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Review

# Traditional Chinese medicines treating macrophage: A particular strategy for atherosclerosis

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ABSTRACT

Atherosclerosis is a major cause of cardiovascular disease and one of the most deadly diseases in the world. Macrophages are the main contributors in the development of atherosclerosis, a target that drugs inhibit the inflammation and regulate lipid metabolism. In this review, we summarized the effects and mechanisms of traditional Chinese medicines and their bioactive compounds on atherosclerosis.



## Contents



## 1. Introduction

Cardiovascular diseases rank first in morbidity worldwide (Mozaffarian et al., 2016). Atherosclerosis (AS), the main cause of cardiovascular diseases, is a chronic inflammatory disease in which macrophage inflammation is a key process. In basic physiology, macrophage can remove oxidized low-density lipoprotein cholesterol (oxLDL-C) from the intercellular space to ensure tissue cholesterol homeostasis. However, if macrophages absorb excessive cholesterol or impair cholesterol release, macrophages become foam cells that are the main component of atherosclerotic plaques (Ouimet & Marcel, 2012). It is merit attention that oxLDL-C can stimulate foam cell production of inflammatory cytokines and chemokines, such as TNF$\alpha$, IL-6, CCL2, which in turn impair macrophage cholesterol efflux and recruit circulating monocytes to the atherosclerotic lesion, leading to further plaque formation and artery occlusion (Chávez-Sánchez et al., 2014). Therefore, macrophage polarization and foam cells formation can lead to novel therapeutic approaches to atherosclerosis. Here, we summarize how Chinese materia medica (CMM) stimulate cholesterol ef-

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flux and reduce inflammation from macrophages, which shed more insights into the understanding and treatment of atherosclerosis.

## 2. Pathogenesis of atherosclerosis

Atherosclerosis is a chronic inflammation disease with a series of pathological changes, such as endothelial cell injury, lipid deposition, mononuclear cell infiltration, foam cell formation and so on (Bergheanu, Bodde, & Jukema, 2017; Hansson, 2005; Libby, Ridker, & Maseri, 2002; Ross, 1999). The pathogenesis of atherosclerosis was shown in Fig. 1.

In the theory of traditional Chinese medicine (TCM), AS usually refers to a vascular problem that is caused by *qi* stagnation, blood stasis, turbid phlegm and heat and toxin (Wang & Zhang, 2009). The imbalance between high-density lipoprotein cholesterol (HDL-C) and LDL-C can lead to the formation of AS plaque, and hyperlipemia can be annotated as turbid phlegm and blood stasis in TCM theory. The turbid phlegm syndrome is closely related to lipid metabolism disorder. Abnormal changes of lipoprotein composition and serum apolipoprotein are the basis of turbid phlegm. Abnormal hemorheology and platelet activation are important biological manifestation of AS blood stasis. Moreover, in the process of AS, vascular endothelial damage, intimal thickening, hemal stricture, tissue necrosis, inflammation media release, and the rupture of vulnerable plaques caused by inflammation are closely related with evil heat and toxin in TCM. Turbid phlegm and blood stasis are related with lipid metabolism disorder and the basis of inflammatory lesions in AS in which macrophages play a vital role, so it is important to regulate lipid metabolism and inhibit inflammation on macrophage *in vivo* and *in vitro*.

## 3. Inflammatory phenotypes in macrophage

Macrophage influenced all stages of AS, whether initiation, progression, or regression of lesions. In the different stage of AS, the number of different macrophage phenotype is different. The ratio of macrophage phenotype in atherosclerotic plaque is a good indicator of disease progress.

Different macrophage subtypes are produced by different stimulating factors and express different surface markers and chemokine receptors (Bories & Leitinger, 2017). Macrophage subtypes include pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages. M1 macrophages are often induced by interferon-$\gamma$ (IFN-$\gamma$), tumor necrosis factor-$\alpha$ (TNF-$\alpha$), and lipopolysaccharide (LPS), alone or in combination (Mantovani, Garlanda, & Locati, 2009). When encountering these stimuli, macrophages secrete high levels of pro-inflammatory cytokines (TNF-$\alpha$, IL-6, IL-1$\beta$, etc), chemokines including monocyte chemoattractant protein-1 (MCP-1), and low levels of IL-10 (Bories & Leitinger, 2017). M2 macrophages can drive towards different phenotypes by different stimuli. The M2a phenotype can be induced by IL-4 and IL-13 (Jenkins et al., 2011); M2b macrophage subtypes are induced by immune complexes in combination with IL-1$\beta$ or LPS; M2c macrophages are induced by IL-10, transforming growth factor-$\beta$ (TGF-$\beta$) (Murray & Wynn, 2011). M2 macrophages usually have the character of anti-inflammation, but M2b subset produces high levels of IL-1 and IL-6. Interestingly, macrophage phenotype can switch from one to another when environmental cues changed due to the plasticity of macrophage. (Lee et al., 2011; Porcheray et al., 2005).

