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Review

Targeting vascular smooth muscle cells with natural compounds to combat atherosclerosis

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ABSTRACT

Atherosclerosis (AS) is widely recognized as the principal pathological substrate underlying chronic cardiovascular diseases (CVDs). It is a chronic, progressive, and inflammatory disease characterized by excessive lipid deposition, oxidative stress, inflammatory response, plaque formation and rupture, thrombosis and vascular calcification (VC). Vascular smooth muscle cells (VSMCs) are essential for maintaining the normal structure of blood vessels and play a pivotal role in the pathological process of AS. Their proliferation, migration, differentiation, senescence and death processes critically influence the progression of AS. The specific mechanism of VSMCs participating in AS remains a central focus of research in the cardiovascular field. In recent years, natural products have garnered considerable attention in the field of AS prevention and treatment, primarily due to their multi-target effects, low toxicity and side effects. However, there is still a lack of systematic review of natural compounds that alleviate AS by regulating the function of VSMCs. This article focuses on the core role of VSMCs in the progression of AS, and systematically reviews the natural compounds targeting VSMCs metabolism and their molecular regulatory mechanisms. By combing the relevant pharmacological activities and potential targets, the pathological function of VSMCs in AS is further elucidated, thereby providing an important theoretical basis for the development of novel and efficient AS treatment strategies.

1. Introduction

Atherosclerosis (AS) is a chronic inflammatory disease characterized by progressive accumulation of plaques in the arterial wall, which can cause coronary heart disease, cerebral infarction, and other serious cardiovascular and cerebrovascular diseases [1]. The disease usually begins in the arterial intima layer and is closely related to abnormal deposition of lipids and metabolites, and is often accompanied by local bleeding and thrombosis. Dyslipidemia is the pathological basis of the occurrence and development of AS. With the continuous progression of the disease, AS eventually causes significant damage to the overall cardiovascular system function. Subsequently, increased fibrous tissue and calcium deposition lead to arterial medial structure deterioration and plaque formation, accompanied by chronic inflammation and secondary related cardiovascular diseases (CVDs) [2].

The key processes of AS include endothelial cell dysfunction, macrophage metabolic abnormalities, and changes in vascular smooth muscle cells (VSMCs). Recent studies have shown that AS is similar to a tumor-like lesion affected by smooth muscle cells [3], suggesting that VSMCs play an important role in the development of AS. VSMCs are mainly distributed in the vascular medial layer and participate in the formation of atherosclerotic plaques. Under physiological homeostasis, these cells are usually maintained in a stationary "contractile" phenotype, which is characterized by high expression of contractile-related proteins. When AS is initiated, these cells undergo phenotypic switching to a "synthetic" phenotype, manifested as decreased contractility, increased proliferation and migration activity, and migration to the intima [4-6]. In the middle stage of AS progression, VSMCs are involved in the formation of fibrous caps dominated by collagen and proteoglycans, and become a key component of plaque structure. With the development of the lesion, lipid and foam cells continue to accumulate, and a soft and unstable lipid core is gradually formed in the plaque. It is noteworthy that the decrease in the number of VSMCs will directly lead to the thinning of the fibrous cap, which may promote the formation of a necrotic core, which is characterized by local tissue necrosis. In addition, the absence of VSMCs also induces calcification in the lesion area, further aggravating plaque instability, and increasing the risk of plaque rupture and secondary vascular obstruction and thrombosis [7]. In the process of AS, the metabolism of VSMCs is not fully studied, which is mainly due to the fact that the cells will be transformed into a less differentiated type. This situation may lead to a wrong judgment of cell origin, and thus ignore the key role of VSMCs in AS. Therefore, it is necessary to further clarify the specific functions of VSMCs in different stages of CVDs, especially in AS.

Although there are many treatments for AS, such as lipid-lowering and anti-inflammatory drugs, their prevention and treatment effects are often unsatisfactory. Long-term use of statins, non-steroidal anti-inflammatory drugs and glucocorticoids

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may even pose a risk of cardiovascular toxicity [8, 9]. In recent years, the research on natural drugs, especially traditional Chinese medicine (TCM), has increased significantly. These drugs have attracted attention for their ability to act on multiple targets at the same time and synergistically improve the disease, which is called the multi-target effect. Therefore, the discovery of new drugs that can improve AS or new compounds derived from natural products has become an important research direction. At present, several natural compounds have been approved for the management and treatment of CVDs, such as tanshinone [10] and salvianolic acid derived from *Salvia miltiorrhiza* [11]. The molecular mechanisms by which natural compounds have anti-atherosclerotic effects are diverse and have been fully studied.

However, the existing reviews are mostly limited to an overview of the potential value of TCM in the treatment of AS, and the specific role of VSMCs in this process has not been explored in depth. There are still literature gaps in the study of drugs targeting VSMCs to exert anti-atherosclerotic effects. Therefore, this paper aims to sort out the physiological process of VSMCs in AS, and systematically summarize the natural compounds that can target the cells to improve the condition, so as to provide a new perspective for the study of the mechanism of VSMCs in this field.

2. The physiological processes of VSMC in atherosclerosis

2.1. The phenotypic switching of VSMC

Under normal physiological conditions, VSMCs located in the vascular media are in a static and highly differentiated state. These cells maintain vascular tension through contractile function and participate in the regulation of blood pressure and blood flow. Its specific markers include *α*-smooth muscle actin (*α*-SMA), smooth muscle myosin heavy chain (SMMHC), and smooth muscle protein 22α (SM22α, also known as transgelin) [12-14]. Studies have shown that these markers have a positive effect on the process of AS [15]. When blood vessels are damaged or pathologically stimulated, VSMCs will change from a "contractile" phenotype to a highly "synthetic" phenotype. This transformation is accompanied by enhanced proliferation and migration, and leads to the dedifferentiation of cells. At the same time, these cells gradually synthesize extracellular matrix (ECM) components, including elastic fibers and collagen microfibers [16]. In the process of dedifferentiation, the above original markers will decrease or even disappear, and VSMCs will turn to express new protein markers. In addition, some proteins (such as CD200 [17]) are specifically expressed in VSMCs and can persist after phenotypic switching.

In recent years, a number of studies based on VSMCs lineage tracing and single-cell sequencing have shown that these cells can transform from a "contractile" phenotype to a variety of other phenotypes in an atherosclerotic environment. In addition, when exposed to different environments, these cells also have the ability to switch between multiple phenotypes and have a unique impact on AS-related markers and plaque stability [4, 18, 19]. In the lesion area, the regulated VSMCs exhibit a variety of phenotypes, including synthetic, macrophage-like, foam cell-like, mesenchymal stem cell-like (MSC-like), osteochondral-like, fibroblast-like, and adipogenic cell-like VSMCs [20-23]. These phenotypic transformations can be stimulated by a variety of cytokines, proteins and pathological factors. Among them, platelet-derived growth factor BB (PDGF-BB), insulin-like growth factor (IGF), angiotensin II (Ang II), epidermal growth factor (EGF), transforming growth factor-β1 (TGF-β1), and ECM proteins such as fibronectin, vimentin, and laminin are worthy of attention [24, 25]. Lipopolysaccharide (LPS) and modified lipoprotein oxidized low-density lipoprotein (ox-LDL) also play an important role. The regulation of these processes is also affected by a variety of transcription factors such as long non-coding ribonucleic acids (lncRNAs) and microRNAs (miRNAs) [26].

Macrophage-like VSMCs up-regulate "macrophage markers" including lectin galactoside-binding soluble 3 (LGALS3) and CD68, as well as various pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and monocyte chemoattractant protein (MCP)-1. TNF-α and IL-1β can further stimulate VSMCs to express inflammatory factors such as intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1, thereby promoting their adhesion to monocytes/macrophages and T cells and changing the intravascular microenvironment [27]. Studies have shown that in human advanced coronary atherosclerotic lesions, 40% of the cells expressing CD68 are actually derived from VSMCs rather than macrophages [23]. Available evidence suggests that the activation of LGALS3 does not serve as a definitive marker for the transformation of VSMCs into macrophage-like states, only suggesting that the cells may be in a transitional phase [28]. In addition, the expression of macrophage markers in VSMCs does not necessarily mean that they have complete macrophage function or cell specificity. The specific impact of this phenomenon on the stability of atherosclerotic plaques remains to be clarified.

Studies have shown that VSMCs can express scavenger receptors. When excess lipids accumulate in the intima, these receptors absorb lipids to convert VSMCs into foam cells. Measurement of the number of cells in human coronary artery disease showed that foam cells derived from VSMCs accounted for more than 50% of the total number of foam cells [28]. However, it is not clear whether VSMCs are directly transformed into foam cells after absorbing sufficient lipoproteins in the original state, or must first be transformed into a phenotype closer to macrophages to obtain lipid transport and foam cell formation by up-regulating the expression of scavenger receptors.

Mesenchymal stem cell-like VSMCs (also known as intermediate dedifferentiated VSMCs) have the potential to further transform into adipocytes, chondrocytes, osteoblasts and macrophage-like VSMCs [29]. Stem cell antigen-1 (Sca-1) is a surface marker of mesenchymal cells. Studies have shown that Sca-1 positive cell populations derived from VSMCs can be detected in mouse atherosclerotic plaques, indicating that there are mesenchymal cell-like subtypes in the VSMCs [23].

Pedigree tracking studies have shown that 98% of osteochondral cells present in atherosclerotic plaques are derived from VSMCs [30]. These cells express runt-related transcription factor 2 (RUNX2), msh-homeobox gene 2 (*Msx2*) and its related proteins bone morphogenetic protein 2 (BMP-2), SRY-related HMG box (SOX9) and osteopontin (OPN), and their alkaline phosphatase (ALP) activity is also enhanced [31]. Osteochondral-like VSMCs release calcification-related vesicles, thereby accelerating the calcification process. Calcium and phosphorus balance, the effectiveness of calcification inhibitors, mitochondrial dysfunction, endoplasmic reticulum stress, and glucose metabolism and other factors affect the transformation process [32-35].

Studies have shown that fibroblast-like VSMCs are found in atherosclerotic lesions in both humans and mice. These cells are concentrated in the fibrous cap area and exhibit a significant increase in the expression of fibrosis-related genes, including fibronectin 1 (*FN1*) and tumor necrosis factor receptor superfamily member 11b (usually called osteoprotegerin), as well as small leucine-rich proteoglycans such as decorin [20].

Long et al. showed that some VSMCs could differentiate into beige adipocytes in cold-exposed mouse models. *In vitro* experiments further confirmed that VSMCs can transform into adipocyte-like cells and express the thermogenic adipocyte marker-mitochondrial brown fat uncoupling protein 1 (UCP-1). This expression may aggravate the inflammatory response after injury [36]. With the development of atherosclerotic lesions, VSMCs will ab-

sorb lipoproteins and present an adipocyte-like phenotype, which is characterized by increased levels of pro-inflammatory and proliferation markers. This phenomenon of lipid uptake may mean that cells are transforming into a foam cell phenotype [37]. So adipocyte-like VSMCs may be regarded as the intermediate stage in the differentiation process [38,39].

