Immunometabolic stress and herbal medicines in atherosclerosis

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Abstract

Atherosclerosis is a widespread illness that gravely endangers human health and is the fundamental pathological foundation of many cardiovascular and cerebrovascular diseases. The absorption and storage of oxidatively modified LDL by certain specofoc cells in immune cells, such as macrophages, causes varieties of immunooxidative processes. These processes of stress lead to plaque rupture through inflammatory processes, and then drives the development of atherosclerotic lesions. Now, the medications for the treatment of atherosclerosis are mostly lipid-lowering, anticoagulant, and thrombolytic agents, but the therapeutic outcomes are insufficient. It is determined that traditional Chinese medicine has achieved good clinical efficacy in treating atherosclerotic illnesses. However, the mechanism of TCM therapy for atherosclerosis needs to be elucidated. This paper highlights the target mechanism and structural features of traditional Chinese medicine components and compounds in controlling the connections mentioned above and then regulating atherosclerosis, hoping to propose novel techniques for treating and preventing the disease.

Immunometabolic stress and herbal medicines in atherosclerosis

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TCM therapy for atherosclerosis needs to be elucidated. This paper highlights the target mechanism and structural features of traditional Chinese medicine components and compounds in controlling the connections mentioned above and then regulating atherosclerosis, hoping to propose novel techniques for treating and preventing the disease.

Keywords: Atherosclerosis; Lipids; Oxidative stress; Immunometabolism; Herbal medicines; Traditional Chinese and Western Medicine

INTRODUCTION

Atherosclerosis is caused by a buildup of cholesterol in the inner lining of the artery wall, which causes inflammation and recruitment of immune cells in the blood arteries, thereby increasing the formation of atherosclerotic plaque (Tabas and Bornfeldt, 2020).

Atherosclerosis is a pathological process of coronary, cerebral, iliac and femoral arteries, and aorta that can lead to cardiovascular, cerebrovascular, and peripheral arterial disease. Sometimes, coronary artery narrowing is sufficient to elicit ischemia discomfort, but not infarction, particularly during physical exercise (angina). In approximately one-third of instances of coronary heart disease, coronary artery blockage results in a deadly arrhythmia (sudden cardiac death) within minutes or hours(Yanik et al., 2000). These syndromes (angina pectoris, myocardial infarction, and sudden cardiac death) are all atherosclerosis-related cardiovascular illnesses. The angina-like episodes mentioned above suggest a high risk for cerebral infarction (stroke) in the patient. Stroke is a clinical state of neurological impairment induced by cerebral infarction produced by thrombus development on atherosclerotic plaques or brain tissue loss caused by artery rupture and bleeding(Yanik et al., 2000). A transient ischemic attack (TIA) is a transitory neurological impairment resulting from a blood clot develops on atherosclerotic plaque in the cerebral arteries and inadequate blood flow to the cerebral arteries(McIvor et al., 1994). Cerebral hemorrhage, which comprises cerebral hemorrhage (bleeding into the brain) and subarachnoid hemorrhage(Montaño et al., 2021), is another kind of stroke. This form of stroke is nearly often accompanied by severe hypertension, which is a key risk factor for cerebral infarction and cerebral hemorrhage because it exacerbates cerebral atherosclerosis(Li et al., 2017). Peripheral arterial disease is atherosclerosis of the abdominal aorta, iliac arteries, femoral arteries and mesenteric arteries and its complications. Atherosclerosis of the lower limb can lead to temporary arterial insufficiency of the lower extremities during exertion (intermittent claudication) or avascular necrosis of the extremities (gangrene)(Guan et al., 2018). In the abdominal aorta, the mediator under the atherosclerotic plaque deteriorates, causing an aneurysm that may fill with thrombus or explode into the abdominal cavity(De Waele et al., 2009). If the mesenteric blood supply arteries caused by atherosclerotic vascular stenosis occlusion occurs, it could cause atheroscle rotic non occlusive mesenteric ischemia, then the intestinal wall ischemic necrosis syndrome caused by blood supply disorder occurs. (Tan VP et al., 2013)In addition, gastrointestinal function is also affected by mesenteric blood supply. Mesenteric insufficiency caused by mesenteric atherosclerosis has become one of the important reasons leading to gastrointestinal function decline in the elderly.

Cholesterol and lipoproteins play crucial roles in atherosclerosis development. Atherosclerotic lesions begin with endothelial cell dysfunction, resulting in alteration of apoB-containing lipoproteins (low-density lipoprotein LDL, very low-density lipoprotein VLDL, remnants) and influx of immune cells(notably monocytes) into the subendothelial region(Feinberg and Jain, 2005; Getz and Reardon, 2018). Macrophages not only internalize retained apoB-containing lipoproteins into foam cells that produce fatty streaks,but it inflammatory pathways are also engaged, leading to increased oxidative stress and cytokine/chemokine release(Tirunavalli et al., 2021), leading to greater LDL/residual oxidation, endothelial cell activation, monocyte recruitment, and foam cell generation. HDL, apoA-I, and endogenous apoE limit lesion development by inhibiting endothelial cell activation, inflammation and oxidative stress, and facilitating cholesterol efflux from foam cells(De Geest et al., 1997). Persistent inflammation results in the transformation of lesions into fibrotic plaques, while macrophage chemoattractants increase the infiltration and proliferation of smooth muscle cells. The extracellular matrix produced by smooth muscle cells forms a persistent fibrous barrier between plaque prothrombotic components and platelets(Linton et al., 2000) Rupture of the thinning fibrous cap increases thrombosis, resulting to ischemic cardiovascular clinical outcomes(Shah, 2014). Infiltration,

retention, and accumulation of lipoproteins in the artery intima have been demonstrated to induce a maladaptive immunological response that influences the genesis, progression, and stability of atherosclerotic lesions(Nakashima et al., 2008). The presence of high levels of modified cholesterol, particularly ox-LDL, is a major risk factor for the development of atherosclerosis. In atherosclerotic plaques, macrophages absorb ox-LDL, resulting in macrophages high in cholesterol, also known as foam cells(Gao et al., 2019). Foam cells contribute to plaque pathogenesis by generating matrix metalloproteinases (MMPs) that breakdown plaque extracellular matrix and by secreting various pro-inflammatory cytokines and chemokines. Atherosclerosis is a chronic lipid-driven arterial inflammatory disease in which cholesterol-rich lipoproteins, particularly LDL(Malekmohammad et al., 2021), accumulate subendothelially in vulnerable artery wall locations, provoking leukocyte infiltration.

Here, how lipids and oxidative stress participate in atherosclerosis via immunometabolism has been reviewed and discussed. As well, main herbal medicines have been summarized in prevention and treatment of this pathological process using integrated Traditional Chinese and Western Medicine. This work will provide a basis for therapy optimization of atherosclerosis from the perspective of lipid and oxidative stress-associated immunometabolism.

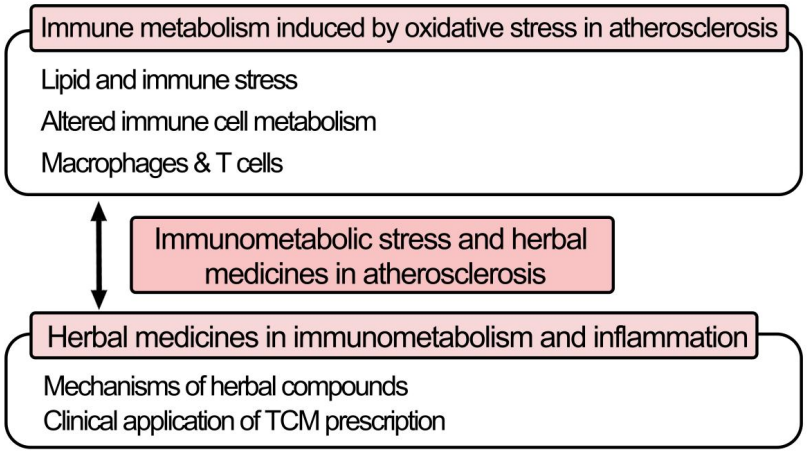

Figure 1. Outline of the review.

OXIDATIVE STRESS-INDUCED IMMUNOMETABOLISM IN ATHEROSCLEROSIS

Atherosclerosis is a chronic lipid-driven inflammatory disease of arterial vessels in which cholesterol-rich lipoproteins, notably LDL, accumulate subendothelial regions of the arterial wall(Wu et al., 2020) that it may be converted to oxidized (ox) LDL in the vascular intima, stimulating blood arteries and innate immune cells(Paiva and Bozza, 2014). Moreover, antigens generated from LDL-derived peptides stimulate T cell activation in atherosclerosis and exacerbate the inflammatory response. Persistent innate and adaptive immune responses enhance plaque formation, ultimately resulting in unstable plaque rupture, which may cause thrombosis and acute clinical symptoms such as myocardial infarction and stroke(Liu et al., 2017). Clinically, atherosclerotic plaques are distinguished by the presence of macrophages and regulatory T cells (Tregs) in excess. Relevant research shows that oxidative stress-activated macrophages and T cells have a greater metabolic propensity for aerobic glycolysis than mitochondrial metabolism(Raud et al., 2018). In contrast, the unoxidized activated immunoregulatory cells, such as M2 macrophages and Tregs, inhibit the metabolism of fatty acids, including oxidation and oxidative phosphorylation. Figure 1 depicts the metabolic alterations generated by oxidative stress in atherosclerosis in macrophages and Treg cells.