## 4. Cholesterol metabolism in macrophage

As a result of the excessive influx of modified LDL and accumulation of cholesterol esters and impaired cholesterol release, macrophages become foam cells. Foam cells play an important role at all stages of atherosclerotic lesion development, from initial lesions to advanced plaques. Foam cells express a variety of scavenger receptors (SR), such as SR-A1, CD36, and lectin-like oxLDL receptor-1 (LOX-1). CD36 and SR-A1 are mainly responsible for uptake of ox-LDL by macrophages (Yu, Fu, Zhang, Yin, & Tang, 2013). ABCA1 and ABCG1 both can promote cholesterol efflux in macrophage (Choi, Sviridov, & Miller, 2017).

### 4.1. Cholesterol uptake

SR-A and CD36 are implicated in the process of cholesterol uptake. In atherosclerosis, the cholesterol handling in macrophages is deregulated. CD36 and SR-A1 expressions are upregulated with

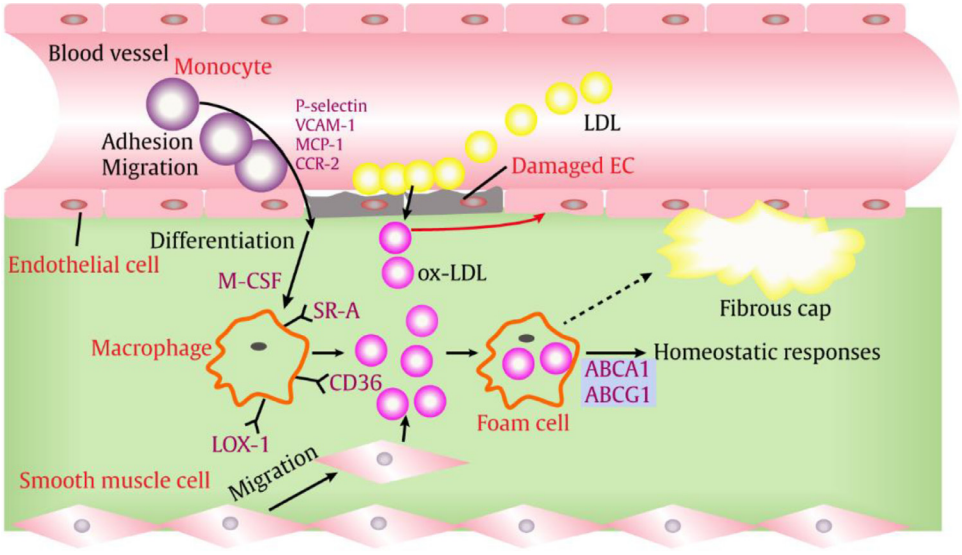


**Fig. 1.** Schematic drawing of formation of atherosclerotic plaques.
Briefly, endothelial injury is the first step of AS that changes the permeability of endothelium and allows LDL-C particles into the arterial cell. Then endothelial cells secrete pro-inflammatory factors, such as monocyte chemotactic protein (MCP-1) and interleukins, e.g., IL-6, to stimulate circulating monocytes adhering to endothelial cells and migrating into subendothelial space. Consequently, macrophages convert into foam cells. Meanwhile, smooth muscle cells (SMCs) proliferate and migrate to the location of lesion. Finally, the plaques of AS develop. VCAM-1: vascular cell adhesion molecule-1; CCR-2: cell chemokine receptor 2; M-CSF: macrophage colony-stimulating factor; LOX-1: Lectin-like oxidized low density lipoprotein recaptor-1; SR-A: scavenger receptor A; ABCA1: ATP-binding cassette transporter 1; ABCG1: ATP-binding cassette sub-family G member 1.