In conclusion, the phenotypic differentiation of VSMCs is considered to have a dual role in AS (Fig. 1). When it is transformed into macrophage-like cells with inflammatory characteristics, it may reduce the stability of atherosclerotic plaques. Conversely, if transformed into synthetic fibrotic smooth muscle cells, they can enhance stability by thickening the protective fibrous cap around the plaque. These different physiological processes involved in VSMCs affect the development of AS.

2.2. The proliferation and migration of VSMC

In fact, the above key phenotypic changes are often accompanied by significant changes in VSMCs proliferation and migration. In advanced lesions, maintaining a protective fibrous cap on the surface of the thrombotic lipid core is also crucial for plaque stability. Many factors such as PDGF-BB, TGF-β, ox-LDL, AngII and TNF-α can promote VSMCs proliferation and migration with different phenotypes. In addition, studies have shown that cadherin (FAT1) may promote the migration of VSMCs [40], but whether its migration and proliferation processes occur in sequence remains to be elucidated.

The formation of fibrous caps depends on the extensive proliferation and migration of middle VSMCs. Rupture-prone unstable atherosclerotic plaques usually have thinner fibrous caps, dense macrophage aggregation, and large necrotic cores [6]. Conversely, stable plaques are characterized by the formation of ECM and strong fibrous cap. The thickness of the fibrous cap is positively correlated with plaque stability [41]. VSMCs and the collagen and fiber produced by them are the main components of the fibrous cap. VSMCs located in the fibrous cap re-express smooth muscle cell differentiation-related genes (such as *α-SMA* and *SM22*) that help maintain plaque stability. In addition, specific proteins such as CD98 expressed by VSMCs can promote their proliferation and enhance plaque stability [42]. However, in the late stage of AS, this proliferation ability will gradually weaken or even be lost. Dedifferentiated VSMCs and macrophages with decreased phagocytic function will continue to secrete pro-inflammatory mediators such as TNFα, IL-1β, and IL-6, which will further aggravate the dedifferentiation of VSMCs, lead to the decomposition of ECM, and promote the thinning of the fibrous cap [43]. At the same time, extracellular proteases, especially matrix metalloproteinases (a class of zinc-dependent endopeptidases), are produced in large quantities. Among them, MMP-2 and MMP-9 can degrade ECM and induce the migration of VSMCs, which will aggravate plaque instability [44,45].

The early stage of VSMCs proliferation depends on the normal initiation of the cell cycle. This key process is coordinated by a variety of regulatory proteins. In this process, cyclins and cyclin-dependent kinases (CDKs) jointly promote cycle operation, and cyclin-dependent kinase inhibitors are involved in regulating cell

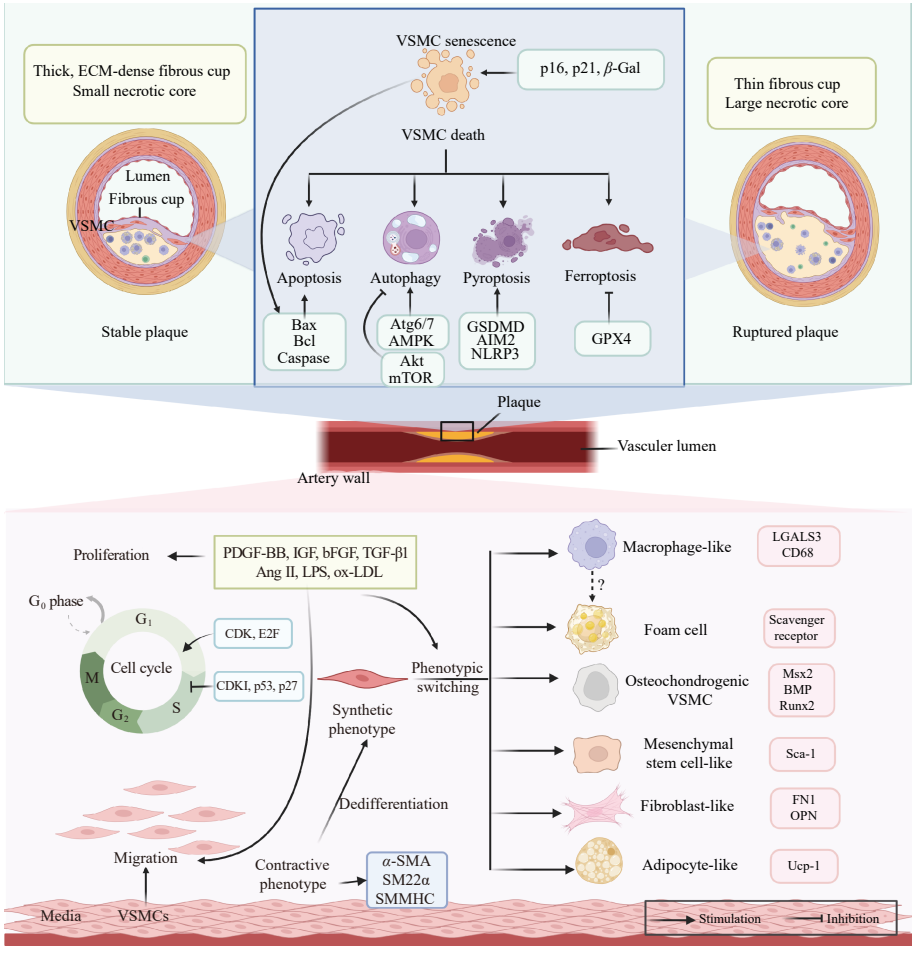


Fig. 1 Key physiological processes of VSMCs in AS progression. VSMCs located in the media of blood vessels migrate to the intima of blood vessels under pathological stimulation. This process initiates the transition of the cell cycle from S phase to G phase, thereby enhancing cell proliferation. At the same time, the cells that migrate to the intima undergo phenotypic changes, which in turn express characteristic markers of multiple cell types. These migrating VSMCs form fibrous caps on the outer layer of the plaque to promote plaque stability, while experiencing a series of cellular processes such as senescence, apoptosis, autophagy, pyroptosis and ferroptosis.

cycle progression to maintain cell homeostasis [46]. It was found that proliferating cell nuclear antigen (PCNA), c-jun, c-myc, and c-fos were significantly increased in the cell cycle transition stage, which promoted the cell cycle to advance to the S phase. The transition from G_1 phase to S phase is essential for the initiation of standard mitosis in VSMCs. A variety of transcription factors and proteins such as p53, p21, and p27 play a blocking role in this process, while the transcription factor E2F plays an enhancing role [47].

In conclusion, the continuous proliferation and migration of VSMCs are crucial in the development of AS. Although fibrous caps help stabilize plaques, inhibiting the proliferation and migration of early VSMCs is considered to be a key strategy for the prevention and treatment of AS.

2.3. The senescence and death of VSMC

With the progress of AS, VSMCs no longer proliferate and migrate, showing significant functional decline and cell death. VSMCs derived from human late plaques showed decreased proliferation and early senescence characteristics in both culture environment [48] and *in vivo* studies [49]. In addition, VSMCs located in the fibrous cap region showed significant DNA damage, telomere shortening and expression of senescence markers such as p16, p21, and *β*-galactosidase (*β*-Gal), and increased sensitivity to apoptosis. The accumulation of these characteristics leads to abnormal lipid metabolism in VSMCs during AS, which in turn leads to the thinning of the fibrous cap, increases the risk of plaque rupture and weakens the ability of plaque repair, and ultimately has a negative impact on disease progression. Therefore, reducing the senescence of VSMCs has become a feasible strategy for the treatment of AS. For example, studies have confirmed that statins can delay the replicative senescence of VSMCs and reduce related DNA damage [50].

Recent studies have confirmed a variety of cell death types including apoptosis, autophagy, pyroptosis and ferroptosis. Apoptosis is a form of programmed cell death, which is affected by a variety of genes, including the apoptosis regulator B-cell lymphoma-2 (*Bcl-2*), Bcl-2-associated X (Bax) protein and the caspase protein family, and involves the participation of oncogenes and tumor suppressor genes [51]. Bcl-2 plays a role in inhibiting apoptosis, while Bax promotes the process of apoptosis. The ratio of Bcl-2 to Bax is crucial to determine the direction of apoptosis. An increase in the ratio inhibits apoptosis, and vice versa promotes apoptosis. VSMCs in normal arterial tissues have the ability to resist apoptosis, but in the pathological microenvironment of AS, the expression levels of various pro-apoptotic factors (such as Bax and calpain I) are abnormally increased, resulting in a significant increase in the susceptibility of VSMCs to apoptosis [52]. Apoptosis of VSMCs in the necrotic core area can cause the fiber cap to become thinner and the mechanical strength to decrease, thereby significantly increasing the risk of plaque rupture. Therefore, by regulating the apoptosis process of VSMCs, it may become a potential strategy for the treatment of atherosclerotic plaques.

Autophagy is a degradation process in cells, which generates autophagosomes (AP) by forming phagocytic vacuoles to encapsulate some cytoplasm and damaged organelles. Subsequently, AP fuses with lysosomes to form autophagic lysosomes [53], which decompose the encapsulated cell components into small molecules such as amino acids and nucleotides, thereby maintaining cell homeostasis [54]. Autophagy is also essential for the phenotypic differentiation, proliferation, and migration of VSMCs. Studies have shown that autophagy is an important mechanism to support the survival of VSMCs and has a dual regulatory effect on atherosclerotic lesions. In the early stages of the disease, autophagy in VSMCs helps to eliminate myogenic foam cells (a process known as lipophagy), thereby reducing the likelihood of necrotic core formation. At the same time, this process can also reduce the production of reactive oxygen species (ROS) in blood vessels, thereby alleviating oxidative stress and stress-stimulated apoptosis. However, with the progression of AS, increased oxidative stress, inflammatory response, and lipid accumulation, such as cholesterol crystals may lead to lysosomal membrane damage and impaired autophagy function [55, 56]. The activatesprotein kinase B (Akt)/mammalian target of rapamycin (mTOR) signaling pathway is the main negative regulatory mechanism of autophagy [57], while AMP-activated protein kinase (AMPK) is a positive regulator of this process [58]. In addition, autophagy-related genes (*Atg*), including *Atg6* (commonly referred to as beclin-1) and *Atg7*, positively influence autophagy. The loss of *Atg7* gene accelerates oxidative stress-stimulated cell senescence, inhibits cell proliferation, promotes apoptosis, and aggravates the progression of AS [59, 60]. In contrast, a number of studies have shown that oxidative stress and TNF-α, PDGF-BB may activate autophagy of VSMCs, promote VSMCs transformation from contractile phenotype to synthetic phenotype, and promote the development of AS [61-64]. In addition, excessive autophagy may lead to VSMCs death due to excessive cell digestion. At present, studies have confirmed that a variety of proteins, including heat shock proteins [65], can play an anti-atherosclerotic role by enhancing autophagy and inhibiting VSMCs apoptosis.