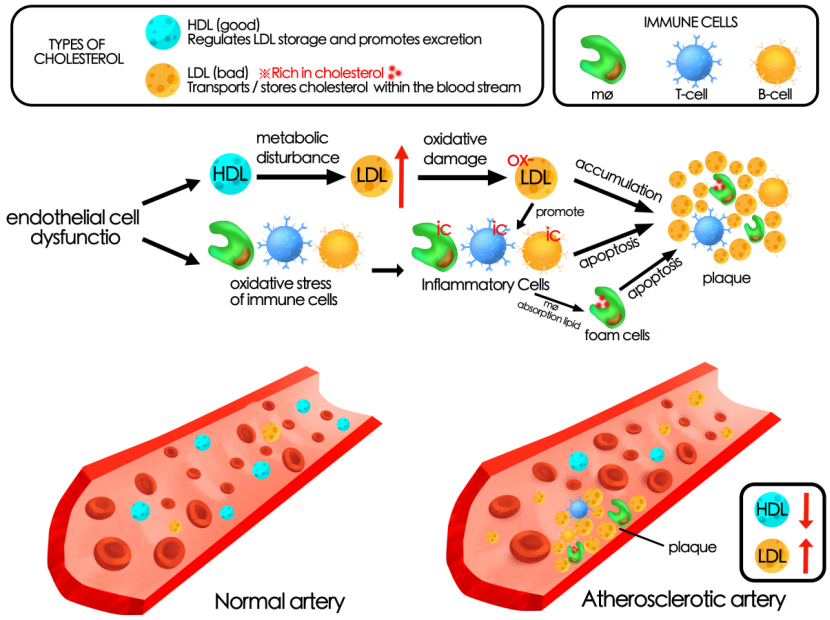

Figure 2. Immunometabolic stress and lipids in atherosclerosis, accompanied by a comparison of normal and plaque arteries.

1 Altered immune cell metabolism in atherosclerosis

In an inflammatory milieu, immune cells are extremely active and must meet various metabolic demands(Ketelhuth and Hansson, 2016; Tabas and Bornfeldt, 2016). Immune cells are capable of adapting to differences in environmental cues (e.g., oxygen, nutrition, growth hormones) as well as energy and biosynthetic requirements upon activation (metabolic reprogramming)(O'Neill et al., 2016). Immune cells have at least seven primary cellular metabolic processes documented(Cole et al., 2018; Winkels et al., 2018),namely immune cell survival, growth, and activation are regulated by the interconnected pathways of glycolysis, the pentose phosphate pathway (PPP), the tricarboxylic acid (TCA) cycle, oxidative phosphorylation (OXPHOS), mitochondrial fatty acid -oxidation (FAO), fatty acid synthesis, and amino acid metabolism. Metabolic alterations in immune cells, also known as metabolic flexibility or reprogramming, not only occur in response to inflammatory mediators and other environmental cues, but are also essential for immune cells to induce inflammation, terminate the inflammatory response, and initiate tissue healing(Ridker et al., 2017).Metabolic changes are the key characteristics that determine the function of immune cells and subsequent disease progression. New insights into the molecular processes that drive immunity and inflammation reveal that changes in intracellular metabolic pathways are significant drivers of immune cell survival, proliferation, and function. Recent research indicates that immunometabolism plays a crucial role in the course of diseases such as atherosclerosis(Hotamisligil, 2017). LDL particles may be converted to oxidized (ox) LDL in the vascular intima, which stimulates blood arteries and innate immune cells. Therefore, antigens generated from LDL-derived peptides stimulate T cell activation in atherosclerosis and exacerbate the inflammatory response,and then enhance plaque formation, ultimately resulting in unstable plaque rupture, which may cause thrombosis and acute clinical symptoms such as myocardial infarction and stroke.

2 Macrophages

Macrophages are an essential component of mammals, distributed throughout the body to maintain immunological homeostasis in tissues(Russell et al., 2019). They display extraordinary plasticity and the ability to

alter their functional phenotype in response to the local environment(Koelwyn et al., 2018). Macrophages must rely on metabolic pathways and metabolic intermediates to govern cell fate to conduct various actions essential for host defense and tissue repair, such as phagocytosis of apoptotic cells and infections (intrinsic cellular processes and exogenous cellular responses)(Groh et al., 2018). Macrophages are a significant component of plaque in atherosclerosis. Retention of cholesterol-rich lipoproteins within the walls of large and medium-sized arteries results in sterile inflammation and promote the accumulation of cholesterol-rich macrophage foam cells that is contribute to plaque development(Robbins et al., 2013; Andrejeva and Rathmell, 2017; van Tuijl et al., 2019). These macrophage foam cells have limited migratory capacity and produce pro-inflammatory cytokines and chemokines that recruit immune response enhancers, such as extra monocytes, T cells, and neutrophils(Lachmandas et al., 2016; Tabas and Lichtman, 2017; Groh et al., 2018). The complex milieu of plaques induces various activation modes of macrophages with a more complex and varied reconfiguration of metabolic pathways than typically activated macrophage phenotypes(O'Neill et al., 2016).

A significant contributor to the development of atherosclerosis is cellular oxidative stress(Moore et al., 2013; Sergin et al., 2014). Mitochondrial oxidative metabolism, NADPH oxidase, peroxidase, NO synthase, cyclooxygenase, and lipoxygenase generate reactive oxygen species (ROS) in macrophages during atherosclerosis(West et al., 2015; Mills et al., 2017). However, oxidative stress alters the transcription and regulation of antioxidant genes in plaque macrophages(Marsch et al., 2014; Jha et al., 2015). The inhibition of mitochondrial transport of the antioxidant glutathione (GSH) exacerbates arterial wall inflammation(Tabas and Glass, 2013). For instance, NADPH oxidase-derived ROS from macrophages has been demonstrated to increase LDL oxidation in artery walls, enhancing the development of macrophage foam cells.

Moreover, mtROS formed as byproducts of the electron transport chain process can damage mitochondrial DNA (mtDNA), proteins, and lipids(Van den Bossche et al., 2017). These have been demonstrated to increase atherosclerosis in mice. Oxidation or release of mitochondrial DNA can activate innate immune signaling pathways in macrophages, including the CpG DNA receptor TLR9, the NLRP3 inflammasome, and the cyclic GMP-AMP synthase (cGAS) - Stimulator of interferon genes (STING) pathway(Guo et al., 2015; Cochain et al., 2018). Relevant studies have also confirmed that reducing mitochondrial oxidative stress in macrophages decreases atherosclerotic load in mice and avoids inflammation in plaques(Van den Bossche et al., 2016; Correction to: Mitochondrial respiration is reduced in atherosclerosis, promoting necrotic core formation and reducing relative fibrous cap thickness, 2018). Oxidative stress greatly influences the metabolic reprogramming of macrophages, leading to a greater dependence on glycolysis(Folco and Sukhova, 2014; Nomura et al., 2016). The key to this metabolic transition is activating the hypoxia-inducible factor 1 (HIF-1) transcription factor, which stimulates the expression of GLUT-1 and glycolytic enzymes (such as HK, PFK, and PFKB3), enhances glucose absorption, and restricts oxidative phosphate acidification and lactic acid generation(Baardman et al., 2015; Tan et al., 2015; Shirai et al., 2016). Activation of the HIF-1 pathway, particularly in macrophages, regulates oxidative stress-induced metabolic alterations and inflammatory consequences in atherosclerotic lesions(Mills et al., 2018). In atherosclerotic plaques, oxidative stress-induced HIF-1 expression leads to pathologically elevated GLUT1, GLUT3, HK1, and HK2 in macrophages, whereas macrophages lacking HIF-1 produce inflammatory genes (e.g., monocytogenes)(Stienstra et al., 2017; Miska et al., 2022). This pathogenic response is characterized by decreased expression of nuclear chemoattractant protein-1 (osteopontin) and apoptosis, suggesting that HIF-1 activation and enhanced glycolysis are essential(Littlewood-Evans et al., 2016).

3 T cells

To prevent autoimmunity and chronic inflammation, Tregs can dampen overactive immune responses(Tabas and Lichtman, 2017; Baardman and Lutgens, 2020). Treg deficiency or dysfunction is linked to the pathogenesis of atherosclerosis(Newton et al., 2016; Pacella and Piconese, 2019; Saigusa et al., 2020). More and more data suggest that the intracellular metabolism of Tregs is a critical regulator of their proliferation, inhibitory activity, and stability(Buck et al., 2015; Georgiev et al., 2019; Sakaguchi et al., 2020). Foxp3 inhibits glycolysis (NAD+ consumption pathway) and promotes monophosphate (NAD+ production) to compensate for the drop in NAD+ levels and enable Treg to tolerate a low-glucose, high-lactate environment(Tomas et

al., 2018; Ketelhuth et al., 2019). Oxidative stress and other factors downregulate the expression of Foxp3 and disrupt this metabolic advantage, resulting in decreased Treg function and disease development(Marsch et al., 2013; Hsu and Lai, 2018).

In the peculiar milieu of atherosclerotic plaques, ROS causes oxLDL synthesis, and intracellular accumulation following oxLDL uptake inhibits the mevalonate pathway(Wang et al., 2016; Mailer et al., 2017), downregulates Foxp3 expression, and reduces the atheroprotective capacity of Tregs(De Rosa et al., 2015; Becker et al., 2017; Kälin et al., 2017). On the other hand, the hypoxic environment of atherosclerotic plaques regulates HIF-1 via oxidative stress, promotes the shunting of pyruvate to lactate, upregulates glycolysis(Cole et al., 2015; Polyzos et al., 2015; Forteza et al., 2018), and causes Foxp3 ubiquitination and proteasomal degradation, which affects Treg function. While HIF-1 increases suppressive activity in Tregs, it decreases their migratory capacity, indicating that glycolysis is essential for Treg migration and that oxidative stress leads to atherosclerosis(Chang et al., 2013; Gerriets et al., 2016). The precise effect of HIF-1 on Tregs in sclerotic plaques requires further investigation(Gerriets et al., 2015). The downregulation of Foxp3 and the increase in glycolysis are essential to this pathological response(Gaddis et al., 2018).