the increasing uptake of ox-LDL, leading to increased lipid uptake (Chistiakov, Melnichenko, Myasoedova, Grechko, & Orekhov, 2017.). A previous study reported that apoE$^{-/-}$ mice lacking CD36 or SR-A display increased aortic sinus atherosclerotic lesion area and abundant macrophage foam cells in the aortic intima (Moore et al., 2005). Inhibition of SR-A in macrophages significantly ameliorates foam cell formation and atherosclerosis in apoE$^{-/-}$ mice. Moreover, clinical studies showed that patients with CD36 deficiency are associated with more severe atherosclerotic diseases (Yuasa-Kawase et al., 2012). Therefore, CD36 and SR-A1 could be identified as proatherogenic mediators of ox-LDL uptake.

### 4.2. Cholesterol efflux

Several ATP-binding cassette (ABC) transporters including ABCA1 and ABCG1 critically maintain cellular cholesterol homeostasis by regulating reverse cholesterol transport (RCT) in lipid trafficking. ABCA1 and ABCG1 both can promote cholesterol efflux. ABCA1 mediates cholesterol efflux to lipid-poor apolipoproteins A-I, while ABCG1 promotes cholesterol efflux to the mature forms of HDL. Mice lacking ABCA1 display severe hypocholesterolemia and foam cell accumulation without atherosclerosis, mainly due to the absence of proatherogenic lipoproteins (Zhao et al., 2011). However, ABCA1 overexpression in the liver of LDLR$^{-/-}$mice results in accumulation of proatherogenic lipoproteins and enhanced atherosclerosis (Joyce et al., 2006). Lack of macrophage ABCG1 has been reported to cause a modest increase in atherosclerotic lesions (Out et al., 2006). However, the absence of ABCG1 leads to increased lesions in the early stage of atherosclerosis and causes retarded lesion progression in more advanced stage of AS in LDLR$^{-/-}$ mice, suggesting that the influence of ABCG1 deficiency on lesion development depends on the stage of AS (Meurs et al., 2012). Thus, in regarding to these contradictory observations, a careful re-evaluation of ABCA1 and ABCG1 as potent antiatherogenic agents is necessary.

## 5. Intervention of CMM in macrophage

Many Chinese medicinal materials have been widely used to treat AS in China. According to the theory of TCM, CMM compounds and formula can be divided into the following categories: promoting blood circulation to remove blood stasis, eliminating phlegm, clearing away evil heat and toxin, *et al.* Commonly used CMM for promoting blood circulation and removing blood stasis include *Crataegi Fructus, Notoginseng Radix* et *Rhizoma, Salviae Miltiorrhizae Radix* et *Rhizoma, Carthami Flos, Atractylodis Rhizoma, Astragali Radix*, and formula, such as Simiao Yong'an Decoction, Siwu Decoction, and Xuefu Zhuyu Decoction. Chinese medicines of clearing heat and removing toxin include *Andrographis Herba, Scutellariae Radix, Polygoni Multiflori Radix, Moutan Cortex*, etc. In addition, most of them are bitter in taste and slightly cold in nature.

### 5.1. Regulation of lipid metabolism

*Salviae Miltiorrhizae Radix* et *Rhizoma*, a little cold in nature and bitter in taste, can promote blood circulation and remove blood stasis, which has been widely used in the prevention and treatment of cardiovascular diseases for many years (Hong, He, Yang, & An, 2017; Lin & Hsieh, 2010). Many components of *Salviae Miltiorrhizae Radix* et *Rhizoma* can inhibit lipid accumulation. Tanshinol, the major water-soluble component extracted from *Salviae Miltiorrhizae Radix* et *Rhizoma*, showed anti-atherosclerosis, anti-inflammatory, and anti-oxidative damage (Yu et al., 2014). Tanshinol regulated intracellular lipid level through reducing the uptake of extracellular lipid depots into macrophages mainly via inhibiting CD36 and SR-BI, and promoting the efflux of intracellular cholesterol partly due to the stimulation of ABCA1 and ABCG1 (Gao et al., 2016). On the contrary to tanshinol, tanshinone IIA (TSIIA) is a lipophilic bioactive compound that significantly attenuates the atherosclerotic lesion in ApoE$^{-/-}$ mice and inhibits the formation of foam cells in atherosclerotic lesion mainly through down-regulating PPAR$\gamma$-mediated CD36 expression by both inhibiting the mRNA expression and antagonizing the activation of PPAR$\gamma$ (Tang et al., 2011). In addition, Liu et al found that TSIIA markedly reduced the expression of SR-A and increased the expression of ABCA1 and ABCG1 by the activation of ERK/Nrf2/HO-1 pathway (Liu et al., 2014). Similarly, Tanshindiol C (Tan C) can activate Nrf2 and SIRT1 followed by peroxiredoxin 1 (Prdx1) up-regulation, resulting in the decrease of lipid accumulation in macrophage (Yang et al., 2017).

*Moutan Cortex*, slightly cold in nature and bitter in taste, is a kind of heat-clearing Chinese medicine that promotes blood circulation and removes blood stasis. Paeonol, the main active ingredient in *Moutan Cortex*, is originally used to treat inflammatory diseases, also has effects on cholesterol metabolism. Zhao et al reported that paeonol could enhance the expression of ABCA1 and decrease ABCG1 in mRNA and protein levels. Moreover, the activity of nuclear translocation of liver X receptor alpha (LXR$\alpha$) was induced (Zhao et al., 2013).

*Carthami Flos*, warm in nature and pungent in taste, is a classic Chinese medicine for promoting blood circulation and removing blood stasis. Kaempferol, a flavonoid compound extracted from this herb, inhibits ox-LDL uptake by macrophage, in which kaempferol down-regulates the mRNA and protein expressions of CD36 in a c-Jun-activator protein-1 (AP-1) dependent manner and mediates the HO-1-dependent upregulation of ABCG1, SR-BI, and ABCA1 (Li, Kong, Li, He, & Zhou, 2013).

*Andrographis Herba,* cold in nature and bitter in taste, is an important Chinese medicine in China and has strong anti-inflammatory and detoxification properties. Andrographolide, one of bioactive components of *Andrographis Herba*, is a potential candidate to prevent AS. Andrographolide prevented CD36-mediated oxLDL uptake and induced ABCA1- and ABCG1-dependent cholesterol efflux, which was dependent on enhancing LXR nuclear translocation and DNA binding activity (Lin et al., 2018).

*Crataegi Fructus* can reduce blood lipids, promote blood circulation, and eliminate phlegm. *Ginkgo Folium* also promotes blood circulation, removes blood stasis and relieves pain. They both prevent cardiovascular diseases. Quercetin is the shared ingredient in them with anti-oxidant, anti-inflammatory, and anti-atherogenic properties (Ishizawa et al., 2011). Choi et al reported that quercetin could induce the gene and protein expression of CD36 and SR-A, mainly through preventing the activation of the protein kinase C (PKC) and PPAR-$\gamma$ signaling pathway, resulting in inhibition of oxidized LDL uptake by macrophages (Choi et al., 2010). On the other hand, quercetin regulates cholesterol reverse transport via interfering with the expression of the cholesterol transport gene, ABCA1, as well as its transcription factors PPAR-$\gamma$ and LXR$\alpha$, which had anti-atherogenic effects in some ways via suppressing the foam cell formation (Lee, Moon, Cho, Chung, & Shin, 2013).

*Curcumae Longae Rhizoma,* warm in nature and bitter in taste, can remove *qi* and blood stasis. Curcumin, the main active polyphenol extracted from *Curcumae Longae Rhizoma* is beneficial to cardiovascular patients such as diabetes and AS (Olszanecki et al., 2005; Wongcharoen & Phrommintikul, 2009). In macrophages treated with curcumin, oxLDL-induced cholesterol accumulation was attenuated by reducing SR-A and promoting ABCA1 by a proteasome- and LXR-dependent pathway, respectively (Zhao et al., 2012). In addition, Min et al also reported that curcumin reduced CD36 expression and foam cell formation in a p38 MAPK dependent manner (Min, Um, Cho, & Kwon, 2013). Zhou et al found that curcumin showed anti-atherosclerosis by increasing

thrombospondin-4 (THBS-4) expression in mouse macrophages (Zhou, Chen, Wang, Tian, & Fan, 2014).