Pyroptosis is a kind of programmed cell death accompanied by pro-inflammatory response, which can be caused by various pathological factors such as oxidative stress, hyperglycemia, lipid abnormality, and inflammation [66]. This mechanism leads to the rupture of the plasma membrane, which in turn releases pro-inflammatory substances and cell contents, thereby exacerbating the inflammatory response. The classical pyroptosis pathway begins with the formation of inflammasomes, which in turn cleave gasdermin D (GSDMD) and release inflammatory mediators such as IL-1β and IL-18. These processes may aggravate AS [67]. A variety of inflammasomes, including NOD-like receptor family pyrin domains containing 3 (NLRP3) [56] and absent in melanoma 2 (AIM2) [68], have been shown to promote pyroptosis and accelerate plaque formation. Studies have shown that reducing pyroptosis of VSMCs can effectively alleviate the formation of AS in apolipoprotein E knockout ($ApoE^{-/-}$) mouse models [69].

Ferroptosis is a newly identified form of iron-dependent regulatory cell death. This process starts from the accumulation of iron ions and lipid peroxidation in VSMCs in the plaque, and then participates in the unstable development of advanced atherosclerosis-related plaques [70]. This process is closely related to the biosynthesis of glutathione, NADPH, and phospholipids [71], in which glutathione peroxidase 4 (GPX4) has been identified as a key negative regulator of ferroptosis [72]. In the rat aortic injury model, the triggering of ferroptosis will aggravate the neointimal hyperplasia caused by common carotid artery ligation. In addition, studies of VSMCs *in vitro* have shown that the activation of ferroptosis promotes the differentiation of cells from a "contractile" phenotype to a "synthetic" phenotype [73]. Therefore, regulating ferroptosis may be a potential strategy for treating AS.

In summary, various senescence and death of VSMCs occur simultaneously during AS (Fig. 1). Regulating the occurrence of these processes provides new strategies for the treatment of AS.

3. The mechanism of natural compounds targeting VSMC to improve AS

3.1. Inhibition of VSMC proliferation and migration

Triggered by different exogenous and endogenous pathological factors, the proliferation and migration of VSMCs involve

many signaling pathways in the process of AS. The mitogen-activated protein kinase (MAPK) pathway is a serine/threonine kinase that regulates the proliferation, migration and survival of mammalian cells [74, 75]. The family consists of 14 members, which can be divided into seven subgroups: extracellular regulated kinase (ERK1/2), C-Jun *N*-terminal kinase (JNK), p38 MAPK, ERK5, ERK3/4, ERK7/8, and nemo-like kinase (NLK) [76]. In addition, nuclear transcription factor κB (NF-κB) exists in the cytoplasm in the form of dimers and forms complexes with p50, p65, and nuclear factor κB inhibitory protein-α (IκBα) [77]. When stimulated by pro-inflammatory factors, IκBα is phosphorylated and degraded by 26*S* proteasome, so that the NF-κB dimer is transported to the nucleus to bind to specific DNA sites (κB sites), and then initiates the regulation of downstream transcription factors related to VSMCs proliferation, inflammation, and oxidative stress [78]. Additionally, phosphatidylinositol 3-kinase (PI3K) is a kind of lipid kinase related to the plasma membrane. AKT is a key serine/threonine protein kinase, which is activated by upstream PI3K signal. The PI3K/AKT signaling pathway plays a core regulatory role in cell growth, proliferation, movement, and metabolism [79]. A variety of natural compounds inhibit VSMCs proliferation and migration by interacting with these three signaling pathways.

Ginsenoside is the main active ingredient in *Panax ginseng*. Ginsenoside Rb1 (**1**) reduces the phosphorylation level of ERK1/2 in fetal bovine serum (FBS)-stimulated VSMCs, thus arresting the cell cycle in G_1 phase and ultimately inhibiting cell proliferation [80]. P90 ribosomal S6 kinase (p90RSK), which serves as a downstream effector of ERK1/2, can be inhibited by ginsenoside Rh1 (**2**), consequently reducing the proliferation and migration of Ang II-stimulated rat aortic vascular smooth cells (RASMCs) [81]. Protocatechuic aldehyde (PCA, **3**), a natural compound obtained from the roots of *Salvia miltiorrhiza*, inhibits the S-phase cell cycle arrest of RASMCs isolated from PDGF-stimulated rats by downregulating the PI3K/Akt and MAPK signaling pathways, while also arresting the cell cycle [82]. Vinpocetine (**4**), an alkaloid derived from vincamine (extracted from the periwinkle plant *Vinca minor*), inhibits cell proliferation by reducing the phosphorylation levels of Akt and IκBα in RASMCs stimulated by high glucose [83]. (−)-Epicatechin gallate (ECG, **5**) is one of the main active compounds derived from green tea. In ox-LDL-stimulated mouse aortic smooth muscle cells (MOVAS), ECG can reduce the phosphorylation of IκBα and NF-κB p65 by inhibiting the activation of MAPK pathway, thereby regulating cell cycle and exerting anti-proliferation effects. In addition, ECG can also inhibit cell migration by inhibiting the activity of MMP-2 and ICAM-1 [84]. In Ang II-stimulated RASMCs, ECG can also inhibit PI3K phosphorylation, thereby preventing excessive cell proliferation [85]. Pterostilbene (**6**) is a natural flavonoid widely distributed in blueberries, grapes and other plants. Studies have shown that in ox-LDL-stimulated rat thoracic aortic smooth muscle cell line A7r5, pterostilbene inhibits cell migration and reduce MMP-2 activity by promoting ERK1/2 phosphorylation [86]. Myristicin (**7**), a natural compound isolated from the edible plant *Myristica fragrans*, reduces the phosphorylation of Akt and p65 in ox-LDL-stimulated human aortic smooth muscle cells (HASMCs), thereby inhibiting cell proliferation and migration [87]. Evodiamine (**8**) is a key bioactive alkaloid derived from *Evodia rutaecarpa* [88] and mulberry leaf extract (MLE). Evodiamine and its principal ingredient—neochlorogenic acid (nCGA, **9**) [89] can inhibit the PI3K/Akt signaling pathway, thereby effectively blocking VSMCs proliferation and migration. In addition to the PI3K/Akt pathway, a variety of TCM extracts can also regulate other related signal cascades, showing similar anti-proliferation and anti-migration activities. For example, the extract of leech enzymes (LEE) reduces the expression of inflammatory factors and adhesion molecules in LPS-stimulated RASMCs by targeting the p38 MAPK and NF-κB signaling pathways [90]. Glossogyne tenuifolia (GT), also known as Xiang-Ru, is a traditional herba native to Penghu Island in Taiwan, China. Its ethanol extract (GTE) effectively suppresses the phosphorylation of the NF-κB and MAPK signaling pathways stimulated by PDGE-BB, and down-regulates the expression of MMP-2 and MMP-9, thereby blocking PDGF-BB-stimulated cell migration. Chlorogenic acid (**10**), luteolin-7-glucoside (**11**), and luteolin (**12**) [91] were identified as the main components of anti-proliferation activity in GTE. An extract enriched with furostanol saponins (FSEE) is obtained from the aerial portions of *Tribulus terrestris*. This extract considerably diminishes the area of atherosclerotic plaques of $ApoE^{-/-}$ mice subjected to a high-fat diet (HFD). In A7r5 cells stimulated by ox-LDL and FBS, FSEE inhibits the phosphorylation within the Akt/ERK signaling pathway [92].

The receptor tyrosine kinase commonly associated with PDGF is PDGFRβ, which has PDGF-BB as its natural ligand. Myricanol (**13**), a chemical component isolated from *Myrica rubra* [93], and theaflavin-3,3′-digallate (TF3, **14**), a beneficial component found in black tea [94], both have the capacity to reduce the phosphorylation of PDGFRβ in RASMCs. This decrease inhibits the activation of phospholipase C-γ1 (PLC-γ1) by ligand binding and inhibits the phosphorylation of Src family proteins, thereby regulating the downstream MAPK signaling pathway. These natural compounds show notable anti-proliferation and anti-migration effects on VSMCs. The extracts from evening primrose stem (EVP), derived from a plant native to Korea, have similar biological activity by down-regulating the expression of cell cycle-related proteins such as retinoblastoma protein (Rb) and inhibiting phosphorylation of Akt and mTOR [95]. In addition, myricanol inhibits the phosphorylation of IκBα and p65, and blocks the translocation of p65 to the nucleus, thereby weakening NF-κB signaling [93]. Importantly, both TF3 and myricanol significantly inhibit intimal hyperplasia in the carotid artery ligation model [94].

Toll-like receptors (TLRs) are key signaling molecules in the innate immune system. Studies have shown that TLR4 can promote the migration of VSMCs by activating MAPK and ERK1/2 signaling pathways [96]. In addition, TLR4 ligands induce the activation of a variety of transcription factors, including NF-κB and interferon regulatory factors (IRFs) and further participate in the regulation of inflammation and immune-related genes [97]. Corilagin (**15**), an extract of *Phyllanthus urinaria*, significantly inhibits the activation of the TLR4 signaling pathway in ox-LDL-stimulated MOVAS. This inhibition can reduce the level of myeloid differentiation factor 88 (MyD88), a downstream signal molecule of TLR4, thereby inhibiting the proliferation of MOVAS. In addition, corilagin can also reduce the expression of TLR4 and MyD88 in the lesion area of the rat femoral artery plaque [98].

Nitric oxide (NO) can inhibit the migration and proliferation of VSMCs stimulated by PDGF. Ferulic acid (FA, **16**) is widely found in a variety of vegetables and fruits, *Ligusticum chuanxiong*, *Angelica sinensis* and other Chinese herbal medicines. In MOVAS, FA activates the endothelial nitric oxide synthase (eNOS) pathway to promote NO production and enhance p21 expression to inhibit cell proliferation and migration. This finding was also verified in $ApoE^{-/-}$ mice [99]. Hydroxysafflor yellow A (HSYA, **17**), a main active ingredient extracted from *Carthamus tinctorius*, increases the level of NO in PDGF-BB-stimulated RASMCs, and then promotes the formation of cyclic guanosine monophosphate (cGMP) to inhibit the proliferation of VSMCs [100]. In addition, ginsenoside Re (**18**) is also confirmed to inhibit the RASMCs proliferation through the eNOS/NO/cGMP signaling pathway [101].

Janus kinase 2 (JAK2) belongs to the family of tyrosine kinases and is essential for hematopoietic processes and cytokine signaling. Elevated kinase activity may lead to enhanced cell proliferation and improved hematopoietic function, and play a role in a variety of diseases. The signal transducers and activators of transcription (STATs) are involved in this process as down-

stream regulators of JAKs [102]. Schisandrin (Sch, **19**), a chemical component extracted from *Schisandra chinensis*, interferes with the cell cycle by blocking the JAK2/STAT3 pathway, thereby reducing the proliferation and migration of ox-LDL-stimulated RASMCs [103]. Additionally, american ginseng extract can (AGE) also inhibit the activation of JAK2/STAT3 pathway, thereby reducing the proliferation and migration of RASMCs stimulated by FBS, PDGF or Ang II [104].