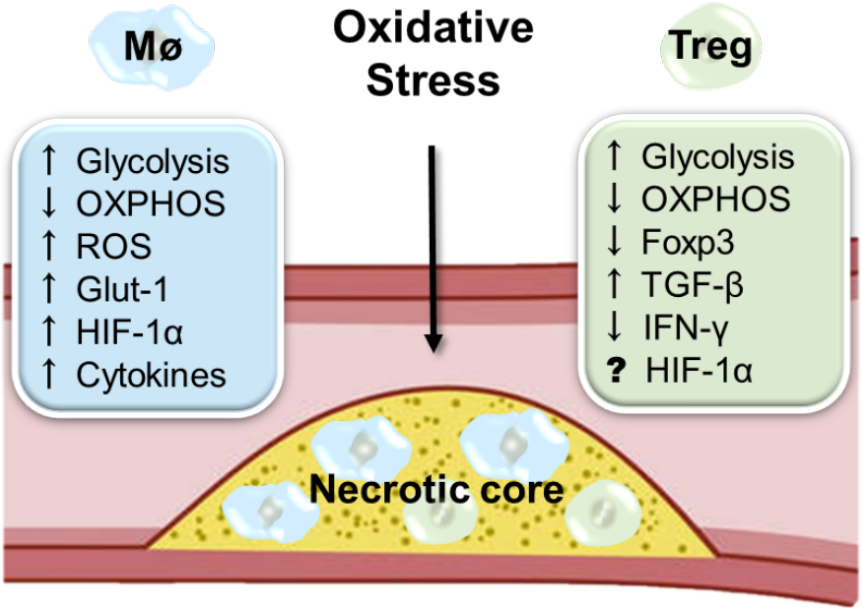

Figure 3. Changes in substance content of immune metabolism induced by oxidative stress in atherosclerosis. Glycolysis plays a crucial role in macrophages and T cells in the pathogenic processes associated with atherosclerotic oxidative stress. Changes in immune cell metabolism can affect plaque formation and stability.

MECHANISMS OF HERBAL MEDICINES ON IMMUNOMETABOLISM AND INFLAMMATION IN ATHEROSCLEROSIS

Recent studies have shown that natural compounds such as flavonoids, alkaloids and teperoids can effectively alleviate atherosclerosis. The mechanisms of action of herbal compounds in this review are summarized as follows. Table 1 below lists some of the herbal mechanisms of action under the paper introduction.

1 Mechanisms of herbal compounds

1.1 Alkaloids

Coptisine inhibits the activation of the MAPK signaling pathway and the nuclear translocation of NF-kB to

have an anti-inflammatory action(Feng et al., 2017). Leonine can balance NO generation driven by ox-LDL in human umbilical vein endothelial cells are and block NF-ϰB/P65 nuclear translocation(Peng et al., 2020), thereby reducing atherosclerosis related inflammation. 13-Methylberberine exerts a cytoprotective effect by inhibiting the activation of NLRP3 inflammasome via autophagy induction in an H2O2-induced HUVEC cell injury model(Ding et al., 2021). Activating autophagy through the AMPK/mTOR signaling pathway, Berberine suppresses inflammatory responses(Fan et al., 2015; Ke et al., 2020; Ma et al., 2020d; Tan et al., 2020). Dendrobium suppresses inflammation, oxidative stress, apoptosis, and aging utilizing ox-LDL autophagy mediated by FKBP1A(Ning et al., 2020; Lou et al., 2022; Wen et al., 2022).

1.2 Terpenoids

Terpenoids are a class of naturally occurring organic chemicals. Most of them are polycyclic structures containing oxygen-containing functional groups and have a wide range of pharmacological effects. Previous studies have shown that natural terpenoids can significantly reduce atherosclerotic lesion area.

MAPK pathway. The iridoid glycoside geniposide reduces the ox-LDL-dependent increase in CD36 expression by decreasing the phosphorylation of p38 MAPK, ERK, JNK, and NF-ϰB p65, inhibiting foam cell production and inflammation. Ginsenoside compound K (CK) inhibited ox-LDL-induced inflammation and apoptosis in HUVEC cells by suppressing the NF-ϰB, p38, and JNK-MAPK signaling pathways. CK also reduced macrophage inflammation and foam cell production.

AMPK pathway. Alisitol A can successfully block arterial plaque formation in $ApoE^{-/-}$ mice fed a high-fat diet, prevent the progression of atherosclerosis, and drastically diminish the expression of inflammatory cytokines in the aorta, including ICAM-1, IL-6, and MMP. Alisitol B 23-acetate enhances cholesterol efflux from dendritic cells, enhancing immune-inflammatory responses and reducing dyslipidemia and inflammation in mice with advanced atherosclerosis. Geniposide coupled with notoginsenoside R1 can improve blood lipid levels and plaque formation in high-fat diet fed $ApoE^{-/-}$ mice, as well as suppress the release of serum inflammatory markers and oxidative stress factors. The combination of geniposide and Panax notoginsenoside R1 reduces the expression of pyrin domain-containing protein 3 (NLRP3) inflammasome-related proteins and Bax/Bcl2/caspase-3 pathway-related proteins. It inhibits H_2O_2-induced human umbilical vein endothelial cells (HUVECs) inflammatory response and apoptosis, primarily related to Nrf2/HO-1 signal activation. The information presented above suggests that geniposide and notoginsenoside R1 can inhibit the NLRP3 inflammasome and the Bax/Bcl2/caspase-3 pathway by activating the AMPK/mTOR/Nrf2 signaling pathway, hence decreasing inflammation and apoptosis in atherosclerosis efficiently.

PI3K/Akt pathway. Ilexgenin A inhibits the expression of active inflammatory cytokines generated by oxidized LDL in THP-1 cells, including IL-6, IL-1, and tumor necrosis factor-α (TNF-α). Moreover, Ilexgenin A reduced ox-LDL induced phosphorylation of phosphatidylinositol 3-kinase (PI3K), protein kinase B (Akt), IKK, and NF-ϰB activity. Gynostemma saponin XVII can effectively decrease the lipid content of apolipoprotein E, boost the expression of antioxidant enzymes, reduce the size of atherosclerotic lesions, and prevent ox-LDL induced endothelial damage. By restoring the normal redox state, upregulating the ratio of Bcl-2 to Bax, and suppressing the expression of cleaved caspase-3, gynoside XVII exerts its effects. Notably, treatment with Gypenoside XVII primarily elevated ERα expression, but not ERβ. Due to its antioxidant characteristics, these findings imply that Gypenoside XVII can mitigate atherosclerosis via the ERα mediated PI3K/Akt pathway. Additionally, Gypenosides can reduce blood cholesterol levels, atherosclerotic plaque formation, and aortic intimal thickening. This impact may result in the ability of Gypenosides to activate the PI3K/Akt/Bad signaling pathway and regulate apoptosis in the aorta.

NF-ϰB signaling pathway. Artesunate can block LPS induced elevation of HIF-1 expression and activate the NF-ϰB signaling pathway, reducing atherosclerotic plaque. Catalpol suppressed NF-ϰB transcriptional activity and reduced the overexpression of Nox4, ICAM-1, VCAM-1, and MCP-1 proteins. Catalpol raised the expression of Bcl-2 protein, decreased the expression of Bax, caspase-3, and caspase-9 protein, and inhibited endoplasmic reticulum stress-related sensor activation. Catalpol ameliorates blood cell oxidation, apoptosis, and inflammation by decreasing Nox4/NF-ϰB and endoplasmic reticulum stress and is correlated

with enhanced ERα expression and macrophage polarization inhibition.

In addition, the following may be included in the mechanism of action of terpenoids on atherosclerosis: Paeoniflorin can inhibit the HMGB1-RAGE/TLR-2/TLR-4-NF-ϰB pathway; Ginsenoside Rb1 can regulate miR-33 and its target genes PEDF; Ginkgolide B can inhibit PCSK-9, block the NF-ϰB signaling pathway, and inhibit the generation of ROS; Diosgenin can regulate the PGC-1α/ERα pathway; Triptolide can activate liver X receptor α (LXRα)expression.

1.3 Flavonoids

Flavonoids have previously been proposed to affect the development of atherosclerosis through a variety of mechanisms, including improved lipid profiles, reduced LDL-oxidation, and reduction of many inflammatory cells and mediators.

PPAR-γ signaling. Total flavonoids of *Psoralea corylifolia*inhibits adhesion molecules' mRNA and protein expression (VCAM-1, ICAM-1, and E-selectin) to prevent leukocyte and endothelial cell adhesion; inhibits the NF-ϰB pathway to avoid oxidative hypodensity(Wang et al., 2018; Ma et al., 2022). Inflammation of HUVEC induced by lipoprotein stimulation(Zhuo et al., 2019); activation of cholesterol efflux via PPARγ-ABCA1/ABCG1 significantly ameliorated macrophage-directed foam cell production generated by ox-LDL and reduced atherosclerotic lesion size and intraplaque macrophage proliferation(Xue et al., 2017; Zhang et al., 2021). Anti-atherosclerosis activity of formononetin involves 14 hub genes intimately associated with inflammation, oxidative stress, and apoptosis(Ma et al., 2020a; Duan et al., 2022; Liu et al., 2022). It reduces ox-LDL-induced endothelium damage in HUVECs via activating the PPAR-γ signaling pathway(Sun et al., 2017; Meng et al., 2022).

Nrf2 pathway. By upregulating Wnt/β-catenin and Nrf2 signaling pathways, vitexin rescued HUVECs from damage caused by high hyperglycemia(Yang et al., 2020). G protein-coupled estrogen receptor (GPER) mediated activation of the PI3K/AKT/Nrf pathway is responsible for the therapeutic effects of kaempferol on atherosclerosis(Luo et al., 2017; Feng et al., 2021). Homoplantaginin, and dihydrohomoplantagin prevent enhanced ROS production, ERK phosphorylation, and nuclear translocation of NF-ϰB(Mo et al., 2018), promote nuclear translocation of Nrf2 and boost the antioxidant downstream HO-1 protein in HUVECs and plaque endothelial cells, thereby decreasing atherosclerosis(Zhang et al., 2022a).

MAPK signaling pathway. Puerarin can considerably decrease the mRNA expression levels of IL-6 and TNF- in oxidized low-density lipoprotein (ox-LDL) stimulated vascular smooth muscle cells (VSMC), reduce MDA generation, boost SOD activity, and inhibit p38 and JNK activation(Hu et al., 2016; Chang et al., 2021). Myricetin can suppress early plaque development in atherosclerosis, prevent and ameliorate H_2O_2 induced endothelial damage related to dramatically decreasing p53 gene expression(Cao et al., 2019), activating caspase-3 and MAPK signaling pathways, and altering pro-apoptotic and anti-apoptotic gene expression patterns(Sun et al., 2013; Hu et al., 2020). Icariin can significantly inhibit blood lipid levels, serum IL-6 and TNF-α concentrations, tissue mRNA concentrations, and p-p38 MAPK expression(Ma et al., 2020b; Li et al., 2021a).

NF-ϰB pathway. Total flavonoids of *Astragalus membranaceus*suppressed the activity of ABCA1/G1 and reduced inflammation by inhibiting the miR-33 and NFB pathways(Meng et al., 2021). Morin hydrate can enhance vascular endothelial autophagy, lower tumor necrosis TNF-α and IL-6 expression, and increase vascular endothelial autophagy to treat atherosclerosis(Bo and Zhishan, 2017). By expanding the LXRα-ABCA1/ABCG1 pathway and decreasing NF-ϰB activation, Kuwanon G dramatically reduced fat accumulation and cytokine mRNA levels in macrophages(Liu et al., 2018a).

1.4 Glycosides

Through MAPKs, AP-1, and NF-ϰB p65 signaling pathways, amygdalin can relieve atherosclerosis and exert anti-inflammatory actions(Wang et al., 2020a). *Ganoderma lucidum* triterpenes and *Ganoderma lucidum* polysaccharides can reduce ROS and malondialdehyde (MDA) by preventing the up-regulation of NF-ϰB p65 and associated receptor LOX-1; inhibit the inflammatory polarization of macrophages and reduce TNF-α

via modulating Notch1 and DLL4 pathways(Ku et al., 2021; Wei et al., 2021). Crocin lowers adipogenesis and decreases inflammation by boosting M2 macrophage polarization and potentially reducing NF-ϰB p65 nuclear translocation(Li et al., 2018; Lin et al., 2021). 2,3,5,4'-Tetrahydroxy-stilbene-2-O-β-D-glucoside can suppress inflammation by lowering blood levels of IL-6, TNF-α, VCAM-1, and MCP-1. It also significantly reduced the production of atherosclerosis plaques.*Dendrobium huoshanensis* polysaccharide increased superoxide dismutase (SOD) activity, decreased plaque formation, decreased neutrophil recruitment, and decreased total cholesterol (TC), triglyceride (TG), malondialdehyde (MDA), and ROS levels in parallel flow chambers, ameliorating low-shear stress-induced oxidative stress and endothelial cell dysfunction(Fan et al., 2020). Gastrodin and Gastrodia extract can lower TC and LDL-C levels in atherosclerosis mice's peripheral blood while rescuing gut bacteria(Li et al., 2020; Liu et al., 2021). *Poria cocos* polysaccharides block TLR4/NF-ϰB pathway activation in the aorta, lower serum inflammatory mediators (,TNF-α, IL-6 and NO) and lipids (low-density lipoprotein cholesterol, triglycerides, and TC)(Huang et al., 2018; Sun et al., 2020; Li et al., 2021b).

1.5 Phenylpropanoids

Curcumin can turn down LCN2, interfere with the ERK1/2 signaling pathway for ROS(Yuan et al., 2019a), stop aldosterone from making vascular smooth muscle cells make C-reactive protein, control the AMPK/mTOR/p70S6K signaling pathway to reduce endothelial lipotoxicity and control autophagy(Pai et al., 2021; Ji et al., 2022), and improve the hardening of the arteries caused by atherosclerosis(Wan et al., 2016; Zhang et al., 2020; Xiang et al., 2021; Zhao et al., 2021a). Paeonol stops the activation of the downstream NLRP3 inflammasome and NF-ϰB pathway by increasing the exosomal miR-223(Liu et al., 2018b; Shi et al., 2020), promoting the expression of miR126(Yuan et al., 2016), up-regulating the expression of caveolin-1, and decreasing the expression of STAT3 and p-STAT3(Tang et al., 2020). Block PI3K/Akt/NF-ϰB signaling pathway(Lei et al., 2019; Li et al., 2019; Liu et al., 2020b). Salvianolic acid A can increase the activity of antioxidant enzymes, up-regulate the nuclear factor erythroid 2-related factor 2/heme oxygenase-1 pathway, down-regulate the expression of p47phox and p22phox, reduce oxidative stress by a lot, and block the toll-like receptor 4/nuclear factor erythroid 2-related factor 2 pathway(Song et al., 2019). The factor kappaB pathway decreases pro-inflammatory mediators, lowers serum levels of hs-CRP, and stops the NLRP3 inflammasome and NF-ϰB signaling pathways from turning on(Ma et al., 2020c). Salvianolic acid B can reduce inflammation through the MAPKs/NF-ϰB signaling pathway(Zhang et al., 2022b).

1.6 Quinones

The main mechanisms of action of Tanshinone IIA in the treatment of atherosclerosis include: interfering with RAGE and NFB and down-regulating downstream inflammatory factors, including ICAM1, VCAM, and MMP2, 3, and 9(Zhao et al., 2016a); activating NRF2 to inhibit ferroptosis(He et al., 2021); mediating miR-130b and WNT5A(Yuan et al., 2020); inhibiting miR-375 to reduce atherosclerosis, activate KLF4(Chen et al., 2019), and promote autophagy and M2 polarization in macrophages(Zhao et al., 2021b). By decreasing CLIC1 expression and membrane translocation, Tanshinone IIA Sodium sulfonate exhibits antioxidant and anti-inflammatory actions(Zhu et al., 2017); Dihydrotanshinone I stabilizes susceptible plaques by inhibiting rip3-mediated macrophage necrosis and suppressing NOX4/NF-ϰB signaling pathway directed by LOX-1(Zhao et al., 2016b). Shikonin can significantly ameliorate atherosclerosis in HHcy ApoE$^{-/-}$ mice due to its ability to prevent the inflammatory activation of CD4+ T cells via PKM2 dependent metabolic inhibition(Lü et al., 2020).

TABLE 1 | Mechanisms of Herbal medicines

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Notes: In Level, A represents in vitro; B represents in vivo; B1 represents rats; B2 represents mice; B3 represents rabbit; C

2 Mechanisms of Chinese medicines and formulae

2.1 NF-κB signaling pathway

By modulating the expression of KLF2 and the NF-κB signaling pathway in HUVECs, Yiqi-Huoxue granule can inhibit PAI-1 and TF, exhibiting considerable antithrombotic action(Wu et al., 2019). Xiao-Zhi formula

can reduce atherosclerotic plaques(Li et al., 2021c), control blood lipid levels and serum TMAO levels, and increase reverse cholesterol transport in macrophages by increasing the expression of cholesterol efflux-related genes PPARγ/LXRα/ABCA1/ABCG1(Mao et al., 2012; Gao et al., 2018), thus suppressing inflammation. Through MAPK, ERK5/STAT3, and AKT/NF-κB p65 signaling pathways, Taoren Honghua drug mitigate atherosclerosis and exert anti-inflammatory effects(Wang et al., 2020b). By reducing the expression of the AP-1 and AKT/NF-κB signaling pathways, Suxiao Jiuxin Pill suppresses CD137(L i et al., 2011). The Shexiang Baoxin Pill can decrease lipid absorption and increase lipid outflow. Shenmai Fang decreases the mRNA and protein expressions of IL-1, IL-6, TNF-α, and intercellular adhesion molecules and reduces lactate dehydrogenation enzyme content in the supernatant of lipopolysaccharide-injured cardiac microvascular endothelial cells to play an anti-inflammatory role.

2.2 NRF2 pathway

BuYangHuanWu decoction promotes revascularization in HLI db/db mice by targeting antioxidant, anti-inflammatory, and angiogenesis via the AKT/GSK3β/NRF2 pathway(Liu et al., 2020a; Bao et al., 2021).*Salvia miltiorrhiza* extract stimulates HO-1 expression via the PI3K/Akt-MEK1-Nrf2 pathway(Lee et al., 2012), which lowers intracellular ROS generation and protects cells from oxidative stress-induced cell damage(Guo et al., 2021). The alcohol extract of *Schisandra chinensis* decreased the aortic plaque area, adjusted blood lipid levels, increased antioxidant enzyme activity, reduced malondialdehyde levels, up-regulated the expressions of Nrf-2 and HO-1, and decreased oxidized LDL, endothelin-1, and thromboxane B2 levels while increasing 6-ketoprostaglandin F1 levels(Chen et al., 2018).

2.3 ABCA1 pathway

The PPAR-LXR-ABCA1 pathway is involved in lipid regulation and inflammatory activity in Fufang Guanxinkang. *Hirudo nipponica*extraction can significantly reduce endothelial cell inflammatory injury and the development and death of macrophage foam cells by regulating the LOX-1/LXR-α/ABCA1 pathway(Lu et al., 2019a), avoiding atherosclerosis. Polypeptides in *Hirudo nipponica* could be the active ingredients(Xiong et al., 2015; Lu et al., 2019b).

TABLE 2 | Mechanisms of Chinese medicines and formulae

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Notes: In Level, A represents in vitro; B represents in vivo; B1 represents rats; B2 represents mice; B3 represents rabbit; C

3 Clinical examples of Chinese medicines and formulae treating atherosclerotic disease

In addition to the mechanism of action of the chemical components of Chinese herbal medicine described in the previous chapter, there have been many research results on the application of Chinese herbal medicine to clinical aspects in recent years. In a recent study, 1212 patients with focal carotid intima-media thickness (IMT)[?]1.2 mm received the traditional Chinese medicine Tongxinluo(TXL) or placebo capsules in addition to usual care. Studies have found that Tongxinluo can delay the progression of carotid IMT, plaque area and vascular remodeling with good safety(Zhang M et al.,2019). Percutaneous coronary intervention (PCI)

is the main method for the treatment of coronary atherosclerotic heart disease (CHD). However, many patients develop restenosis within 6 months after PCI. According to the existing research evidence, a total of 1383 patients after PCI clinical treatment study found that Chinese herbal medicine can prevent restenosis. Traditional Chinese medicine can reduce the rate of restenosis and angina recurrence after PCI, even if the evidence is limited(Wu J et al., 2019). Of the 574 potential atherosclerotic targets identified in the latest study, cassia had 99 overlapping targets. Topological analysis of Cytoscape revealed that cassia seed has positive regulatory effects on smooth muscle cell proliferation, inflammatory response, tumor necrosis factor (TNF) signaling pathway, vascular endothelial growth factor (VEGF) signaling pathway and arachidonic acid (ARA) metabolism. These results indicate that the anti-atherosclerosis mechanism of cassia seed has multi-component, multi-target and multi-pathway mechanism(Zhang, Sen MDa et al., 2019). A 2022 study investigated the effect of traditional Chinese medicine Dengzhanshengmai capsule(DZSM) and aspirin on carotid intima-media thickness (IMT), involving 150 patients. Analysis of the treatment results showed that DZSM was no less effective than aspirin in the treatment of carotid atherosclerotic plaque, and its safety was better than aspirin. This study offers new avenues for treating carotid plaque, particularly in patients with aspirin intolerance(Shen X et al., 2022). Qing-Xin-Jie-Yu Granule (QXJYG) is an integrated traditional Chinese medicine formula used to treat atherosclerotic (AS) cardiovascular diseases. Clinical studies have shown that QXJYG inhibits ferroptosis in vulnerable AS plaques partially via the GPX4/xCT signaling pathway.(Zhang J et al., 2023). In addition, PADMA 28, a Tibetan medicinal preparation used in China, has been shown to be effective in reducing atherosclerosis symptoms in patients with mild hypercholesterolemia by reducing lipid oxidation capacity(Brunner-La Rocca HP et al., 2005).

DISCUSSION

1 Relationship between immunometabolic stress and atherosclerosis

The underlying cause of heart attacks and strokes is atherosclerosis(Jones et al., 2021). High LDL cholesterol levels and apolipoprotein B (apoB) 100, the primary structural protein of LDL, are directly connected with the risk of atherosclerotic cardiovascular events, according to studies (ASCVE)(Tokgozoglu and Kayikcioglu, 2021). Infiltration and retention of apoB-containing lipoproteins in artery walls are critical beginning events that initiate an inflammatory response and promote atherosclerosis progression(Banaszak and Ranatunga, 2008). Endothelial dysfunction is caused by arterial damage, which promotes the alteration of apoB-containing lipoproteins and monocyte infiltration into the subendothelial region. Internalization of apoB-containing lipoproteins by macrophages increases the development of foam cells, a defining characteristic of the fatty streak phase of atherosclerosis(Laccotripe et al., 1997). Inflammation of macrophages increases oxidative stress and cytokine/chemokine release, leading to an increase in LDL/residual oxidation, endothelial cell activation, monocyte recruitment, and foam cell formation. All lipoproteins containing apoB are atherogenic, and residual lipoproteins high in triglycerides and Lp(a) cause atherothrombosis(Enas et al., 2019).

2 Significance of traditional Chinese medicines and formulae in regulating immunometabolic stress and treating atherosclerosis

Current studies have confirmed that endothelial cell apoptosis is the first step of atherosclerosis. Excessive endothelial cell apoptosis induced by atherosclerosis risk factors is a preliminary event in the development of atherosclerosis and may be a target for prevention and treatment of atherosclerosis. The extracts of natural herbs have obvious effects on the regulation and improvement of immune metabolism pathways. Accumulating evidence suggests that natural drugs have great potential to treat atherosclerosis by inhibiting endothelial cell apoptosis.(Duan H et al., 2021)However, at present, most of the clinical studies have only a very small sample size, and the lack of high-quality clinical trials hinders the application of herbal medicine in patients with diabetic atherosclerosis.

3 Recommendations for future atherosclerosis research

3.1 Mechanisms of lipid action

The retention of various lipoproteins(LDL,HDL,IDL,VLDL...) on the arterial wall is a necessary factor that causes oxidative immune stress, immune cell necrosis and accumulation, and then they leads to the formation of atherosclerosis. For example, lipoprotein lipase (LPL) and hepatic lipase convert plasma VLDL to intermediate low-density lipoprotein (IDL) and LDL particles high in cholesterol esters by hydrolysis of triglycerides (HL). LDL becomes more sensitive to oxidation and aggregation when it binds to proteoglycans, boosting foam cell production and proinflammatory reactions. In addition, OxLDL, which is converted from LDL by peroxidation, not only causes macrophages to release inflammatory cytokines and stimulate other inflammatory cell types, leading to macrophage death, but also induces many cellular responses in macrophages, dendritic cells, endothelial cells, T cells, and smooth muscle cells. Thus increases inflammation, lesion development, atherosclerosis, and unstable atherosclerotic plaques. Current and future obstacles include the need to characterize better the anti-atherosclerotic features of HDL in health and the pro-atherosclerotic impacts of HDL in illness to manage HDL activity better and possibly prevent and cure CVD. Interfering with the retention of apoB-containing lipoproteins in the artery wall is a possible atherosclerosis prevention method.

3.2 Immunometabolic mechanisms of macrophages

Smoking, hypertension, dyslipidemia, sedentary lifestyle, and diabetes are risk factors that impact the advancement of atherosclerosis(Santos et al., 2008). The significant residual cardiovascular risk persists after adequate medical treatment with antihypertensive and cholesterol-lowering medications such as statins. Targeting the inflammatory components of atherosclerosis and creating methods to modify the inflammatory phenotype of plaque macrophages are thus of significant interest. In a recent major clinical trial, the hopeful result that antibody-mediated IL-1 suppression lowers cardiovascular events in high-risk persons lends confidence to this strategy's efficacy(McCulloch et al., 2019). The immunometabolic pathways that influence the inflammatory response of macrophages during atherosclerosis may represent the emergence of novel targets for therapeutic intervention.

3.3 Other mechanisms of immunometabolic action

Whether these pathways may represent new therapeutic intervention targets. M1 macrophages, Th1, and Th17 cells are often catabolic, whereas M2 macrophages and Treg are more anabolic(Zha et al., 2022). Apolipoprotein B lipoproteins are deposited in artery walls due to an imbalance in cellular and systemic cholesterol homeostasis(Sniderman et al., 2019). Under the effect of oxidative stress, it becomes pro-inflammatory and stimulates the migration of monocyte-derived cells into the subendothelial region. The transformation of monocytes into macrophages. Plaque macrophages absorb modified LDL, most of which become lipid-rich foam cells but can also be activated by lipoprotein-derived antigens, including phospholipids, cholesterol crystals, and apolipoprotein B peptides(de Graaf et al., 1991). In plaques, macrophages are exposed to oxidative stress and multiple pro-inflammatory cytokines(Cáceres et al., 2020), forming a complex microenvironment with metabolic reprogramming of glycolysis promotion and oxidative phosphorylation inhibition, releasing lipid content and other inflammatory debris to form a necrotic core, resulting in permanent macrophage inflammation, low-grade inflammation, and long-term plaque progression(Ip et al., 2017). This process's critical metabolic processes include arginine metabolism, glycolysis, and oxidative phosphorylation (OXPHOS). First, the amino acid arginine metabolism is the basis for M1 and M2 classification. Second, inflammatory macrophages must swiftly discharge their inflammatory contents to rapidly supply energy and biosynthetic products(Aghasafari et al., 2019). In contrast, anti-inflammatory macrophages require a more stable energy source for a long-lasting repair response. Consequently, inflammatory macrophages demonstrate increased glucose absorption via the glucose transporter GLUT1 and accelerated aerobic glycolysis(Mattmiller et al., 2011), while oxidative phosphorylation via the TCA cycle is reduced. During this process, pyruvate, produced by the glycolytic pathway, is transformed into lactate, creating two ATP molecules and causing ROS(Olsen et al., 2013). Increasing the flux of glucose intermediates concurrently increases PPP, increasing NADPH synthesis, which is essential for cholesterol and fatty acid synthesis and required for phagocytosis and endoplasmic reticulum(Ying et al., 2021). High ratios of OXPHOS and FAO are a hallmark of anti-inflammatory macrophages.Both pyruvate and fatty acids enter the whole TCA

cycle in the form of acetyl-CoA in these macrophages(Stacpoole, 2017), resulting in the continual synthesis of ATP via oxonate and the activation of genes involved in tissue healing. However, the significance of FAO in anti-inflammatory macrophage activity has recently been questioned because etomoxide-mediated FAO suppression or CPT2 impairment, an enzyme essential for fatty acid import, did not affect the M2 phenotype(Ma et al., 2018). It has also been established that the availability and metabolism of specific amino acids regulate innate immune cell responses. Glutathione can control macrophage IL-1β secretion, NO generation, and M2 polarization.Arginine metabolism is increased through the citrulline route and iNOS, leading to the generation of nitric oxide, which is related to the M1 phenotype(Early et al., 2018). Acetyl-CoA and S-adenosylmethionine can control epigenetic enzymes that acetylate and methylate histones through distinct pathways, thereby converting metabolic rearrangement into regulating gene expression and macrophage function(Su et al., 2016). In addition, the microenvironment of atherosclerotic plaques has a harmful impact on inhibitory Treg function. To improve immunological tolerance and homeostasis, Tregs dampen exaggerated inflammatory responses(Yuan et al., 2019b).This particular subpopulation of CD4+ T cells is characterized by constitutively high surface expression of the IL-2 receptor alpha chain (CD25)(Sakaguchi et al., 1995). Moreover, forkhead box protein 3 (Foxp3) is a lineage-specific marker and master regulator of Tregs. Tregs limit inflammatory responses by several methods, such as reduction of effector T cell proliferation, production of immunoregulatory cytokines such as IL-10 and transforming growth factor beta (TGFβ), and through cytotoxic T lymphocyte-associated protein 4 (CTLA-4) (APCs). Oxidative stress stimulates the synthesis of oxidized LDL particles, induces the proteasomal degradation of Foxp3, decreases OXPHOS in Treg, diminishes the suppressive Treg phenotype, and inhibits its activity CTRP6(Neupane et al., 2019). Further investigation of how the aforementioned metabolic mechanisms of macrophages and Treg cells are interrelated and combine to create an inflammatory response in atherosclerosis.

SUMMARIZE

In conclusion, this manuscript explains how lipids and oxidative stress-induced immune cell metabolism is reorganized and changed in atherosclerosis, as well as traditional Chinese medicines, compounds, and active ingredients that interfere with this process in the long-term medical practice of traditional Chinese medicine, to discover and identify immunometabolic markers/targets for the prevention and treatment of atherosclerosis. In terms of lipids, the retention of lipoproteins in the vascular wall of arteries is an important factor in triggering atherosclerosis. In the pathology of atherosclerosis caused by oxidative stress, glycolysis is a vital part of the response of macrophages and T cells. Changes in the metabolism of these immune cells affect the growth and stability of plaques. Even though these results look good, there is insufficient research on how immune cell metabolism responds to pathological changes in vivo. Putting any therapies mentioned above into practice in the real world is still hard. More early research funding and large-scale randomized clinical trials will help find new ways to prevent and treat this disease.

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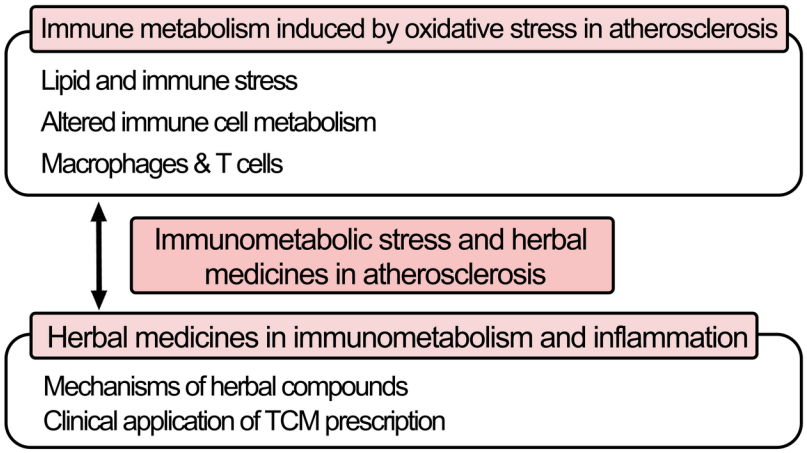

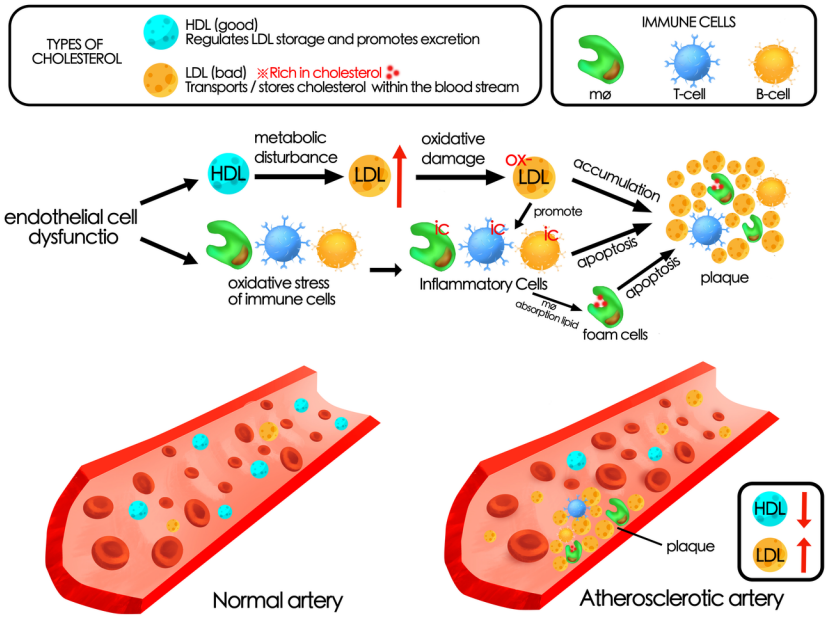

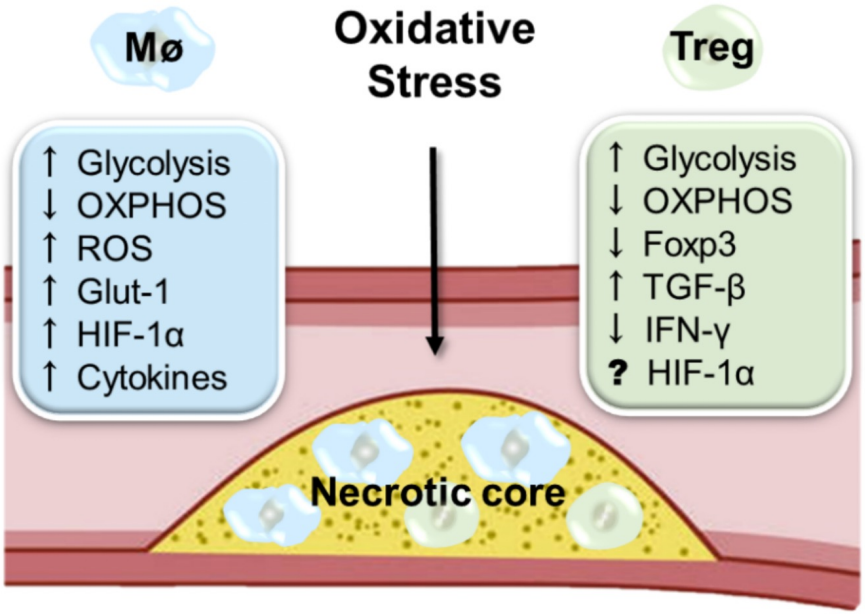

TABLE 1 | Mechanisms of Alkaloids

No.	components and herbs	Level	Mechanism on oxidative stress	Mechanism on inflammation	reference
1	13-Methylberberine	A		inhibiting NLRP3 inflammasome activation via autophagy induction in HUVECs	Peng et al., 2020
2	Berberine	B2		changed Ampk and Nf-κb gene expression	Ma et al., 2020
3	Berberine	B1		promoting autophagy	Ke et al., 2020
4	Berberine	B2	reduced aortic reactive oxygen species (ROS) generation and reduced the serum levels of malondialdehyde (MDA), oxidized low-density lipoprotein (ox-LDL), and interleukin-6 (IL-6)		Tan et al., 2020
5	Berberine	A		activation of the AMPK/mTOR signaling pathway.	Fan et al., 2015
6	betaine	B1		Betaine could inhibit the development of atherosclerosis via anti-inflammation.	Fan et al., 2008
7	Coptisine	B2		inhibiting activation of MAPK signaling pathways and NF-κB nuclear translocation	Feng et al., 2017
8	Dehydrocorydaline	A,B2		targeting macrophage p65- and ERK1/2-mediated pathways	Wen et al., 2021
9	Dendrobine	A	FKBP1A-involved autophagy ox-LDL-treated HUVECs	FKBP1A-involved autophagy ox-LDL-treated HUVECs	Lou et al., 2022
10	Leonurine	A,B2	suppressed the NF-κB signaling pathway	balanced NO production and inhibited NF-κB/P65 nuclear translocation	Ning et al., 2020
11	Tetrahydropalmatine	B2 (Golden hamster	protects against HLP through the TLR4-NF-κB signaling pathway	protects against HLP through the TLR4-NF-κB signaling pathway	Ding et al., 2021

Notes: In Level, A represents in vitro; B represents in vivo; B1 represents rats; B2 represents mice; B3 represents rabbit; C represents network pharmacology.

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TABLE 2 | Mechanisms of Flavonoids

No.	components and herbs	Level	Mechanism on oxidative stress	Mechanism on inflammation	reference
1	6-gingerol	B2		increased plaque formation, elevation of plasma total cholesterol, triglyceride, low-density lipoprotein cholesterin, and proinflammatory cytokines including	Wang et al., 2018
2	Calycosin	B2		improved autophagy through KLF2-MLKL signalling pathway modulation	Ma et al., 2022
3	dihydromyricetin	A,B2		demonstrate that endothelial miR-21-inhibited	Yang et al., 2020
4	Dihydromyricetin	A	activating Akt and ERK1/2, which		Luo et al., 2017
5	Flavone of Hippophae	B2		upregulating CTRP6	Zhuo et al., 2019
6	Flavonoids	A,B2		inhibiting mRNA and protein expression, inhibiting the NF-κB	Liu et al., 2022
7	Formononetin	C	alleviates ox-LDL-induced		Zhang et al., 2021
8	Formononetin	A,B2		regulation of interplay between KLF4 and SRA	Ma et al., 2020
9	Hesperidin	A		alleviate BaP-induced inflammatory response by decreasing IL-1β and TNF-α expression	Duan et al., 2022
10	Hesperidin	B2	pleiotropic effects, including improvement of		Sun et al., 2017
11	Homoplantaginin, dihydrohomoplantagin	A,B2	protected VECs by activating Nrf2		Meng et al., 2022
12	Icariin	B1	associated with the anti-inflammation,		Hu et al., 2016
13	kaempferol	A,B2	PI3K/AKT/Nrf2 pathways		Feng et al., 2021
14	Kuwanon G	A,B2		decreased intracellular lipid accumulation and inflammatory	Liu et al., 2018
15	Morin hydrate	A,B2		activation of the PI3K/Akt1/NFκB signaling pathway	Meng et al., 2021
16	Myricitrin	A,B2	inhibition of p53 gene expression, activation of caspase-3 and the MAPK signaling pathway, and alteration of the patterns of pro-apoptotic and anti-apoptotic gene expression		Sun et al., 2013

17	naringenin	A	activating AMPKα/Sirt1 signaling pathway		Li et al., 2021
18	Puerarin	A	increased SIRT-1 expression, reducing excessive production of ROS and inhibiting the expression of inflammatory factors and oxidative stress injury		Chang et al., 2021
19	Puerarin	A	inhibition of the p38 MAPK and JNK signaling		Hu et al., 2020
20	Quercetin	B2		enhancement of autophagy and upregulation of P21 and P53 expression	Cao et al., 2019
21	Quercetin	C	block the expression of lectin-like oxidized LDL receptor-1 (LOX-1) in cultured macrophages	decrease of multiple inflammatory cytokines in transcript level	Xue et al., 2017
22	Scutellarin	A,B3	In H2O2 injured-HUVECs the deleterious alterations in ROS levels and		Mo et al., 2018
23	Total flavone	A,B2		dual suppression of miR-33 and NFκB pathway	Ma et al., 2020
24	total flavonoids	B2			Bo et al., 2017
25	total flavonoids of Engelhardia roxburghiana	A,B2		inhibiting AKT and mTOR phosphorylation	Wei et al., 2021
26	Vitexin	A	up-regulation of Wnt/β-catenin and Nrf2 signalling pathway		Zhang et al., 2022
27	Flavonol	B2	increased the collagen content of plaque lesions and decreased the expression of CD44.	significantly reduced the area of aortic atherosclerotic lesions	Phie J et al., . 2017

Notes: In Level, A represents in vitro; B represents in vivo; B1 represents rats; B2 **represents mice; B**3 **represents rabbit;** C represents network pharmacology.

TABLE 3 | Mechanisms of Glycosides

No.	components and herbs	Level	Mechanism on oxidative stress	Mechanism on inflammation	reference
1	2,3,5,4'-Tetrahydroxy-stilbene-2 -O-β-D-glucoside	B2		down-regulation of IL-6, TNF-α, VCAM-1 and	Li et al., 2019
2	amygdalin	A,B2		MAPKs, AP-1 and NF-κB p65 signaling pathways	Wang et al., 2020

3	polysaccharide CM1	B2	Integrated bioinformatics analysis revealed that CM1 interacted with multiple		Lin et al., 2021
4	Crocin	A,B1		promoting M2 macrophage polarization and maybe by inhibiting NF-κB p65	Li et al., 2018
5	Dendrobium huoshanense C. Z. Tang et S. J. Cheng polysaccharide	A,B (Zebrafish)	improved HCD-induced lipid deposition, oxidative stress, and inflammatory response, mainly showing that DHP significantly increased superoxide dismutase (SOD) activity, decreased plaque formation,		Fan et al., 2020
6	Gastrodin	B2		attenuate the lipid deposition and foam cells on the inner membrane	Liu et al., 2021
7	Poria cocos polysaccharides	A,B2		reducing inflammatory factors and blood lipid levels	Li et al., 2021
8	cordycepin	A		PI3K/Akt/eNOS signaling pathway	Ku et al., 2021
9	Polydatin	A,B2		down-regulation of PBEF and inhibition of PBEF-inducing cholesterol deposits in macrophages	Huang et al., 2018
10	Pseudoprotodioscin	A,B2		regulated adhesion molecule expression in HUVECs through an	Sun et al., 2020

Notes: In Level, A represents in vitro; B represents in vivo; B1 represents rats; B2 represents mice; B3 represents rabbit; C represents network pharmacology.

TABLE 4 | Mechanisms of Phenylpropanoids

No.	components and herbs	Level	Mechanism on oxidative stress	Mechanism on inflammation	reference
1	5,2'-dibromo-2,4',5'-trihydroxydiphenylmethanone	A	activates HMBOX1, which is an inducible protective mechanism that inhibits	activates HMBOX1, which is an inducible protective mechanism that inhibits LPS-induced	Yuan et al., 2019
2	Benzoinum	A		regulation of the NF-κB and caspase-9 signaling pathways	Zhang et al., 2019

3	Bergaptol	A		inhibitory effects on c-Jun N-terminal kinase (JNK), P38, P65, IκBα and IκKα/β phosphorylation,	Shen et al., 2020
4	Cinnamaldehyde	B2		the IκB/NF-κB signaling pathway.	Li et al., 2019
5	Curcumin	A	AMPK/mTOR/p70S6K pathway		Zhao et al., 2021
6	Curcumin	A		interfering with the reactive oxygen species-ERK1/2 signal pathway.	Zhang et al., 2020
7	Curcumin	B2		related to LCN2 down-regulation, anti-hyperlipidemia effect as well as the inhibition of inflammation	Wan et al., 2016
8	curcumin, Nicotinic-curcumin	A		reduced endothelial EVs secretion	Xiang et al., 2021
9	Epigallocatechin gallate	A	enhancing SIRT1/AMPK as well as Akt/eNOS signaling pathways		Pai et al., 2021
10	Honokiol	B2	decreased reactive oxygen species level and enhanced superoxide dismutase activity.	downregulated the expression of pro-inflammatory markers, like tumor necrosis factor-α, interleukin	Liu et al., 2020
11	Imperatorin	A,B2		Matrix metalloproteinase-2 (MMP-2) expression in aorta was down-regulated by IMP. IMP could inhibit the phosphorylation of MAPKs pathway in the aorta and VSMCs, resulting in a significant decrease in the contents of p-ERK 1/2, p-JNK and p-P38.	Li et al., 2021
12	Paeonol	A,B2		inhibited the downstream NLRP3 inflammasome pathway by increasing the level of miR-223 in plasma derived exosomes of hyperlipidemic rats	Shi et al., 2020
13	paeonol	A,B1		up-regulating the expression of caveolin-1 and inhibiting the activation of NF-κB pathway	Liu et al., 2020
14	Paeonol	A,B2		increase the expression of miR-223 in THP-1 derived exosomes and in HUVECs after uptake of exosomes, whereas decrease the expression of STAT3, p-STAT3 in HUVECs.	Liu et al., 2018

15	Paeonol	B3		promotes miR-126 expression to inhibit monocyte adhesion to ox-LDL-injured VECs and block	Yuan et al., 2016
16	phthalides	B2		suppressing the expression of AP-1 and AKT/NF-κB signaling pathway	Lei et al., 2019
17	Pterostilbene	A,B1	regulation of the Nrf2-mediated AMPK/STAT3 pathway		Tang et al., 2020
18	Punicalagin, pomegranate peel polyphenols	A,B2		inhibiting force-specific activation of Smad1/5 in ECs	Anwaier et al., 2021
19	Resveratrol	A,B2	downregulating the PI3K/AKT/mTOR signaling pathway		Ji et al., 2022
20	Resveratrol	B3		down-regulation phosphorylation of NF-κB, and MAPKs signaling	Song et al., 2013
21	Salvianic acid A	A,B2	increasing antioxidant enzymes activity, upregulating	inhibiting the toll-like receptor 4/nuclear factor kappa B pathway	Song et al., 2019
22	Salvianolic acid A	B1		decreased serum hs-CRP levels and suppressed the activation of NLRP3 inflammasome and NF-κB	Ma et al., 2020
23	Salvianolic acid B	A,B2		MAPKs/NF-κB signaling pathways	Zhang et al., 2022

Notes: In Level, A represents in vitro; B represents in vivo; B1 represents rats; B2 represents mice; B3 represents rabbit; C represents network pharmacology.

TABLE 5 | Mechanisms of quinones

No.	components and herbs	Level	Mechanism on oxidative stress	Mechanism on inflammation	reference
1	Dihydrotanshinone I	A,B2		suppressing RIP3-mediated necroptosis of macrophage	Zhao et al., 2021
2	Dihydrotanshinone I	A,B2	inhibition of LOX-1 mediated by NOX4/NF-κB signaling pathways		Zhao et al., 2016
3	Shikonin	A,B1		inhibition of SKN on CD4+ T cell inflammatory activation	Lü et al., 2020
4	Tanshinone II A	B2		interfering with RAGE and NF-κB activation, and downregulation of downstream inflammatory factors, including ICAM-1, VCAM-1, and MMP-2, -3 and -9	Zhao et al., 2016

5	Tanshinone IIA	A	TSA represses ferroptosis via activation of NRF2 in HCAECs.		He et al., 2021
6	Tanshinone IIA	A		mediating miR-130b and WNT5A	Yuan et al., 2020
7	Tanshinone IIA	A,B2		activate KLF4 and enhance autophagy as well as M2 polarization of macrophages by inhibiting miR-375 to Attenuate Atherosclerosis	Chen et al., 2019
8	Tanshinone IIA Sodium sulfonate	A,B2	The anti-oxidant, and anti-inflammation properties of STS in preventing AS is mediated by its inhibition of CLIC1 expression and membrane translocation.		Zhu et al., 2017

Notes: In Level, A represents in vitro; B represents in vivo; B1 represents rats; B2 represents mice; B3 represents rabbit; C represents network pharmacology.

TABLE 2 | Mechanisms of Chinese medicines and formulae

No.	Chinese medicines and formulae	Level	Mechanism on oxidative stress	Mechanism on inflammation	reference
				induced ApoE-/- mice early and mid-term AS model via regulating Th17/Treg balance, inhibiting chronic inflammation, reducing plaque collagen fibers, and reducing inflammatory cells infiltration, to exert its multi-channel multi-target	
1	Angong Niuhuang Pill (Formula)	A,B2			Fan et al., 2020
2	Bazi Bushen capsule (Formula)	A,B2		GPER1-dependent anti-inflammatory and anti-apoptotic mechanisms	Huang et al., 2021
3	Bushen Jiangzhi formula (Formula)	B2		regulating the expression of autophagy-related proteins LC3, Beclin 1, and p62,	Cao et al., 2020
4	Bushen Kangshuai Tablet (Formula)	B3		suppress the inflammation reaction in rabbits to prevent AS formation	Zhang et al., 2009
5	Buyang Huanwu decoction (Formula)	B2	promote revascularization on db/db mice with HLI through targeting antioxidation, anti-inflammation, and angiogenesis via the AKT/GSK3β/NRF2 pathway.		Bao et al., 2021
6	BuYangHuanWu decoction (Formula)	B1		inflammatory cytokines were suppressed and that the NF-κB signaling pathway	Liu et al., 2019
7	Cardiotonic pills (Formula)	B2		downregulation of plasma macrophage inflammatory protein-1α and intercellular cell adhesion molecule-1.	Deng et al., 2019
8	Chaihu-Shugan-San (Formula)	A,B2		regulation of proinflammatory factors and BDNF-TrkB signaling	Li et al., 2019

9	Compound Danshen tablet (Formula)	B2	reduced the levels of the oxidative damage molecule 4-HNE	reduced the levels of the inflammatory factor ICAM-1	Guo et al., 2021
10	Danggui Buxue Decoction (Formula)	C		improvement of extracellular matrix (ECM) deposition in the blood vessel wall and the anti-vascular local inflammatory response	Xu et al., 2021
11	Danhong injection (Formula)	B2		attenuation of lipopolysaccharide-induced expression of TNF-α, IL-1β, IL-6 in macrophages	Chen et al., 2014
12	Dan-Lou prescription (Formula)	A		effectively attenuated macrophage foam cell formation via the TLR4/NF-κB and PPARγ signaling pathways	Gao et al., 2018
13	Danshen-shanzha(Formula)	B2		decreased the concentrations of interleukin (IL)-1β and IL-18	Zhang et al., 2019
14	Danlou tablet (Formula)	B2		regulating the NF-κB signaling pathway.	Gao et al., 2020
15	Danlou tablet (Formula)	B2		suppressing NF-κB signaling and triggering PPARα/ABCA1 signaling pathway	Hao et al., 2019
16	Dingxin recipe (Formula)	A,B2		downregulation of TNF-α, IL-6, ICAM-1 and VCAM-1 through mitogen-activated protein kinase pathways	Cui et al., 2020
17	Formula of removing both phlegm and blood stasis (Formula)	B (Pig)		controlling NF-kappaB p65 nuclear translocation	Ren et al., 2014
18	Fufang-Zhenzhu-Tiaozhi Capsule (Formula)	B3		activation of APN signaling pathway	Li et al., 2020
19	Guanxinkang (Formula)	B2		regulating PPARγ, LXRα and ABCA1 interactions in the ApoE-knockout mice	Mao et al., 2012

20	Guanxinkang decoction (Formula)	A,B2		efferocytosis and MAPKs signaling pathways in LDLR-/- mice and RAW264.7 cells	Zhang et al., 2021
21	Guanxinshutong capsule (Formula)	A	reduced the activity of oxidative parameter MDA and upregulated the activities of antioxidant enzymes (SOD and GSH)	modulated lipid profile, downregulated the level of inflammatory cytokines and NF-κBp65.	Lu et al., 2020
22	Huotan Jiedu Tongluo (Formula)	B3	inhibition of BH4/eNOS uncoupling and the reduction of oxidative stress		Li et al., 2018
23	Hwangryunhaedok-tang (Formula)	A	modulating LDL oxidation and VSMC proliferation		Seo et al., 2015
24	Jianpi Huazhuo Tiaozhi granules (Formula)	A	inhibiting the NOX/ROS-NF-κB pathway.		Liu et al., 2020
25	Kangshuanyihao formula (Formula)	B1		regulating the SIRT1/TLR4/NF-κB signaling pathway	Han et al., 2017
26	modified Yuejuwan (Formula)	A	Inhibiting the Activity of the TRIM37/TRAF2/NF-κ B Pathway		Gui et al., 2022
27	Rongban Tongmai granule (Formula)	B3	prevent atherosclerosis by antioxidative stress and correcting unbalance of redox.		Lin et al., 2011
28	Shen-Hong-Tong-Luo formula (Formula)	A,B2		activating the PPAR-γ/LXR-α/ABCA1 pathway	Zhang et al., 2020
29	Shenmai formula (Formula)	A		suppress the NF-κB p65 expression and IκBα phosphorylation	Zhu et al., 2017
30	Shen-Yuan-Dan Capsule (Formula)	A,B2	up-regulated Beclin1 and LC3II/I proteins	inhibited AKT phosphorylation at Ser473 and mTOR phosphorylation	Zhou et al., 2019

31	Shexiang Baoxin Pill (Formula)	B2		the level elevation of Mfn2 and reduced phosphorylation of p38, JNK, and NF-κB., reduced the level of SR-A and LOX-1 and elevated the content of LXRα, ABCA1, and ABCG1 in the arterial wall	Lu et al., 2019
32	Shexiang Tongxin dropping (Formula)	B1		the levels of pro-inflammatory cytokines including IL-2, IL-6, TNF-α and γ-IFN were markedly reduced	Xiong et al., 2015
33	Shenlian extract	A,B (Dog)		NF-κB signaling pathway	Guo et al., 2020
34	Sobokchukeo-Tang (Formula)	C		inhibited TNF-α and IL-6	Lee et al., 2017
35	Suxiao Jiuxin Pill (Formula)	B1	elevate the activity of serum SOD, decrease serum level of MDA and ox-LDL, and reduce the expression of PPARgamma and NF-kappaB proteins		L i et al., 2011
36	Taoren Honghua drug (Formula)	A,B2		MAPKs, ERK5/STAT3, and AKT/NF-κB p65 signaling pathways	Wang et al., 2020
37	The Angong Niuhuang Pill (Formula)	B1	decreased aortic membrane thickness, the maximum platelet aggregation rates, and the ratio of low density lipoprotein cholesterol (LDL) to high density lipoprotein cholesterol (HDL)		Fu et al., 2017

38	Tiaogan-Liqi prescription (Formula)	A,B2		reduce plasma lipid profiles and plasma inflammatory cytokines, reduce intracellular lipid accumulation, suppress the production of inflammatory cytokines of macrophages induced by oxidized-LDL, and inhibit the protein expression of heat shock protein 90 and toll-like receptor 4	Chen et al., 2021
39	Tiaopi Huxin recipe (Formula)	A,B2		decreased expression of caveolin-1 and NF-κB	Wen et al., 2019
40	Tongxinluo (Formula)	A,B2	inhibiting the expression of p22(phox), p47(phox) and HO-1	inhibiting the expression and activation of NF-κB	Wu et al., 2015
41	Tongxinluo (Formula)	B1		reducing expression of inflammatory cytokine MCP-1 and ICAM-1	Yao et al., 2014
42	Tongxinluo (Formula)	A,B2		Suppression of miR-155 expression mediated by Akt1 and blockade of the feedback loop between miR-155 and TNF-α are important pathways whereby	Zhang et al., 2014
43	Tongxinluo (Formula)	B3		inhibit the NLRP3 inflammatory pathway	Qi et al., 2022
44	Tongxinluo capsule (Formula)	B2		The comprehensive mechanisms, in addition to inflammation and lipid metabolism, might also involve cell physical function, hormone secretion, protein binding, and immune response process.	Ma et al., 2019

45	Xiao-Zhi formula (Formula)	A,B2		promotes lipid efflux and inhibits macrophage-mediated inflammation, producing a therapeutic effect against atherosclerosis	Li et al., 2021
46	Xin-mai-jia (Formula)	A,B1	reduced NO levels and increased ROS productions		Yin et al., 2017
47	Yangyin Qingre Huoxue Prescription (Formula)	A,B2		Suppressed IL-6-p-STAT3 signaling and restored IL-2-p-STAT5 signaling in the presence of YQHP may partake in the regulation of Th17 and Treg differentiation. Moreover, YQHP modulated transcriptional levels of costimulator CD80 in aortas as well corresponding to the downregulation of GM-CSF in serum and CD3 expression in CD4+ T cells	Qiu et al., 2019
48	Yindanxinnaotong (Formula)	B1		inhibiting the nuclear factor-kappa B signal pathway	Cheng et al., 2015
49	Yiqi-Huoxue granule (Formula)	A		regulating the KLF2 expression and NF-κB signaling pathway	Wu et al., 2019
50	Yirui capsules (Formula)	B2		reduces the atherosclerotic plaque burden, thereby alleviating AS by modulating the lipid profile and inhibiting inflammation	Xu et al., 2018
51	Zhixiong Capsule (Formula)	B1		IL-4, IL-13, MAPK1, MAPK14, JUN and P53 were confirmed as key targets	Zhai et al., 2019
52	Zhizi Chuanxiong Capsule (Formula)	B3		treat AS through regulating the abnormal hypermethylated and hypomethylated genes in AS rabbit model.	Zhou et al., 2018

53	Dendrobium catenatum Lindl.	B (Zebrafish)	alleviate the lipid metabolism disorder, oxidative stress, and inflammation to reduce the plaque formation of AS zebrafish larval model.		Han et al., 2021
54	Fermentum Rubrum	B2		reduced the protein levels of NF-κB and MMP-9 of the aorta	Wu et al., 2017
55	Ginkgo biloba	B2		inhibition of mTOR	Tian et al., 2019
56	Hirudo nipponica	A		regulating the LOX-1/LXR-α/ABCA1 pathway	Lu et al., 2019
57	Patrinia villosa Juss., Patrinia scabiosaefolia Fisch.	B2		reversing lysophosphatidylcholine (LPC) in the glycerophospholipid metabolic pathway	Su et al., 2022
58	Pueraria lobata	A	protected HUVECs against rotenone-induced oxidative stress and apoptosis		Gao et al., 2016
59	Salvia miltiorrhiza	A	induced HO-1 expression through PI3K/Akt-MEK1-Nrf2 pathway and reduced intracellular production of reactive oxygen species via induction of HO-1 expression		Lee et al., 2012
60	Schisandra chinensis	B1	reduced the malondialdehyde levels (72.5, 69.3, 67.3%), and up-regulated the Nrf-2 and HO-1 expression ($p < 0.05$).		Chen et al., 2018

61	Usnea diffracta Vain.	B1	promoting the expression of serum IL-10 and inhibition of TLR5/NF-κB signaling pathway.	Zhao et al., 2019
62	Astragali Radix, Coptis Rhizoma	C	M1/M2 and Th1/Th2 immune balance	Li et al., 2022

Notes: In Level, A represents in vitro; B represents in vivo; B1 represents rats; B2 represents mice; B3 represents rabbit; C represents network pharmacology.