Di'ao Xinxuekang Capsule is a formula for coronary heart disease due tocontaining saponins extracted from *Dioscoreae Rhizoma*. It can relieve AS by increasing the expression of ABCA1 and ABCG1, stimulating cholesterol efflux, and reducing aortic atherosclerotic lesion area. Moreover, it increased HDL synthesis (Dong et al., 2017).

Shexiang Tongxin Dropping Pills (STDP) is a formula including *Moschus, Fel Ursi*, total saponins of *Ginseng Radix* et *Rhizoma, Salviae Miltiorrhizae Radix* et *Rhizoma*, etc, which is used to treat coronary heart disease. Xiong et al reported that STDP attenuated atherosclerotic lesions in ApoE$^{-/-}$ mouse model. Moreover, STDP reduced lipid deposition, decreased the level of CHO, TG, and ox-LDL, and increased the level of HDL. Additionally, the levels of pro-inflammatory cytokines including IL-2, IL-6, TNF-$\alpha$, and $\gamma$-IFN were markedly reduced (Xiong et al., 2015).

Danhong Injection, composed of *Salviae Miltiorrhizae Radix* et *Rhizoma* and *Carthami Flos*, has been prescribed to patients with various syndromes of coronary heart disease in China. In TCM theory, *Salviae Miltiorrhizae Radix* et *Rhizoma* is cold, whereas *Carthami Flos* is warm in nature, and their combination can enhance efficacy and reduce the side effects in treating cardiovascular diseases. Danhong Injection can dose-dependently decrease the levels of TG, TC, and LDL-C, and increase the CPT1 and PPAR-$\alpha$ expression in rats model (Chen et al., 2014). It also induced ABCA1 expression and reduced macrophage accumulation in male ApoE$^{-/-}$ mice and both male and female LDLR$^{-/-}$ mice, meanwhile, Danhong Injection inhibited the expression of TNF-$\alpha$, IL-1$\beta$, and IL-6 mRNA *in vitro* and TNF-$\alpha$ protein expression in aortic root in both ApoE$^{-/-}$ and LDLR$^{-/-}$ mice (Chen et al., 2014).

Some TCM formulas and bioactive compounds for regulation of lipid metabolism in treating of AS were summarized in Table 1.

### 5.2. Modulating macrophage polarization

In clinical practice, *Dioscoreae Rhizoma* combined with roots of *Hemsleya chinensis* Cogn. ex Forbes et Hemsl. and *Sophora flavescens* Ait. can treat coronary heart disease partly due to macrophage polyrization from pro-inflammation to anti-inflamation. Cucurbitacin IIa (CuIIa), a member of cucurbitacin family and purified from roots of *H. chinensis*, induced apoptosis and enhanced autophagy in LPS-stimulated RAW 264.7 cells, but failed to suppress the mitogen-activated protein kinases (MAPKs) and NF-$\kappa$B activation and TNF-$\alpha$ expression. These suggested a novel mechanism for the anti-inflammation action of CuIIa (He et al., 2013).

*Polygoni Cuspidati Rhizoma* et *Radix* is a little cold in nature and slightly bitter in taste and has the effect of clearing heat and detoxification, dispelling stasis and relieving pain, relieving cough and reducing phlegm. Resveratrol, a polyphenolic compound extracted from this herb, downregulated LPS-induced expression of inflammatory markers, such as TNF-$\alpha$ and IL-6, and inhibited the phosphorylation of mitogen-activated protein kinases (MAPKs) and signal transducer and activator of transcription STAT1/STAT3 (Ma, Wang, Shen, & Cai, 2017). Resveratrol also upregulated the production of suppressor of cytokine signaling 1 (SOCS1; a STAT inhibitor) and suppressed the expression of miR-155, which plays an essential role in the macrophage polarization.

Besides inhibiting foam cell formation, *Salviae Miltiorrhizae Radix* et *Rhizoma* can inhibit inflammation and improve the macrophage polarization. *Salvia miltiorrhiza* polysaccharides (SMP) could protect macrophage against LPS-induced inflammation, mainly through inhibiting the mRNA transcriptions of TNF-$\alpha$, IL-6, iNOS, and COX-2, and the protein expressions of NF-$\kappa$B, p-p65, and p-I$\kappa$B$\alpha$ (Han, Yang, Song, Wang, & Shi, 2018). Also, neocryptotanshinone (NCTS) has the anti-inflammatory effects by suppressing the expression of inflammatory cytokines through NF-$\kappa$B and iNOS signaling pathways (Wu, Zhao, Zhang, & Chen, 2015).

*Notoginseng Radix* et *Rhizoma*, warm in nature and slightly bitter in taste, is a kind of Chinese medicines for promoting blood circulation and removing blood stasis, in which ginsenoside Rb1 (Rb1) is one of the major active ingredient. Rb1 promoted the expression of M2 macrophage markers, such as arginase-I (Arg-I) and macrophage mannose receptor (CD206), and inhibited the expression of M1 macrophage markers, such as iNOS partly by increasing the production of IL-4, IL-13, and STAT6 phosphorylation (Zhang et al., 2018). We found that ginsenoside F1 (GF1), a metabolite by hydrolysis of ginsenosides Re and Rg1, had anti-atherosclerosis effect; in HFD-induced ApoE$^{-/-}$ mice, GF1 could significantly reduce plaque formation and reduce MPO expression (Qin et al., 2017).

Dan-Lou formula, derived from a Chinese ancient formula of *Trichosanthis Fructus-Allii Macrostemonis Bulbus-Pinelliae Rhizoma* decoction, has been used to treat chest discomfort (coronary atherosclerosis) for thousands of years in China. It has anti-inflammatory activities; The ethanol extract inhibited iNOS/NO, COX-2/prostaglandin (PGE2), and cytokine expression, and alleviated ox-LDL-induced foam cell formation in macrophage by antagonizing the mRNA and protein over-expression of PPAR$\gamma$, blocking the phosphorylation of IKK$\alpha/\beta$, IkB$\alpha$, and NF-$\kappa$B p65, and maintaining the expression balance between Bax and Bcl-2 (Gao et al., 2018).

**Table 1**
Lipid metabolism in macrophage in AS models regulated by TCM formulas and bioactive compounds.

| Formulas or compounds | Herbs | Targets or pathways | References |
|---|---|---|---|
| Tanshinol | *Salviae Miltiorrhizae Radix* et *Rhizoma* | CD36, SR-B1, ABCA1, ABCG1 | Yu et al. (2014), Gao et al. (2016) |
| Tanshinone IIA | *Salviae Miltiorrhizae Radix* et *Rhizoma* | PPAR$\gamma$, CD36, SR-A1, ABCA1, ABCG1, ERK/Nrf2/HO-1 pathway | Tang et al. (2011), Liu et al. (2014) |
| Tanshindiol C | *Salviae Miltiorrhizae Radix* et *Rhizoma* | Nrf2 and SIRT1 pathways | Yang et al. (2017) |
| Paeonol | *Moutan Cortex* | LXR$\alpha$, ABCA1, ABCG1 | Zhao et al. (2013) |
| Kaempferol | *Carthami Flos* | CD36, ABCA1, ABCG1, SR-B1, AP-1 and HO-1 pathways | Li et al. (2013) |
| Andrographolide | *Andrographis Herba* | CD36, ABCA1, ABCG1, LXR | Lin et al. (2018) |
| Quercetin | *Crataegi Fructus* | CD36, SR-A1, PPAR$\gamma$, LXR$\alpha$, PKC pathway | Lee et al. (2013) |
| Curcumin | *Curcumae Longae Rhizoma* | SR-A1, ABCA1, LXR, P38 pathway | Zhao et al. (2012), Min et al. (2013), Zhou et al. (2014) |
| Di'ao Xinxuekang Capsules | *Dioscoreae Rhizoma* | ABCA1, ABCG1, HDL | Dong et al. (2017) |
| Shexiang Tongxin Dropping Pills | *Moschus, Fel Ursi*, total saponins of *Ginseng Radix* et *Rhizoma* and *Salviae Miltiorrhizae Radix* et *Rhizoma* | CHO, TG, LDL, HDL, IL-2, IL-6, TNF-$\alpha$ and $\gamma$-IFN | Xiong et al. (2015) |
| Danhong Injection | *Salviae Miltiorrhizae Radix* et *Rhizoma* and *Carthami Flos* | TG, TC, LDL-C, PPAR-$\alpha$, ABCA1, TNF-$\alpha$, IL-1$\beta$, IL-6 | Chen et al. (2014) |

Cardiotonic Pills consisting of *Salviae Miltiorrhizae Radix* et *Rhizoma, Notoginseng Radix* et *Rhizoma*, and *Borneolum Syntheticum*, has been used to treat cardiovascular disease for many years. This pill can downregulate VCAM-1 expression and inhibit atherosclerotic plaque development. Chen et al found that the Cardiotonic Pills could postpone atherosclerotic plaque development and stabilize vulnerable plaque by inhibiting the expression of adhesion molecules (Chen et al., 2016).

Some TCM formulas and bioactive compounds for modulation of macrophage polarization in treating of AS were summarized in Table 2.

## 6. Discussion

AS is a chronic complex disease involving multiple targets and pathways, in which macrophages play an important role. The key strategy to prevent and treat AS is to inhibit the inflammation and regulate lipid metabolism. Currently, statins are the commonly used anti-atherosclerosis drugs. However, synthesis drugs only work on a single target and cannot be used for comprehensive treatment of AS. Additionally, the side effects of statins cannot be ignored, including statin-associated muscle symptoms, diabetes mellitus, and gastrointestinal discomfort. Reducing the side effects of statins can be treated with other lipid-lowering therapy. The role of CMM in treating chronic diseases should not be overlooked owing to the great advantages and potential in the prevention and treatment of AS; They contain many components that can regulate the multi-targets and multi-pathways in the following aspects, such as CD36 and SR-B1, the targets regulating cholesterol uptake; ABCA1 and ABCG1, the targets involving in cholesterol and phospholipid efflux and RCT; the inflammatory factors including TNF-$\alpha$, IL-6 and so on (Fig. 2). Moreover, CMM show better efficency combined with synthesis drugs. For instance, *Panax notoginseng* saponin combined with aspirin is more effective in the treatment of cardiovascular diseases than aspirin alone (Tian et al., 2017; Zhu et al., 2018).

**Table 2**
TCM formulas and bioactive compounds for modulation of macrophage polarization in AS.

| Formulas or compounds | Herbs | Targets or pathways | References |
|---|---|---|---|
| Cucurbitacin IIa | *Hemsleya Amabilis* | MAPK and NF-$\kappa$B pathways | He et al. (2013) |
| Resveratrol | *Polygoni Cuspidati Rhizoma* et *Radix* | TNF-$\alpha$, IL-6, MAPK and STAT1/STAT3 pathways | Ma et al. (2017) |
| *Salvia miltiorrhiza* polysaccharides | *Salviae Miltiorrhizae Radix* et *Rhizoma* | TNF-$\alpha$, IL-6, iNOS, COX-2, NF-$\kappa$B pathway | Han et al. (2018) |
| Neocryptotanshinone | *Salviae Miltiorrhizae Radix* et *Rhizoma* | NF-$\kappa$B and iNOS pathways | Wu et al. (2015) |
| Ginsenoside Rb1 | *Notoginseng Radix* et *Rhizoma* | Arg-I, CD206, IL-4, IL-13, iNOS, STAT6 | Zhang et al. (2018) |
| Ginsenoside F1 | *Notoginseng Radix* et *Rhizoma* | MPO, TLR4, NF-$\kappa$B pathway | Qin et al. (2017) |
| Dan-Lou formula | *Trichosanthis Fructus, Allii Macrostemonis Bulbus, Pinelliae Rhizoma* | iNOS/NO, COX-2/ PGE2, NF-$\kappa$B pathway | Gao et al. (2018) |
| Cardiotonic Pills | *Salviae Miltiorrhizae Radix* et *Rhizoma, Notoginseng Radix* et *Rhizoma, Borneolum Syntheticum* | ICAM-1, VCAM-1, LDL-C | Chen et al. (2016) |

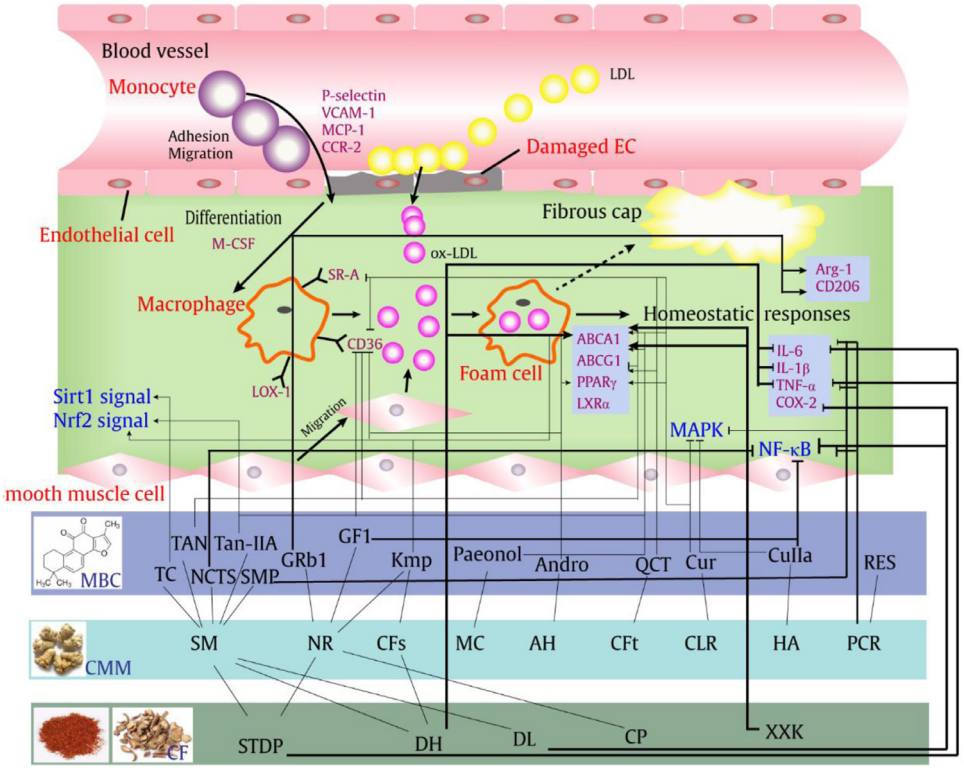


**Fig. 2.** Therapeutic mechanisms of TCM and major bioactive components in foam cell formation and macrophage polarization.
AH: *Andrographis Herba*; Andro: Andrographolide; CF: formula; CFs: *Carthami Flos*; CFt: *Crataegi Fructus*; CLR: *Curcumae Longae Rhizoma*; CMM: Chinese materia medica; CP: Cardiotonic Pill; CulIa: Cucurbitacin IIa; Cur: Curcumin; DH: Danhong Injection; DL: Dan-Lou prescription; TAN: Tanshinol; GF1: Ginsenoside F1; GRb1: Ginsenoside Rb1; HA: *Hemsleya Amabilis*; Kmp: Kaempferol; MBC: Major bioactive component; MC: *Moutan Cortex*; NCTS: Neocryptotanshinone; NR: *Notoginseng Radix et Rhizoma*; PCR: *Polygoni Cuspidati Rhizoma et Radix*; QCT: Quercetin; RES: Resveratrol; SM: *Salviae Miltiorrhizae Radix et Rhizoma*; SMP: Salvia miltiorrhiza polysaccharides; STDP: Shexiang Tongxin Dropping Pill; Tan-IIA: Tanshinone IIA; TC: Tanshindiol C; XXK: Di'ao xinxuekang Capsules.

Although some achievements have been made, there are still some challenges. Firstly, it is not clear that what are the exact targets and pathways on which individual compounds of CMM act. It is necessary to use proteomics and genomics to deeply explore the regulatory targets of CMM compounds. Activity-based protein profiling, a technology combined activity-based probe and proteomics technologies together, could also help us to understand the mechanisms of compounds and the modes of action. Secondly, most experiments of individual compounds are conducted on mouse models and lack clinical trials. The environment human existing is complex, so it is more difficult to stop plaque inflammation in humans. In humans, except inflammation, many risk factors, such as smoking, hypertension, and diabetes, may induce inflammation and furthermore form atherosclerosis plaque, in which the mechanisms are not well understood. Thirdly, most researchers pay more attention to the study of single compound of CMM and lack of discussion in-depth on TCM formula. Formula is the main form in clinical practice, and we should pay more attention to the study of TCM formula. The composition of formula is complex and the medicinal ingredients are not clear, so bioinformatics analysis, such as network pharmacology can be carried out to explore the composition and target information of TCM formulas. The active ingredients in the formulas can also be determined by high-throughput screening. Therefore, the original formula will be improved by adding or deleting some components.

## Conflict of interest

The authors declare that they have no competing interests.

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