MicroRNAs (miRs) are a class of endogenous regulatory RNAs derived from DNA transcription, which are ubiquitous in animals and plants and play an important role in the regulation of post-translational modification. A variety of microRNAs significantly affect VSMCs proliferation and migration [105, 106]. Icariin (ICA, **20**) is an active ingredient extracted from *Epimedium brevicornu*. By constructing a microRNA chip for analysis, it was revealed that miR-205-5p can be up-regulated in both $ApoE^{-/-}$ mice and HASMCs treated with ICA. This upregulation leads to a reduction in the phosphorylation of its target protein ERBB4, which subsequently inhibits Akt phosphorylation, thereby decreasing VSMCs migration and proliferation stimulated by ox-LDL [107]. Moreover, target prediction by comparing the toxicological genomics database showed that puerarin (**21**) derived from *Pueraria lobata* inhibits miR-29b-3p in ox-LDL-stimulated HASMCs, thereby inhibiting proliferation by enhancing the level of its downstream target gene *IGF1* [108]. Additionally, MiR-145 has been shown to have regulatory functions in AS. In homocysteine (Hcy)-stimulated HASMCs, the expression of miR-145 was decreased, while the expression of its target gene *CD40* was increased. Tanshinone IIA (**22**), the main component of *Salvia miltiorrhiza*, inhibits VSMCs proliferation and migration by up-regulating the expression of miR-145 and reducing the expression of CD40 [109]. *Lycium barbarum* polysaccharide (LBP), an active substance in *Lycium barbarum*, also increases miR-145 expression in Hcy-stimulated HASMCs and suppressing the activation of PI3K/Akt signaling pathway [110]. Additionally, Nelumbo nucifera polyphenol extract (NLPE) and its main active ingredient gallic acid (GA, **23**), can increase the expression levels of phosphatase and tensin homolog (PTEN), Ras kinase inhibitor 2 and inducible nitric oxide synthase (iNOS) by inhibiting the Ras signaling pathway, thereby inhibiting the proliferation of TNF-α-stimulated A7r5 cells. The inhibitory effect was related to the up-regulation of miR-143 and miR-145 expression, and the down-regulation of miR-21 expression further enhanced the activity of PTEN [111].

Peroxisome proliferator-activated receptor γ (PPARγ) is an important member of the nuclear receptor superfamily. As a ligand-activated transcription factor, PPARγ plays a key regulatory role in the occurrence and development of various CVDs [112, 113], and can regulate VSMCs proliferation and migration in the process of AS. Ginsenoside Rg3 activates this receptor in MOVAS, thereby inhibiting cell proliferation and migration, in which the activity of the *S*-type isomer is significantly stronger than that of the *R*-type. In a mouse model of diabetic atherosclerosis, 20(*S*)-Rg3 (**24**) has been shown to effectively inhibit VSMCs proliferation and migration and reduce plaque area [114]. In addition, the main phase I metabolite of curcumin, hexahydrocurcumin (HHC, **25**), restores the expression of Ang-II-inhibited receptor and its coactivator peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) in RASMCs, thereby inhibiting NF-κB activity [115].

Ras homologous gene family member A (RhoA) is a small GTPase that regulates cell function. Rho-related kinase (ROCK), a key downstream effector molecule, is involved in the migration of VSMCs and vascular remodeling by regulating the assembly and localization of microfilament cytoskeleton. RhoA activates the downstream ROCK1/2 protein, which phosphorylates myosin light chain phosphatase and activates JNK kinase, thereby triggering cell contraction. Bunao Fuyuan Decoction (BNFY) is a TCM prescription. Zhang et al. prepared this prescription by decocting method and concentrated it to 1 $g \cdot mL^{-1}$, and then gave rats by gavage. After continuous administration, the serum of these rats was used to treat ox-LDL-stimulated VSMCs. The results showed that this treatment could reduce the expression of RhoA/ROCK signaling pathway-related proteins, thereby inhibiting cell proliferation, migration, and invasion [116]. Earlier research has shown that the expression of c-Myc can trigger the production of MMPs [117]. Ligustilide (**26**) is the main active ingredient found in the volatile oil of *Angelica sinensis*. In Ang II-stimulated RASMCs, ligustilide inhibits the c-Myc/MMP2 and the ROCK-JNK signaling pathways, thereby exerting an anti-migration effect [118]. In A7r5 cells, overexpression of KRas can up-regulate the levels of RhoA, Rac1, CDC42, and phosphorylated focal adhesion kinase (FAK), while mulberry polyphenol extract (MPE) can inhibit the expression of these proteins, thus effectively blocking VSMCs migration. In addition, MPE also promotes the binding of IκBα to NF-κB and further regulates related signaling pathways [119]. TGF-β is a multifunctional cytokine secreted by a variety of cells and plays a key role in cell proliferation and differentiation [120]. TGF-β, as a ligand of TGF-β receptor type II (TGFβR2), can recruit and phosphorylate TGF-β receptor type I (TGFβR1) after binding to it. This activation process is dependent on the ROCK signaling pathway and ultimately triggers Smad2/3 phosphorylation and regulates downstream gene transcription [121]. Curcumin (**27**), the main active ingredient of turmeric, inhibits the transactivation of TGFβR1 and the expression of MCP-1 stimulated by lysophosphatidic acid by blocking the ROCK signaling pathway in HASMCs [122]. Myricetin (**28**) is a representative chemical component of bayberry, which can directly bind to TGFβR1 and inhibit its kinase activity, reduce the phosphorylation level of TGFβR1 and Smad2/3, thereby inhibiting the migration and proliferation of HASMCs [123].

In addition to the above pathways, a variety of signaling pathways also mediate the role of natural compounds in anti-atherosclerotic. Silent information regulator 1 (SIRT1), as a ribozyme, is significantly down-regulated in AS plaque tissues and ox-LDL-stimulated HASMCs [124]. Liquiritin (**29**), a flavonoid primarily found in *Glycyrrhiza uralensis*, regulates cell proliferation and migration by up-regulating the expression of SIRT1 in ox-LDL-stimulated HASMCs, and plays an anti-coronary atherosclerosis role [125]. Another phenolic compound eugenol (**30**), derived from the Piperaceae family, attenuates ox-LDL-stimulated HASMCs proliferation and migration by inhibiting the Ang II/MFG-E8 (a widely expressed glycoprotein)/MCP-1 signaling pathway [126]. Chemokine is a recently discovered adipocytokine. Studies have shown that the expression of chemokine-like receptor 1 (CMKLR1) is up-regulated in atherosclerotic tissues stimulated by HFD, and its expression level is positively correlated with the degree of aortic tissue proliferation. Lipocalin-2 (LCN2) plays a key role in the proliferation and migration of VSMCs mediated by chemokine/CMKLR1, involving signal cascades such as p38/MAPK and Wnt/*β*-catenin (which is closely related to growth and development). Curcumin (**27**) inhibits VSMCs proliferation and migration by targeting the chemerin/CMKLR1/LCN2 axis, thereby delaying the progression of AS [127]. Fat mass and obesity-related protein (FTO) plays a key regulatory role in Ang II-stimulated VSMCs proliferation and inflammatory response. As a semi-synthetic derivative of artemisinin, dihydroartemisinin (DHA, **31**) down-regulates the expression of FTO and increases the methylation level of downstream factor *NR4A3* messenger RNA (mRNA), thereby inhibiting Ang II-stimulated proliferation of MOVAS and related inflammatory responses [128].

In addition to the above signaling pathways, some natural compounds can also block VSMCs in the G_1/G_0 phase by regulating the expression of cell cycle-related proteins, thereby inhibiting their proliferation. (2*S*)-Naringenin (**32**), isolated from *Typha latifolia*, reduces the protein expression levels of cyclin D1,

cyclin E, CDK2 and CDK4 in rat aortic smooth muscle cells (RAVSMCs) [129]. Astragaloside IV (**33**), a key active ingredient of *Astragalus membranaceus*, decreases Cdc25 (a phosphatase activated by CDK2 [130]) expression, thereby inhibiting CDK2 activity and ultimately blocking Ang II-stimulated rat aortic smooth muscle cell line A10 proliferation [131]. Gossypetin (GTIN, **34**), also known as 3,5,7,8,30,40-hexahydroxyflavone, is a natural hydroxylated flavone. This substance enhances the expression of phosphorylated p53 and its downstream targets, while inhibiting the activation of CDK-2, thereby interfering with the phosphorylation of Rb protein and preventing the dissociation of Rb/E2F1 transcription factor complex, and ultimately reducing the proliferation of FBS-stimulated A7r5 cells [132]. Zhao et al. confirmed that ginsenoside Rb1 (**1**) can directly bind to cyclin D1 (CCND1) protein, prevent the interaction between CCND1 and CDK4, and then inhibit the proliferation of VSMCs by pharmacological analysis of protein interaction network and co-immunoprecipitation of HASMCs *in vitro* [133].

In addition, calcium ions (Ca^{2+}) play an important role in the regulation of VSMCs proliferation [134]. Extracellular Ca^{2+} influx activates calcium-sensitive signaling proteins, such as calmodulin-dependent protein kinase and MAPK, thereby promoting cell proliferation [135, 136]. The calmodulin family (including Calm1–4 subtypes) acts as a calcium-sensitive receptor, and the expression level of Calm4 is significantly increased in proliferating VSMCs. Studies have shown that the aporphine alkaloid nuciferine (**35**) extracted from the lotus leaf can inhibit the proliferation and migration of ApoE$^{-/-}$ mice and MOVAS by regulating the Calm4/MMP12/AKT signaling pathway, showing anti-atherosclerotic activity. The above results suggest that Calm4 may be a potential new target for the treatment of AS [137]. Intracellular Ca^{2+} concentration is precisely regulated by a variety of membrane channels and transporters. Isoflavone compound genistein (**36**) inhibits L-type calcium channel current and down-regulates the expression of oxidized low-density lipoprotein receptor 1 (LOX-1). This effect reduces the proliferation, migration and foaming of ox-LDL-stimulated VSMCs, and decreases the expression level of the SRC/CACNA1C/LOX-1 pathway protein, and ultimately reduces the plaque area and lipid deposition of AS rats [138]. Transient receptor potential channel 5 (TRPC5) is an important member of the calcium ion store-operated channels, which can be activated by 1,4,5-trisphosphate (IP3) in VSMCs and mediate sustained and slow calcium influx. Isoliquiritigenin (ISL, **37**), a flavonoid compound isolated from *Glycyrrhiza uralensis*, reduces the degree of atherosclerotic lesions and blood lipid levels in ApoE$^{-/-}$ mice, and inhibits the expression of TRPC5. Moreover, studies *in vitro* have confirmed that ISL effectively inhibits the expression of TRPC5 and PCNA stimulated by Ang II in a dose-dependent manner, thereby blocking VSMCs proliferation [139].

In summary, a variety of natural compounds can improve AS by regulating VSMCs proliferation and migration (Fig. 2). These findings highlight the potential value of natural compounds to treat VSMCs dysfunction-related CVDs. Further elucidation of the mechanism of these compounds will provide important clues for understanding the role of VSMCs in CVDs and promote the development of new therapeutic strategies.

3.2. Regulation of VSMC phenotypic switching

The differentiation of VSMCs into osteochondrogenicl-like cells significantly contributes to vascular calcification (VC), which frequently coexists with atherosclerotic plaques. A hallmark of VC is the deposition of calcium phosphate in arterial walls, predominantly affecting the intima and endothelial lining, and is widely recognized as a key component of AS. During AS, multiple factors—including inflammatory microenvironment, oxidative stress, ROS and hydrogen peroxide (H_2O_2)—activate transcription factors such as RUNX2, promoting VSMCs osteogenic differentiation [140]. Under pathological conditions like hypercholesterolemia or excessive vitamin D exposure, VC can also be triggered [141]. Thus, VSMCs differentiation into osteochondral-like cells is typically driven by the interplay between oxidative stress and inflammation. *In vitro*, studies commonly use H_2O_2 and inorganic phosphate to induce VSMCs calcification, whereas animal models often employ vitamin D3 plus nicotine (VDN) to establish VC. Genistein (Gen, **36**) markedly reduces the expression of the osteogenic marker RUNX2 in human aortic VSMCs (HAVSMs) stimulated by inorganic phosphate [142]. *Ganoderma lucidum* is a TCM

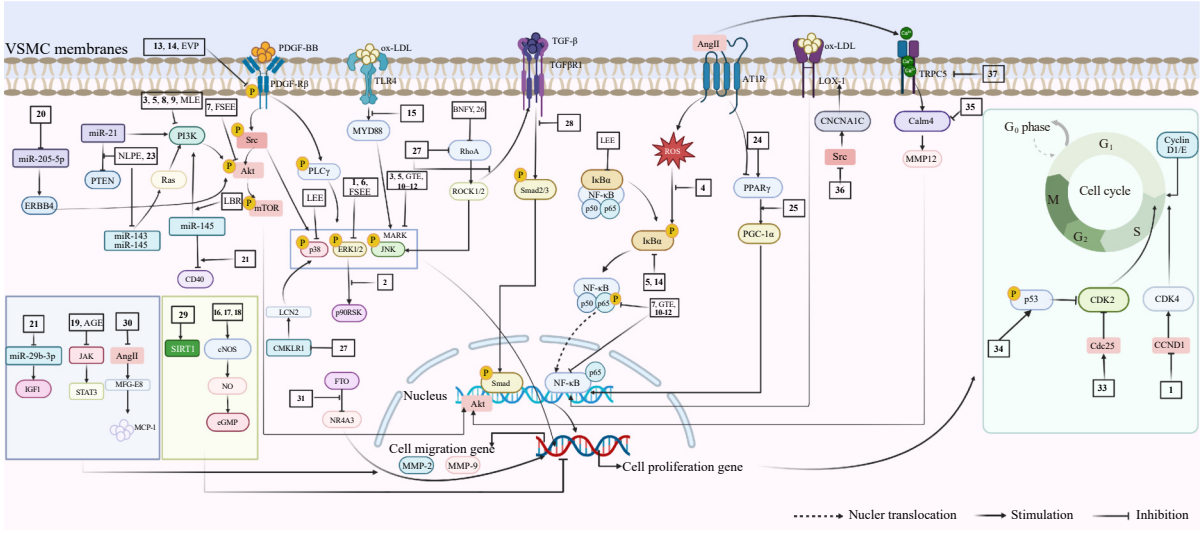


Fig. 2 Mechanisms and targets of natural compounds inhibiting VSMCs proliferation and migration. Under pathological stimulation, VSMCs can activate intracellular signaling pathways such as NF-κB and MAPK, thereby driving the transcription of cell cycle-related genes and promoting cell proliferation. Additionally, VSMCs enhance their migratory ability from the medial to the intimal layer by up-regulating the expression of MMPs and other migration-related proteins. The compounds involved include: **1**, ginsenoside Rb1; **2**, ginsenoside Rh1; **3**, protocatechuic aldehyde; **4**, vinpocetine; **5**, (−)-epicatechin gallate; **6**, pterostilbene; **7**, myristicin; **8**, evodiamine; MLE, mulberry leaf extract; **9**, neochlorogenic acid; LEE, extract of leech enzymes; GTE, ethanol extract of Glossogyne tenuifolia; **10**, chlorogenic acid; **11**, luteolin-7-glucoside; **12**, luteolin; FSEE, extract enriched with furostanol saponins; **13**, myricanol; **14**, theaflavin-3,3′-digallate; EVP, evening primrose stem; **15**, corilagin; **16**, ferulic acid; **17**, hydroxysafflor yellow A; **18**, ginsenoside Re; **19**, schisandrin; AGE, American ginseng extract; **20**, icariin; **21**, puerarin; **22**, tanshinone IIA; LBP, polysaccharide derived from *Lycium barbarum*; **23**, gallic acid; **24**, 20(*S*)-ginsenoside Rg3; BNFY, Bunao-Fuyuan Decoction; **25**, hexahydrocurcumin; **26**, ligustilide; **27**, curcumin; **28**, myricetin; **29**, liquiritin; **30**, eugenol; **31**, dihydroartemisinin; **32**, (2*S*)-naringenin; **33**, astragaloside IV; **34**, gossypetin; **35**, nuciferine; **36**, genistein; **37**, isoliquiritigenin.

with dual medicinal and nutritional value. Its spore powder (GLSP) reduces RUNX2 expression in aortic plaques of low-density lipoprotein receptors knock out ($LDLR^{-/-}$) mice and in calcification medium-stimulated HASMCs [143].

The expression of vascular calcification markers is regulated by multiple signaling pathways. In a VDN-stimulated VC rat model, triptolide (TP, **38**), extracted from *Tripterygium wilfordii*, inhibits BMP2 and RUNX2 expression in VSMCs by upregulating miR-204 [144]. Additionally, curcumin (**27**) can not only reduce the calcium salt deposition in the aorta of VC model rats, but also inhibit the expression of EGFR, STAT3 and RUNX2 in RAVSMCs cultured under high calcium conditions, thereby reducing the calcification process [145]. *In vitro* studies have shown that tanshinone IIA (**22**) significantly reduces the mRNA expression of *Runx2*, *Bmp2*, *Msx2* and *ALP* in high-phosphorus-stimulated HASMCs by inhibiting NF-κB and *β*-catenin signaling pathways, thereby reducing osteogenic differentiation and the risk of vascular calcification [146]. Xanthohumol (XN, **39**), a polyphenolic chalcone compound only present in hops, reduces aortic calcium content, ALP activity, superoxide and ROS production, thereby alleviating vascular calcification in rat models [147]. The active ingredient baicalein (**40**) of *Scutellaria baicalensis* also showed a similar anti-calcification effect in the same model [148]. In addition, the new pterostilbene-dihydropyrazole compound-(Ptd-1) (**41**) synthesized by Chen et al. can inhibit the activation of the ERK1/2 pathway in vascular calcification and phosphate-stimulated HASMCs, thereby down-regulating the level of *β*-catenin and exerting anti-calcification effect. This effect subsequently suppresses the IL-6/STAT3 signaling pathway, reduces inflammatory markers, and prevents VSMC osteogenic transformation [149]. Notoginseng saponin R1 (**42**) and protocatechuic aldehyde (PCA, **3**), major bioactive components of *Panax notoginseng* and *Salvia miltiorrhiza* respectively, were tested in a co-culture system of VSMCs and endothelial cells (ECs). The R1-PCA combination reduces inflammation and *β*-glycerophosphate disodium salt hydrate (*β*-GP)-stimulated calcification in VSMCs. In terms of mechanism, R1-PCA promotes the release of NO from ECs, thereby inhibiting the activation of TGF-βR1 in VSMCs. This inhibitory effect can reduce the phosphorylation of Smad2/3, thereby inhibiting the translocation of YAP/TAZ protein interacting with Smad2/3 into the nucleus. At the same time, the inhibition of YAP also blocks the nuclear translocation of NF-κB and reduces the expression level of NF-κB in VSMCs. The above results indicate that targeting intercellular signal transduction may provide a new strategy for the intervention of VC [150].

Besides preventing osteochondrogenic transition, certain natural compounds can also inhibit the shift of VSMCs from a "contractile" to a "synthetic" phenotype. The results of RNA sequencing of aortic tissue of $ApoE^{-/-}$ mice treated with artemisinin (ART, **43**) revealed that contractile function-related genes expression in VSMCs was significantly increased. *In vitro*, ART effectively reverses the migration and proliferation of PDGF-BB-stimulated MOVAS and increase the level of contractile phenotype-related proteins [151]. Nicotinate-curcumin (NC, **44**), a new derivative combined by nicotinic acid and curcumin, enhances multifunctional death domain-related proteins and phosphatase and tensin homolog (PTEN) protein expression, thereby blocking the activation of the downstream PI3K/Akt signaling pathway and inhibiting Ang II-stimulated phenotypic differentiation of VSMCs [152]. The Notch signaling pathway can also regulate the phenotypic transformation of VSMCs. Its ligands Jagged1, Jagged2, Dll1 (Delta-like 1), Dll3 and Dll4 activate this pathway by binding to Notch receptors, thereby promoting the conversion of VSMCs between contractile and synthetic phenotype. Matrine (**45**) is an active ingredient extracted from the medicinal plant *Sophora alpecuroides*. In AGEs-stimulated human coronary artery smooth muscle cells (HCSMCs), matrine inhibits the activation of protein kinase RNA-like endoplasmic reticulum kinase (PERK), which is involved in the Dll4-Notch pathway, thereby preventing cell phenotypic switching [153]. Liuwei Dihuang Soft Capsule (LWDH) is a widely used Chinese patent medicine. In RASMCs and $ApoE^{-/-}$ mice, LWDH enhances the activity of myogenic protein by up-regulating the expression of estrogen receptor ERα and promoting its interaction with steroid receptor coactivator 3 (SRC3), thereby inhibiting the phenotypic differentiation of VSMCs [154].

Beyond the aforementioned phenotypic transitions, quercetin (**46**), a flavonoid compound widely found in plants, prevents VSMCs from transforming into macrophage-like cells. In $ApoE^{-/-}$ mice, phosphorylated JAK2, phosphorylated STAT3 and high expression of KLF4 were co-localized with macrophage-like VSMCs in the aggregation area of aortic plaque foam cells, and quercetin could reduce this co-localization. In ox-LDL-stimulated MOVAS, quercetin inhibits the expression of KLF4, LGALS3, CD68 and F4/80 by inhibiting the JAK2/STAT3 signaling pathway, thereby blocking KLF4-stimulated VSMCs to macrophage-like phenotype differentiation [155].

In summary, the phenotypic differentiation of VSMCs constitutes a critical part in the progression of AS. Natural compounds regulate this differentiation process by modulating relevant signaling pathways, altering the expression levels of key proteins, and influencing intercellular interactions (Fig. 3). These findings highlight the unique value of natural compounds in improving AS through targeting VSMCs phenotypic differentiation. Further studies are required to elucidate the underlying molecular mechanisms and to evaluate the clinical application potential of these compounds in improving vascular health.

3.3. Regulation of VSMC senescence and death

In a variety of intervention strategies for VSMCs, in addition to regulating their phenotypic differentiation, delaying or reversing their senescence process is also an important treatment direction. Rutin (**47**) is a flavonoid compound widely found in leguminous plants. In a mouse model of diabetic AS, rutin reduces the expression of *β*-Gal, reduces the number of senescent cells, and increases the proportion of VSMCs in aortic root plaques. In addition, in the oxidative stress model of MOVAS stimulated by H_2O_2, rutin can alleviate oxidative stress-stimulated premature cell senescence by inhibiting the production of reactive oxygen species and reducing the expression of malondialdehyde (MDA) [156]. Paeonol (Pae, **48**), an active compound extracted from the root bark of *Paeonia suffruticosa*, reduces the plaque area and the expression of cell senescence markers in $ApoE^{-/-}$ mice. *In vitro*, Pae directly binds to SIRT1 and reduces the levels of its downstream target protein p53 and telomere repeat binding factor 2, thereby reducing the expression of p16 and p21, alleviating telomere damage, and ultimately inhibiting the senescence of VSMCs [157].

During AS, the removal of lipid-loaded foam cells through autophagy, known as lipophagy, can avoid excessive lipid accumulation. The autophagy process is usually initiated by microtubule-associated protein 1 light chain 3II (LC3II), which forms APs by recognizing and isolating lipid droplet membrane proteins, and then APs fuse with lysosomes to form autolysosomes [158]. At the same time, lipid droplets abundant in cholesterol esters are hydrolyzed into free cholesterol by lipophagy, and then excreted by cholesterol efflux proteins such as ATP-binding cassette transporter A1 (ABCA1), thereby reducing foam cell formation and maintaining lipid homeostasis [159]. Bisdemethoxycurcumin (BDMC, **49**), one of the active components of *Curcuma kwangsiensis*, reduces the formation of lipid droplets in ox-LDL-stimulated MOVAS. Pyruvate dehydrogenase kinase 1 (PDK1) is identified as the binding target of BDMC by network pharmacology. This target can inhibit the downstream Akt/mTOR signaling pathway,

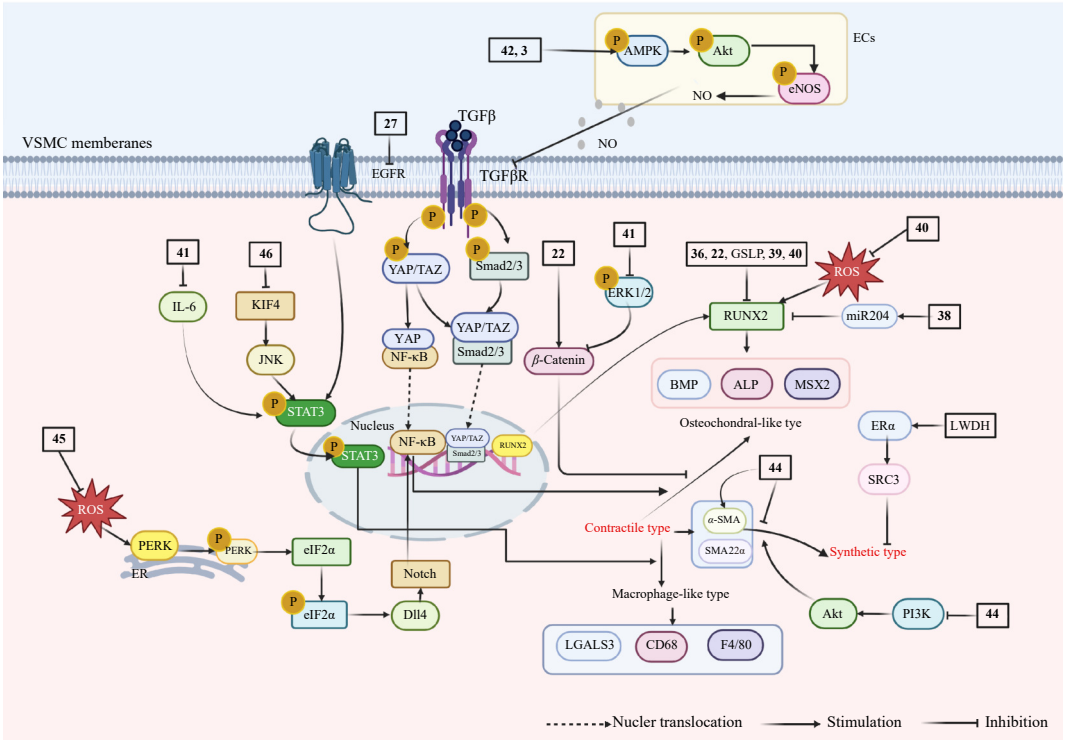


Fig. 3 Mechanisms and targets of natural compounds regulating VSMCs phenotypic transformation. Natural compounds can suppress the calcification process by down-regulating the expression of calcification-related genes and proteins in VSMCs through regulating multiple signaling pathways. Moreover, some of these compounds further promote the expression of relevant marker proteins and then inhibit the differentiation of VSMCs toward a synthetic phenotype or macrophage-like phenotype. The compounds involved include: **36**, genistein; GLSP, spore powder of *Ganoderma lucidum*; **38**, triptolide; **27**, curcumin; **22**, tanshinone IIA; **39**, xanthohumol; **40**, baicalein; **41**, (*E*)-1-(5-(2-(4-fluorobenzyloxy)styryl)-4,6-dimethox-yphenyl)-3-methyl-4,5-dihydro-1H-pyrazole-1-yl) ethyl ketone; **42**, notoginseng saponin R1; **3**, protocatechuic aldehyde; **43**, artemisinin; **44**, nicotinate-curcumin; **45**, matrine; LWDH, Liuwei Dihuang Soft Capsules; **46**, quercetin.

thereby promoting the autophagy process and increasing the expression of ABCA1 to promote cholesterol efflux and inhibit the formation of foam cells in VSMCs. In addition, it can also reduce the inflammatory response and lipid accumulation in ApoE$^{-/-}$ mice [160]. Scutellarin (Scu, **50**) is a flavonoid extracted from marigold flowers. In the oleic acid-stimulated RAVSMC foam cell model, Scu can reduce lipid accumulation by promoting autophagy and inhibiting NLRP3 inflammasome activation. In addition, Scu can also activate liver X receptor α (LXRα), thereby increasing the expression of ATP-binding cassette transporter A1 to promote cholesterol efflux [161]. Celastrol (**51**) is a quinone methyl triterpene compound extracted from the root bark of *Tripterygium wilfordi*. It also exhibits similar effects to Scu in MOVAS and A7r5 cells [162]. The combination of curcumin (**27**) and photodynamic therapy (PDT) by Bai et al. significantly improves the autophagy level of MOVAS and A7r5 cells, reduces the phenotypic transformation and migration activity stimulated by ox-LDL and the number of lipid droplets and foam cell formation [163].

P2RY12 belongs to the P2 receptor family and is highly expressed in atherosclerotic plaques and foam cells. In the process of AS, the activation of P2RY12 increases the formation of foam cells in VSMCs by inhibiting autophagy [164]. Therefore, targeted inhibition of P2RY12 activation may be a potential new strategy to regulate VSMCs behavior and improve AS. Gualou Xiebai (GLXB) is a commonly used drug pair in TCM, usually in a 2∶1 ratio. The drug pair significantly reduces lipid accumulation in ApoE$^{-/-}$ mice and ox-LDL-stimulated MOVAS, and reduces the levels of P2RY12, p62 and lipid droplet-specific protein Plin2 to promote lipophagy, while increasing LC3II protein expression and increasing the number of autophagosomes. The main active components targeting P2RY12 include albiflorin (**52**), apigenin (**53**), luteolin (**54**), kaempferol (**55**), 7,8-dihydroxyflavone (**56**), and hesperetin (**57**) [165]. Huanglian Jiedu Decoction is another TCM prescription. In ApoE$^{-/-}$ mice and ox-LDL-stimulated MOVAS, the prescription inhibits foam cell formation by inhibiting the P2RY12/PI3K/AKT signaling pathway to enhance autophagy [166].

Some natural compounds can also regulate autophagy of VSMCs through the mTOR signaling pathway. Calycosin (**58**) is a flavonoid component in *Astragalus membranaceus*. In β-GP-stimulated A7r5 cells, calycosin initiates the autophagy process by activating the AMPK/mTOR signaling pathway and promotes the formation of soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor complex, thereby promoting the fusion of autophagosomes and lysosomes under the mTORC1-dependent mechanism. This process can restore the autophagy function of calcified VSMCs and effectively inhibit VC [167]. Bavachin (**59**), a phytoestrogen extracted from *Psoralea corylifolia*, induces autophagy by activating the Atg7/mTOR signaling pathway and down-regulating the Wnt/β-catenin pathway [168]. Luteolin (LUT, **60**) is a common natural flavonoid compound in various vegetables such as green pepper and celery. In the VC model and H_2O_2-stimulated A7r5 cells, LUT inhibits oxidative stress and increases autophagy level by activating SIRT1/CXCR4 signaling pathway [169]. However, there are also natural compounds that treat AS by inhibiting autophagy of VSMCs, such as astragaloside IV (AS-IV, **33**). The use of AS-IV in the treatment of ApoE$^{-/-}$ mice can delay the progression of AS, which is related to the decrease of calcium deposition and autophagy level in VSMCs. *In vitro*, AS-IV activates the mTOR signaling pathway by up-regulating the expression of long-chain non-coding RNA H19, and inhibits the related DUSP5-ERK pathway, thereby reducing the calcification and autophagy levels of VSMCs [170].

Some natural compounds improve AS by inhibiting the apoptosis of VSMCs. For example, Pae (**48**) promotes VSMC autophagy by activating the class III phosphatidylinositol 3-kinase (PI3K)/beclin-1 pathway, thereby inhibiting apoptosis [171]. In addition, paeoniflorin can also slow down the AS process of ApoE$^{-/-}$ mice, enhance plaque stability, and is related to reducing T/B lymphocyte infiltration. Activated T/B lymphocytes express LTα1β2, which binds to the LTβR (belonging to the tumor necros-

is factor receptor family) and induces VSMC apoptosis. On the mechanism, paeoniflorin inhibits the apoptosis of MOVAS stimulated by LTα1β2 by blocking the LTβR/NF-κB-stimulated kinase (NIK)/calpain I signaling pathway. These results indicate that paeoniflorin can exert anti-atherosclerotic effects by simultaneously reducing immune cell infiltration and inhibiting VSMC apoptosis, providing a new mechanism for related treatment [172]. Antrodia camphorata (AC), a rare medicinal mushroom from Taiwan, China, improves cell morphological abnormalities and death stimulated by cigarette smoke extract (CSE). AC reduces the accumulation of ROS in A7r5 cells by reducing the ratio of Bax/Bcl-2, increasing the levels of superoxide dismutase (SOD) and catalase (CAT), and inhibiting the degradation of IκBα to block the activation of NF-κB, thereby reducing CSE-stimulated apoptosis. Animal experiments further confirmed that oral administration of AC could inhibit the progression of AS stimulated by CSE in ApoE$^{-/-}$ mice [173].

Recent studies have shown that some natural compounds regulate VSMC pyroptosis and ferroptosis. Ligustrazine (**61**), also known as 2,3,5,6-tetramethylpyrazine (TMP), derived from *Ligusticum chuanxiong*, inhibits the pyroptosis mediated by calpain I/GSDME in *β*-GP-stimulated MOVAS, and reduces ROS, IL-1β, and IL-18 levels [174]. Zhou et al. established a screening system based on mechanical properties to screen compounds that can improve arterial wall stiffness by regulating VSMC-ECM interactions. It was found that the chalcone compound echinatin (**62**) derived from the roots and rhizomes of *Glycyrrhiza inflata* could reduce the hardness of the ECM around cultured VSMCs. In the mouse model of adenine feed and hyperlipidemia combined with 5/6 nephrectomy, echinatin intervention can reduce the progression of AS. RNA sequencing analysis reveals that echinatin upregulates the expression of glutamate-cysteine ligase (GCL) subunits (GCLC and GCLM), supporting GSH metabolism homeostasis. By regulating the GSH synthesis pathway, liquiritigenin further inhibits ferroptosis and affected ECM remodeling [175].

In summary, the senescence and death of VSMCs are complex biological events in the development of AS. A variety of natural compounds can prevent and improve AS by regulating senescence-related pathways and cell death pathways (Fig. 4). Elucidating these mechanisms in depth is expected to provide an important theoretical basis for the development of new treatment strategies.

3.4. Anti-inflammatory and oxidative stress

The inflammatory response and oxidative stress of VSMCs also play an important regulatory role in AS. Inflammatory response is usually accompanied by lipid peroxidation, which produces markers such as MDA. Oxidative stress is derived from the imbalance between the production of ROS and the body's antioxidant system, which often aggravates the inflammatory response. For example, the formation of reactive oxygen species can activate NF-κB, thereby promoting the transcriptional expression of a variety of inflammatory factors, and the release of inflammatory mediators will further aggravate oxidative stress [176]. In addition, oxidative stress can trigger the inflammatory response of VSMCs and aggravate their differentiation, proliferation, and migration, thereby promoting the formation of atherosclerotic plaques. Oxidative stress process involves a variety of oxidases and antioxidant enzymes : oxidase enzymes include NADPH oxidase (Nox), inducible nitric oxide synthase (iNOS), cyclooxygenase (COX) and lipoxygenase; antioxidant enzymes include superoxide dismutase (SOD), catalase (CAT), endothelial nitric oxide synthase (eNOS) and glutathione peroxidase (GSH-Px) [177]. At the same time, the inflammatory response is related to a variety of signaling pathways, such as MAPK and NF-κB, which can regulate the proliferation and migration of VSMCs.

Carvacrol (**63**), a compound extracted from Lamiaceae family, reduces NOX-1 and p38 MAPK expression in RASMCs, and its antioxidant effect may be involved in the process of inhibiting VSMCs migration and proliferation [178]. Tormentic acid (TA, **64**), a triterpenoid extracted from the bark of *Vochysia divergens*, inhibits iNOS and NOX expression in H_2O_2-stimulated RASMCs. In addition, the pretreatment of this component can prevent the phosphorylation of NF-κB subunit p65 and the degradation of IκBα, thereby inhibiting the production of inflammatory factors [179]. Puerarin (**65**), a flavonoid compound extracted from *Pueraria lobata*, significantly reduces the mRNA expression levels of *IL-6* and *TNF-α* in ox-LDL-stimulated HASMCs. It also decreases MDA production and increases SOD activity by inhibiting p38 MAPK and

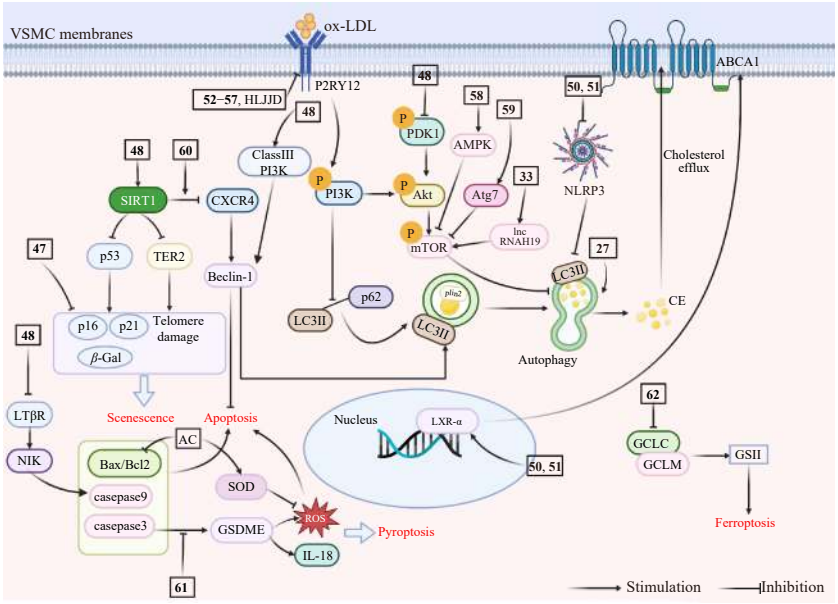


Fig. 4 Mechanisms and targets of natural compounds regulating VSMC senescence and death. Natural compounds can delay the early senescence and death process of VSMCs in AS by down-regulating senescence-related specific markers and related signaling pathways. In addition, these compounds can also block pyroptosis by inhibiting the expression of inflammasomes, regulate glutathione metabolism to resist ferroptosis, and promote lipid autophagy and autophagy levels, thereby reducing lipid accumulation. The compounds involved include: **47**, rutin; **48**, paeonol; **49**, bisdemethoxycurcumin; **50**, scutellarin; **51**, celastrol; **27**, curcumin; GLXB, Gualou and Xiebai; **52**, albiflorin; **53**, apigenin; **54**, luteolin; **55**, kaempferol; **56**, 7,8-dihydroxyflavone; **57**, hesperetin; **58**, calycosin; **59**, bavachin; **60**, luteolin; **61**, ligustrazine; **62**, echinatin.

JNK signaling pathways [180]. Baicalin (**66**), as a glucuronide conjugate of baicalein (**40**), reduces thrombin-stimulated VSMC inflammatory response by inhibiting the activation of the ERK1/2 pathway in RAVSMCs [181]. Baicalin (**40**) shows anti-inflammatory effects in MOVAS, and its mechanism may be related to the activation of the AMPK/mitochondrial fusion protein-2 (Mfn-2) axis, which in turn regulates downstream MAPK and NF-κB pathways [182]. Emodin (**67**), the main active ingredient of *Rheum palmatum*, significantly inhibits the activation of NF-κB in a dose-dependent manner and selectively down-regulates the expression of inflammatory genes stimulated by TNF-α, thus exerting therapeutic effects on VSMCs inflammation [183]. Guo et al. established a co-culture system consisting of ECs, VSMCs and mononuclear cells (MCs) to simulate AS-related inflammatory environment through IL-1β combined with ox-LDL. In this model, tanshinone IIA (**22**) significantly reduces the expression of multiple inflammatory markers, suggesting its potential therapeutic value in alleviating AS-related inflammation [184].

Besides individual compounds, various TCM extracts, clinically used prescriptions, and Chinese patent medicines modulate oxidative stress and inflammation in VSMCs within AS. Aqueous extracts from *Prosopis strombulifera* (AEPs) and *Tessaria absinthioides* (AETa), native Argentine medicinal plants, reduce ROS generation and NOX subunit levels in Ang II-exposed RASMCs. In ApoE$^{-/-}$ mice, these extracts significantly lower triglycerides and lipid peroxides (measured AS plasma thiobarbituric acid reactive substances), enhance total antioxidant status, and increase hepatic GSH peroxidase activity. They also suppress superoxide anion (O^{2-}) production in aortic tissues, demonstrating anti-atherosclerotic effects [185]. Extract of *C. coronarium* (CC) reduces Hcy stimulated ROS accumulation in HASMCs and lowers expression of inflammatory markers such as NOX-4 and soluble epoxide hydrolase, thereby mitigating Hcy-triggered inflammation [186]. Sanhuang Xiexin Decoction (SHXXD), a TCM formula known for purging fire, detoxifying, drying dampness, and clearing heat, significantly inhibits HASMCs migration and proliferation, reduces ROS generation, lowers COX-2 mRNA and protein levels, and blocks ERK1/2 phosphorylation. SHXXD has been shown to significantly suppress the synthesis of pro-inflammatory cytokines, including IL-1β, IL-6, IL-8, and MCP-1 [187]. Gualou Erchen Decoction (GED), a hypolipidemic and anti-inflammatory TCM formula with lipid-lowering and anti-inflammatory properties, has demonstrated efficacy in alleviating hyperlipidemia, reducing aortic plaque accumulation, and improving plaque stability in ApoE$^{-/-}$ mice. Mechanistically, GED decreases the levels of sulfated glycosaminoglycans (sGAGs), chondroitin sulfate proteoglycans (CSPGs), and versican. It also downregulates chondroitin sulfate synthase and multiple inflammatory mediators. *In vitro* studies further reveal that GED inhibits VSMC proliferation and suppresses the production of inflammatory cytokines in ox-LDL- and TNF-α stimulated cells [188]. Xintongtai Granules (XTTG) [189] and *Salvia miltiorrhiza* Injection (SMI) [190] are clinically used Chinese patent medicines for AS. XTTG improves lipid profiles and aortic pathology in ApoE$^{-/-}$ mice, inhibits ox-LDL-stimulated HASMC proliferation and lipid droplet accumulation, reduces MDA levels, increases SOD activity, suppresses NOX4 expression and ROS production, and inhibits NF-κB signaling, thereby alleviating oxidative stress [189]. Krüppel-like factor 10 was initially identified as an early activated gene of TGF-β. Studies have shown that this factor affects the transcription of the heme oxygenase 1 gene (*HO-1*) by directly acting on its promoter region. When the expression of this factor is reduced, SMI can alleviate its inhibitory effect on the expression of this gene, thereby increasing the expression of *HO-1* and reducing the production of ROS. Consequently, SMI exerts an antioxidant effect on MOVAS in a high glucose environment [190].

In summary, oxidative stress and inflammatory response run through the whole process of AS. A variety of natural compounds effectively regulate the inflammatory response and oxidative stress of VSMCs, resulting in positive effects (Fig. 5). These compounds may also inhibit the proliferation of VSMCs through a cascade effect. An in-depth understanding of its interaction mechanism with VSMCs is beneficial to the development of new drugs for the treatment of AS.

4. Discussion

AS is the pathological basis of many cardiovascular diseases. The risk of the disease is significantly increased in patients with

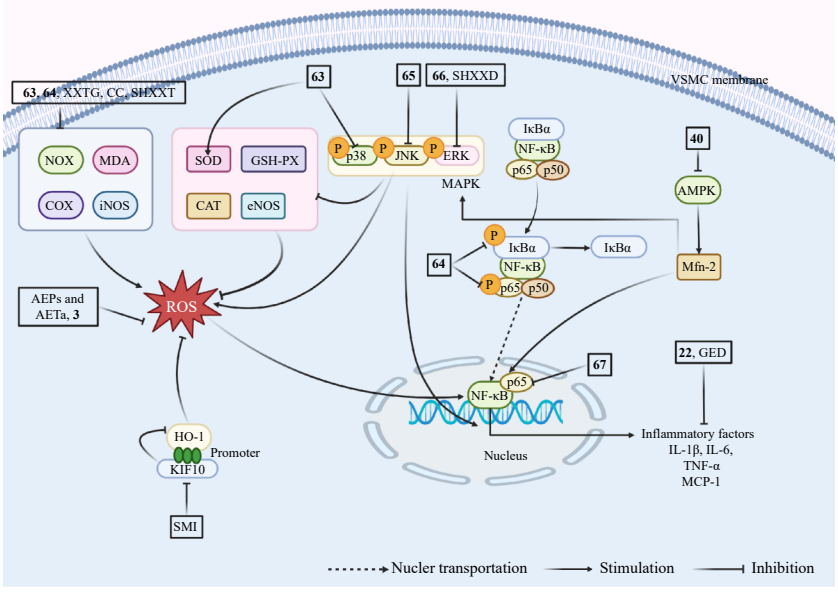


Fig. 5 Mechanisms and targets of natural compounds inhibiting inflammatory response and oxidative stress in VSMCs. Natural compounds combat oxidative stress by promoting the expression of antioxidant enzymes and inhibiting the expression of pro-oxidases, thereby reducing the production of reactive oxygen species. The decrease of reactive oxygen species inhibits the activation of signaling pathways such as NF-κB to further curb the inflammatory response. The compounds involved include: **63**, carvacrol; **64**, tormentic acid; **65**, puerarin; **66**, baicalin; **40**, baicalein; **67**, emodin; **22**, tanshinone IIA; AEPs, aqueous extract from *Prosopis strombulifera*; AETa, aqueous extract from *Tessaria absinthioides*; CC, extract of *C. coronarium*; SHXXD, Sanhuang Xiexin Decoction; GED, Gualou Erchen Decoction; XTTG, Xintongtai Granules; SMI, the injection of *Salvia miltiorrhiza*.

hypertension, hyperglycemia, and hyperlipidemia, and long-term development may lead to a variety of complications. The inducing factors and mechanisms of AS are complex, involving a series of damsenescence events at the cellular level, including inflammatory response, oxidative stress, endothelial dysfunction, phenotypic transformation of VSMCs, and macrophage polarization, as well as a variety of pathophysiological disorders. The key mechanisms include cell recruitment, macrophage-mediated cholesterol efflux, and abnormal proliferation and migration of VSMCs.

As a key cell type involved in the process of AS, VSMCs exhibit complex behavior and interaction patterns in the vascular environment (Fig. 1). Traditionally, this cell is considered to be mainly responsible for maintaining vascular tension and structural stability, but recent studies have revealed that it has significant plasticity and can respond to pathological stimuli into multiple phenotypes. Recent studies have highlighted the key role of multiple phenotypic differentiations of this cell in the progression of AS. For example, single-cell RNA sequencing technology has found different functional subtypes of VSMCs in atherosclerotic plaques. The subgroup known as macrophage-like VSMCs is closely related to plaque instability due to its pro-inflammatory properties [191]. In addition, the inflammatory microenvironment in atherosclerotic lesions significantly affects the behavior of VSMCs [192]. A variety of inflammatory factors and chemokines can lead to decreased contractile properties of VSMCs and the emergence of a variety of alternative phenotypes. These phenotypes may be characterized by macrophages, foam cells, osteochondrocytes and myofibroblasts [193]. In summary, VSMCs can change their phenotypic state in the context of AS, interact with immune system cells, and participate in the inflammatory microenvironment of atherosclerotic lesions. A comprehensive understanding of these interactions is essential for the development of targeted therapies to stabilize plaques and prevent AS-related cardiovascular events.

Compared with traditional drugs, natural compounds have the therapeutic advantages of multi-target, multi-component, and fewer side effects. Studies have shown that a large number of natural compounds and TCM monomers and preparations exert anti-atherosclerotic effects through a variety of related cellular and molecular mechanisms. Although numerous studies have confirmed that natural compounds can effectively target VSMCs and produce beneficial effects, there is no systematic review on this topic. In this paper, the physiological changes of VSMCs in the development of AS are described in detail. These processes cover cell proliferation and migration, phenotypic differentiation, and senescence and death. In addition, this paper systematically summarizes the specific mechanisms and targets of 67 TCM-derived monomers, 10 TCM extracts, 4 TCM prescriptions [116, 166, 187, 188], and 3 clinically used Chinese patent medicines [154, 189, 190] in regulating VSMCs. The chemical structures and categories of all monomer components are listed in Table S1. We numbered them to clarify their targets and mechanisms. The models and specific targets used in the study of each compound are shown in Table S2.

Existing studies have shown that a large number of natural compounds can improve AS by targeting VSMCs, but there are still obvious gaps in related research. For example, previous studies on the regulation of foam cells by natural compounds mainly focused on macrophage-derived foam cells, and studies on the origin of VSMCs are limited. Foam cell formation is usually related to the three key processes of cholesterol uptake, esterification and efflux [194]. Scavenger receptors uptake and internalize cholesterol esters in modified lipoproteins. These esters are hydrolyzed by acidic lipase in lysosomes to form free cholesterol and free fatty acids, and then free cholesterol is re-esterified in the endoplasmic reticulum by acetyl-CoA acetyltransferase and stored in the cytoplasm in the form of lipid droplets. Cholesterol esters accumulated in cells are hydrolyzed into free cholesterol by neutral cholesterol ester hydrolase or hormone-sensitive lipase, and finally cholesterol efflux is achieved by passive diffusion and ABC transporters such as ABCA1 and ABCG1 [195, 196]. However, the specific mechanism of these three cellular metabolic processes in VSMCs remains to be fully elucidated, so there is a broad space for exploration in this field. An in-depth understanding of the process by which VSMCs form foam cells may provide innovative ideas for the treatment of AS. In addition, existing studies mainly focus on cells and animal models. Although a large number of studies have explored the origin and phenotypic changes of VSMCs in human AS [13, 14, 20-23], clinical studies on the effects of natural compounds on these cells are still significantly insufficient. More clinical studies will be helpful to understand the specific mechanism of VSMCs affecting AS and the mechanism of natural compounds in this process.

Through the above review, it can be found that natural compounds provide rich strategic choices for targeting VSMCs and interfering with the multi-factor pathological process of AS. Inhibiting VSMCs proliferation and migration, delaying their senescence and death, enhancing autophagy activity, and regulating inflammatory response may become a new strategy for AS treatment, thereby reducing the risk of related cardiovascular events. Further research is needed to clarify the specific molecular mechanism of VSMCs in the progression of AS, to fully reveal the mechanism and therapeutic potential of natural compounds in this pathological background.

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Declaration of competing interest

There are no conflicts of interest to declare.

References

1 Falk E. Pathogenesis of atherosclerosis. *J Am Coll Cardiol*. 2006;47(8 Suppl): C7-C12. https://doi.org/10.1016/j.jacc.2005.09.068.
2 Kobiyama K, Ley K. Atherosclerosis. *Circ Res*. 2018;123(10):1118-1120. https://doi.org/10.1161/CIRCRESAHA.118.313816.
3 Pan H, Ho SE, Xue C, et al. Atherosclerosis is a smooth muscle cell-driven tumor-like disease. *Circulation*. 2024;149(24):1885-1898. https://doi.org/10.1161/CIRCULATIONAHA.123.067587.
4 Basatemur GL, Jørgensen HF, Clarke MCH, et al. Vascular smooth muscle cells in atherosclerosis. *Nat Rev Cardiol*. 2019;16(12):727-744. https://doi.org/10.1038/s41569-019-0227-9.
5 Grootaert MOJ, Bennett MR. Vascular smooth muscle cells in atherosclerosis: time for a re-assessment. *Cardiovasc Res*. 2021;117(11): 2326-2339. https://doi.org/10.1093/cvr/cvab046.
6 Allahverdian S, Chaabane C, Boukais K, et al. Smooth muscle cell fate and plasticity in atherosclerosis. *Cardiovasc Res*. 2018;114(4):540-550. https://doi.org/10.1093/cvr/cvy022.
7 Grootaert MOJ, Moulis M, Roth L, et al. Vascular smooth muscle cell death, autophagy and senescence in atherosclerosis. *Cardiovasc Res*. 2018;114(4): 622-634. https://doi.org/10.1093/cvr/cvy007.
8 Park E, Ito K, Iqbal R, et al. Prospective changes in diastolic function in patients with rheumatoid arthritis. *Arthritis Res Ther*. 2022;24(1):184. https://doi.org/10.1186/s13075-022-02864-0.
9 Wang C, Niimi M, Watanabe T, et al. Treatment of atherosclerosis by traditional Chinese medicine: questions and quandaries. *Atherosclerosis*. 2018;277:136-144. https://doi.org/10.1016/j.atherosclerosis.2018.08.039.
10 Huang H, Song C, Chang J. Synthesis and biological activity study of tanshinone derivatives: a literature and patent review. *Curr Top Med Chem*. 2020;20(28):2520-2534. https://doi.org/10.2174/1568026620666200922115109.
11 Guo R, Li L, Su J, et al. Pharmacological activity and mechanism of tanshinone IIA in related diseases. *Drug Des Devel Ther*. 2020;14:4735-4748. https://doi.org/10.2147/DDDT.S266911.
12 Owens GK. Regulation of differentiation of vascular smooth muscle cells. *Physiol Rev*. 1995;75(3):487-517. https://doi.org/10.1152/physrev.1995.

75.3.487.
13 Jones BA, Aly HM, Forsyth EA, et al. