol transport (RCT) is the only way for the body to efflux the remaining cholesterol. The cholesterol transporter ATP-binding cassette sub-family A/G member-1 (ABCA/G1) enhances intracellular cholesterol and phospholipid transport to free apolipoprotein A-I (ApoA-I) or HDL. Together, these proteins promote RCT [43]. Thus, upregulation of ABCA1, ABCG1 or HDL enhances RCT and prevents the formation of foam cells. Additionally, activated liver X receptors (LXRs; LXRα and LXRβ) may enhance RCT in macrophages, promote cholesterol efflux, and inhibit the progression of AS [44].

Kuwanon G is a flavonoid isolated from the root bark of *Morus alba* L.. Previous studies have reported kuwanon G has anti-bacterial, anti-inflammatory and neuroprotective properties [45]. The studies reported that kuwanon G could inhibit the progression of AS. Cell cholesterol analysis also indicated that kuwanon G significantly decreased the levels of intracellular TC, free cholesterol (FC) and CE in ox-LDL-induced RAW 264.7 cells. Kuwanon G could prevent macrophage-foam cell formation via enhancing cholesterol efflux, and this process was modulated *via* activating LXRα-ABCA1/ABCG1 pathway. Kuwanon G also reduced the levels of TNF-α, IL-1β, IL-6 and the process was modulated by inhibiting the activation of NF-κB [46]. Previous studies indicated that TCM *XuemaiNing* could suppress the levels of TC, LDL, TG, SR-BI and CD36, then increase levels of HDL in hyperlipidemia rat group. So *XuemaiNing* affects the progression of AS [47]. *XuemaiNing* also could inhibit foam cells formation via up-regulating the expression of ABCA1 and enhancing the process of RCT [48]. Saikosaponin-A is a bioactive compound extracted from *Radix Bupleuri*. The study found that saikosaponin-A significantly decreased lipoprotein uptake and the expressions of LOX-1 and CD36 to inhibit foam cell formation, then increased expression of ABCA1 to enhance cholesterol efflux in ox-LDL-induced THP-1 macrophages [49]. *Salvia miltiorrhiza* (Danshen) is a TCM that is widely used in the treatment of cerebro-cardiovascular diseases. Danshensu (DSS) is a water-soluble compound isolated from the dried root of *Salvia miltiorrhiza* [50]. Previous studies have reported that DSS has pharmacological effects of reducing the expression of ROS and inhibiting platelet aggregation, eventually protecting against AS [51]. DSS significantly suppressed the expressions of CD36 and SR-BI. In addition, DSS promoted the upregulation of cellular cholesterol transporters ABCA1 and ABCG1 to reduce intracellular lipid deposition. These results showed that DSS reduced lipid deposition in oxLDL-induced Raw264.7 cells by mediating the expressions of CD36 and ABCA1 [52].

In summary, foam cell formation significantly affects the development of AS. From the above experiments, we find that some TCM or their active components can inhibit foam cell formation *via* reducing lipids or cholesterol accumulation, and enhancing lipid or cholesterol efflux. Foam cells formation also involves in modulating the inflammatory effect in AS. So many TCM has pharmacological effects of anti-inflammation and inhibiting foam cell formation. The idea of screening TCM to inhibit foam cell formation has attracted the attention from many researchers.

Inhibition of VSMC proliferation and migration

Recent studies have indicated that abnormal VSMC proliferation and migration can affect the development of AS [53]. In atherosclerotic lesions, VSMCs tend to switch from a contractile phenotype to a proliferative phenotype [54]. VSMCs have a function of synthesize interstitial collagen fibers, which protect from atherosclerotic plaque rupture [55]. Some of the cytokines and growth factors produced by macrophages can induce VSMCs to move into the intima, where VSMCs then form extracellular matrix components, eventually resulting in the formation of the fibrous cap. Due to endothelial stress, the migration of VSMCs leads to thickening of the intima. These VSMCs produce ECM and proteoglycans in this environment, where LDL is more susceptible to undergo oxidative stress. The dysregulation between cell survival and death affects the progression of atherosclerotic lesions. Macrophage apoptosis is detected at all stages of AS [20]. VSMC apoptosis can also affect the development of AS and play an important role in vascular remodeling. VSMCs also express scavenger receptors, such as LRP-1 or LOX-1 as well as macrophages, then VSMCs can ingest more oxLDL contributing to form VSMC-foam cells [56].

Luteolin is a common flavonoid that is abundant in some TCM, fruits and vegetables [57]. Previous studies have indicated that luteolin possesses anti-inflammatory, anti-proliferative, anti-migrative, anti-oxidant, anti-apoptotic and other pharmacological effects, most of which affect the progression of AS [58-59]. Compared with the control group, luteolin markedly decreased the expressions of Cyclin D1 and PCNA in A7r5 and HASMC cell. The expressions of Bcl-2 and BAX weren't affected, but the expressions of MMP2 and MMP9 were down-regulated under the administration of luteolin. CyclinD1 and PCNA are regulators of the cell cycle that are served as proliferation indexes [60]. Bcl-2 and BAX are used as cell apoptosis indexes. Many studies have indicated that MMP2 and MMP9 are usually involved in the progression of VSMC migration, so they are usually served as VSMC migration indexes [61]. These findings indicated that luteolin significantly inhibited VSMC proliferation and migration in a dose-dependent manner without inducing VSMC apoptosis [62]. Astragaloside IV is a bioactive compound extracted from the *Astragalus membranaceus* root, which is widely used in the treatment of kidney disease, cardiovascular disease and skin diseases [63]. The research found that astragaloside IV markedly restrained the expressions of cyclin D1, cyclin E, cyclin-dependent kinase CDK2 and CDK4 in PDGF-BB-sti-

mulated HDVSMCs. Previous studies have reported that platelet-derived growth factor PDGF-BB is closely related to promote VSMC proliferation and migration or induce VSMC phenotype switch [64-65]. Treatment with astragaloside IV significantly up-regulated the expression levels of *α*-SMA, desmin and smoothelin. When HDVSMCs transformed into a proliferative phenotype, the expressions of these three markers were markedly down-regulated. These findings demonstrated that astragaloside IV could inhibit the PDGF-BB- induced proliferation VSMC phenotype switch [66].

Suppression of oxidative stress

Disorders of oxidative phosphorylation and increased levels of ROS and NADPH oxidase may lead to oxidative stress. Oxidative stress occurrence may result in cell injury due to cellular protein, lipid, DNA oxidation and activated cell apoptosis pathways, this process accelerates the progression of AS [67-68]. ROS is mainly involved in multiple pathological processes of AS such as endothelial dysfunction, oxLDL formation, VSMC proliferation and inflammatory effect [69]. Considerablein *vivo* studies showed that the upregulated levels of antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GSH), glutathione peroxidase (GPx) in arterial wall would lead to inhibit endothelial dysfunction and oxLDL formation [70].

Polyphenols are widely distributed infruits, vegetables, tea and traditional medicinal herbs. Flavonoids are the most studied polyphenols that exert anti-oxidative property via regulating oxidative stress-related enzyme activity [71]. In a UK women's investigate, polyphenol-rich fruit at consumption of 80 $g \cdot d^{-1}$ could significantly lower CVD mortality by 6%–7% [72]. A clinical study of 40 healthy women, açai (a polyphenol-rich fruit) at consumption of 200 $g \cdot d^{-1}$ for 4 weeks could markedly promote the conversion from CE to HDL, then decrease the levels of ROS and oxLDL, these results showed polyphenol-rich fruit could protect from AS [73]. Numerous in vitro and *in vivo* experiments have demonstrated that polyphenols have pharmacodynamic effects of decreasing the expressions of ROS and SOD, inhibiting oxLDL formation and VSMC proliferation and migration [74]. *β*-Elemene, an active sesquiterpenoids compound extracted from the essential oils of Chinese medicinal herbal *Curcuma wenyujin*, has anti-tumor, anti-inflammatory and anti-oxidant properties. The study found that *β*-elemene affected the progression of AS. It significantly increased the expression levels of GSH, SOD, CAT, GPx, NO and phosphorylation eNOS, then restrained the expression of ROS, oxLDL accumulation and SOD activity in $ApoE^{-/-}$ mice. NO availability related to increased ROS production may aggravate endothelial dysfunction in the progression of AS [75]. These results showed that *β*-elemene exerted anti-atheroclerotic effect though inhibiting oxidative stress and improving endothelial function *in vivo* [76]. Dihydromyricetin is a flavonoid isolated from *Ampelopsis grossedentata* that possesses multiple biological activities, including anti-tumor, cardioprotective and anti-oxidative effects. Dihydromyricetin markedly improved the levels of SOD, CAT and GPx, then decreased the levels of ROS and MDA in ox-LDL-induced HUVECs. Experimental analysis showed an increase in the expressions of caspase-3, caspase-9 and cytochrome C were caused by ox-LDL stimulation, and they could be inhibited under the administration of Dihydromyricetin. Previous studies have indicated that oxidative stress result in EC apoptosis [77]. Caspase-3, caspase-9 and cytochrome C are usually used as cell apoptosis indexes. These results showed dihydromyricetin inhibits oxLDL-induced oxidative stress and apoptosis in HUVECs [78].

Improvement of autophagy

Macrophage apoptosis may lead to plaque necrosis and the formation of thrombus, contributing to myocardial infarction (MI), coronary heart disease (CHD) and stroke, etc [79]. Autophagy is a degradation process of surplus protein and organelles though a lysosome-dependent cell protection mechanism [80]. Autophagy is an essential biological process that maintains cellular homeostasis *via* regulating the survival and apoptosis of VSMCs, ECs and macrophages [81]. Evidence has demonstrated that activated autophagy could induce the occurrence of AS [82]. Macrophage autophagy also plays an important role in atherosclerotic progression [83] and clears cholesterol and lipid deposition in macrophage-foam cells. Macrophage autophagy has also been shown to block necrotic core formation and enhance the stability of atherosclerotic plaques. Increased level of LC3 and decreased level of p62 are indicators of enhanced macrophage autophagy [84]. Autophagy-related gene 5 (Atg5), Atg7 and Beclin-1 are important genes of macrophage autophagy, Atg5 or Atg7 or Beclin-1 knockout mice can promote cell apoptosis and destroy the autophagy process in the plaque [85].

Tongxinluo is a TCM that has been widely used in the treatment of AS, CHD, and stroke [86]. Its underlying mechanism for the treatment of AS is still unclear. The research showed that *Tongxinluo* could inhibit ox-LDL-induced macrophage apoptosis based on flow cytometry and TUNEL assay analysis. *Tongxinluo* could increase the expression of Beclin-1 and alleviate interaction between Beclin-1 and Bcl-2. These results showed *Tongxinluo* inhibited macrophage apoptosis via improving Beclin-1-induced autophagy [87]. *Semen celosiae*is widely existed in some Asian and African countries that has been used in treating pathogenic hepatic fire and hypertension. Celosins are the main active components extracted from the seeds of *Semen celosiae*. It is uncertain whether they have an effect on anti-AS. The studies showed that compared with $ApoE^{-/-}$ mice model group, celosins significantly restrained the expression levels of CD36 and SR-A1 while enhancing the expression levels of ABCA1, ABCG1, LC3 and beclin-1. These results indicated that celosins lowered the levels of lipid and cholesterol and enhanced macrophage autophagy, eventually resulting in anti-AS [88]. Elatoside C is a triterpenoid extracted from the bark and root of *Aralia elata* that exerts anti-oxidative activity.

The research found that compared with oxLDL-induced HUVECs model group, elatoside C increased the extent of autophagosomes, the expression levels of BECN1, LC3II, then reduced the activities of p62 and caspase-3 in ox-LDL-induced HUVECs. When the oxLDL-induced HUVECs were pretreated with autophagy inhibitor 3-MA, these results were reversed. In conclusion, elatoside C attenuated oxLDL-induced HUVECs injury by stimulating autophagy and inhibiting apoptosis. Elatoside C is considered as a potential drug for the prevention and treatment of AS [89].

Inhibition of ECM degradtion

One of the characteristics of an unstable atherosclerotic plaque is that a necrotic core covered by a fibrous cap. The fibrous cap contains VSMCs, ECM, inflammatory cells and foam cells. It is well known that VSMCs can produce the main components of ECM, including elastin, collagen and proteoglycans, these components maintain the fibrous cap structure as well as ECM degradation enzyme such as MMPs, collagenases and gelatinases [90]. Pro-inflammatory macrophages can secrete MMPs, such as MMP-2, MMP-3 and MMP-9. Upregulation of MMP-9 is a direct cause of atherosclerotic plaque rupture [91]. MMPs have proteolytic activity and can degrade the ECM, leading to thinning of the fibrous cap and vascular remodeling [92]. Inhibition of MMPs activities are potential therapeutic approach for targeting AS.

Tanshinon IIA, an active diterpenequinone from *Salvia miltiorrhiza* root, is commonly used for treating AS. However, the mechanism of tanshinone IIA on AS has not been elucidated. Compared with the model group, the treatment of tanshinone IIA remarkedly inhibited the expressions of MMP-2, MMP-3 and MMP-9 in ApoE$^{-/-}$ mice. The contents of SMC and collagen ($P < 0.01$) were higher in atherosclerotic plaques under the administration of tanshinone IIA. These results indicated that tanshinone IIA could up-regulate collagen content via down-regulating the levels of MMPs in the vulnerable plaques [93].

Inhibition of angiogenesis

Angiogenesis is one of the crucial events to produce new vessels from existing vessels. In atherosclerotic lesions, abnormal angiogenesis in the plaque may promote plaque expansion, eventually resulting in intraplaque hemorrhage and rupture. Angiogenesis plays an important role in the progression of atherosclerotic lesion and the stability of plaques that enhances macrophage infiltration in atherosclerotic lesions [94]. The angiogenic mechanism is related to hypoxia, and the hypoxic state promotes the formation of angiogenic factors to stimulate neo-angiogenesis derived from the vasa vasorum. Vascular endothelial growth factor (VEGF) is a pro-angiogenic factor that can induce atherosclerotic lesions and intraplaque hemorrhage. VEGF promotes angiogenesis to produce new vessels from existing vessels from adventitia into the intima. VEGF and its main receptors VEGFR-1 or VEGFR-2 play important roles in regulating intraplaque angiogenesis [95]. VEGF-A is an endothelial growth factor that stimulates neoangiogenesis by activating EC proliferation and transportation [96]. Macrophages can promote angiogenesis by expressing pro-angiogenic VEGF-A and basic fibroblast growth factor (FGF). Macrophages produce pro-angiogenic growth factors such as FGF2 and FGF-β, which affect the progression of angiogenesis. FGF2 can promote the expansion of microvessels within the plaque, leading to intraplaque hemorrhage and thrombosis [97].

Previous studies have determined that *Tongxinluo*, red yeast rice, *Huoxue* capsule and Shumai capsule can inhibit angiogenesis and profect from AS by restraining the expression of VEGF. *Buyang Huanwu* decoction can promote microvessel maturation and inhibit angiogenesis *via* up-regulating the expressions of bFGF and PDGF [98]. *Tongxinluo*, a TCM, has been widely used in the treatment of AS. Previous study indicated that *Tongxinluo* inhibited macrophage apoptosis *via* improving Beclin-1-induced autophagy. The study found that *Tongxinluo* also could restrain the progression of angiogenesis in unstable atherosclerotic plaques. *Tongxinluo* dose-dependently down-regulated the expression of VEGF-A while up-regulating the expression of angiopoietin-1 in ApoE$^{-/-}$ mice. The number of vasa vasorum was significantly down-regulated in the vulnerable plaques of ApoE$^{-/-}$ mice. The content of SMCs and collagen were significantly increased under the administration of *Tongxinluo* [99]. Polydatinis a stilbenoidglucoside that is extracted from the root of *Polygonum cuspidatum* Sieb. It has various pharmaceutical effects, including antioxidant and anti-inflammation effects [100]. The research found that polydatin could serve as a potential therapeutic drug for treatment of angiogenesis-related diseases. According to zebrafish assay, compared to VEGF-induced angiogenesis of HUVECs group, the most vessels possessed less area and fewer branches with the administration of polydatin. VEGF treatment markedly increased the level of phosphorylation of VEGFR2 in HUVECs, but the administration of polydatin remarkably inhibited the VEGF-induced VEGFR2 phosphorylation without affecting the expression of VEGFR2. Polydatin also inhibited VEGF-modulated VEGFR2 downstream signalling molecules, including activated phosphorylations of Akt and JNK [101]. VEGF modulates angiogenesis by binding to VEGFRs, followed by auto-phosphorylation. The majority of VEGF-modulated angiogenesis is controlled by VEGFR2 [102].

Discussion

AS is recognized as a complicated disease caused by interaction among multiple mechanisms, various cell types and factors. In term of different types of drugs, the effects of chemical drugs are superior to that of TCM in a short-term. However, the long-term treatment will result in a series of side effects. In contrast, TCM has a long history in treating AS due to its advantages of low side effect and good efficacy. In particular, Some TCM have shown to play roles in suppression of inflammation, resistance to angiogenesis, inhibi-

tion of oxidative stress, improvement of autophagy and macrophage metabolismis. A range of TCM against AS is summarized in Table 1. Structures of their active compounds are shown in Fig. 2. It is essential for application of AS models to study the underlying mechanisms of TCM in treating diseases. The experimental models of AS are mainly divided into two categories. *In vitro* models include VSMCs, ECs and macrophages, and *in vivo* models include rats, rabbits, pigs. Due to the multifunction of TCM and the complexity of its active components, there are no comprehensive models to address all aspects of AS. Many drugs can target a variety of pathologic mechanisms of AS, the existing models of AS can be used to screen some TCM against AS. Therefore, in order to reveal the pathological mechanisms of TCM against AS, it is essential to develop more comprehensive models that conform with the characteristics of AS.

Table 1 Summary of TCM on mechanisms of anti-AS

Traditional Chinese medicine	Active components or chemicals	Pathological mechanisms	Model	Inducer	Ref.
Brassica rapa	Brassinin (1)	Inhibition of inflammation;	HUVECs	TNF-*α*	[30]
Panax notoginseng	Notoginsenoside R1 (2)	Inhibition of inflammation;	ApoE$^{-/-}$ mice	isoproterenol	[31]
Morus alba	Kuwanon G (3)	Inhibition of the foam cell formation; Improvement of cholesterol efflux;	RAW 264.7 cells	ox-LDL	[46]
Radix Bupleuri	Saikosaponin-A (4)	Inhibition of the foam cell formation; Improvement of cholesterol efflux;	THP-1	ox-LDL	[49]
Salvia miltiorrhiza	Danshensu (5)	Inhibition of lipid deposition;	RAW 264.7 cells	ox-LDL	[52]
Spatholobus suberectus	Luteolin (6)	Inhibition of VSMCs proliferation and migration;	A7r5 cell HASMC cell		[62]
Astragalus membranaceus	Astragaloside IV (7)	Inhibition of VSMCs proliferation and migration and proliferation phenotype switch;	HDVSMCs	PDGF-BB	[66]
Curcuma wenyujin	β-Elemene (8)	Inhibition of oxidative stress; Improvement of endothelial function;	ApoE$^{-/-}$ mice	High-fat diet	[76]
Ampelopsis grossedentata	Dihydromyricetin (9)	Inhibition of oxidative stress and cell apoptosis;	HUVECs	ox-LDL	[78]
Aralia elata	Elatoside C (10)	Improvement of mitophagy;	HUVECs	ox-LDL	[89]
Salvia miltiorrhiza	Tanshinone IIA (11)	Inhibition of ECM degradation;	ApoE$^{-/-}$ mice	High-fat diet	[93]
Polygonum cuspidatum	Polydatin (12)	Inhibition of angiogenesis;	HUVECs	VEGF	[101]
Olea europaea	Oleanolic acid (13)	Inhibition of cell apoptosis; inhibition of inflammation;	HUVECs rabbits	ox-LDL High-fat diet	[103]
Polygonum cuspidatum	Resveratrol (14)	Hypolipidemic; antioxidative; anti-inflammatory;	APOE^{*3}-Leiden. CETP mice	High-fat diet	[104]
Allium sativum	Allicin (15)	Inhibition of oxidative stress and cell apoptosis;	HUVECs	ox-LDL	[105]
Cnidium monnieri	Osthole (16)	Inhibition of inflammation; Inhibition of vascular endothelial injury;	HUVECs	ox-LDL	[106]
Crataegus pinnatifida	Flavonoids	Inhibition of the foam cell formation; Promotion of RCT;	ApoE$^{-/-}$ mice	High-fat diet	[107]
Rheum palmatum	Rhein (17)	Inhibition of the expression of VCAM-1;	HUVECs	LPS	[108]
Rheum palmatum	Emodin (18)	Inhibition of inflammation; Inhibition of ROS production;	THP-1 cell	Light	[109]
Ligusticum striatum	Tetramethylpyrazine (19)	Inhibition of the lipid accumulation; Improvement of cholesterol efflux;	ApoE$^{-/-}$ mice	High-fat diet	[110]
Astragalus membranaceus	*Astragali Radix* extract	Inhibition of inflammation; Downregulation of adhesion molecules;	SVEC4-10 cells THP-1 cells	TNF-α	[111]
Scutellaria baicalensis	Baicalin (20)	Anti-oxidant effect; Anti-inflammation effect;	ApoE$^{-/-}$ mice	High-fat diet	[112]
Allium cepa	Quercetin (21)	Suppression of inflammation and apoptosis;	mice	High fructose	[113]
Gardenia jasminoids	Geniposide (22)	Inhibition of dendritic cells;	ApoE$^{-/-}$ mices	Highcholesterl diet	[114]
Andrographis paniculata	Andrographolide (23)	Inhibition of inflammation, ROS generation, and foam cell formation; Inhibition of cholesterol accumulation;	macrophages	ox-LDL	[115] [116]
Radix Puerariae	Puerarin (24)	Inhibition of VSMCs proliferation;	VSMCs	PM2.5	[117]

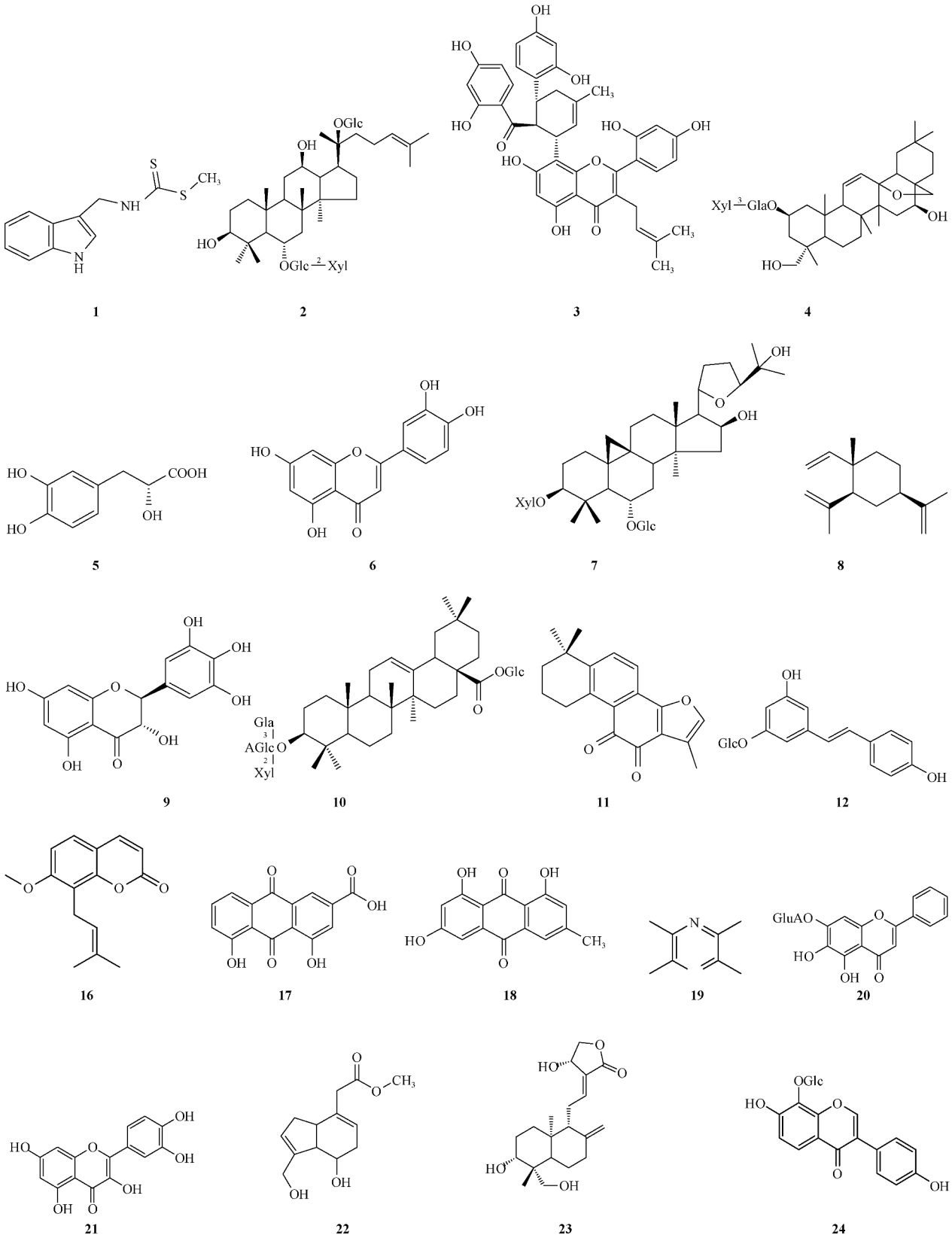

Fig. 2 Structures of active compounds against AS

Future Directions

Although TCM is safe and effective for the disease, it is difficult to ignore the difficulties that the components of TCMare complicated and the mechanisms of action remain unclear. Future directions should be more deeply considered: (1) more bioactive ingredients from TCM should be extracted and screened. Efforts should be made to find a material basis of TCM against AS. (2) TCM should be manufactured into a good dosage form, which can make it easy to take, and the drug can achieve the maximum efficacy, while reducing toxic side effects. (3) the pathological features of AS are different in different periods. Despite the numerous in vivo and in vitro studies, more clinical trials are essential to assess the efficacy of screened drugs in the treatment of AS. Future studies are needed to explore pharmacodyamic material basis and active chemical structures of TCM for AS by means of both basic and clinical research. TCM has a long history for the prevention and treatment of AS due to its less side effects and good efficacy.We believe that the deep studies of the mechanisms of the TCM against AS will bring hope to clinical physician, and provide prosperity in the prevention and treatment of AS.

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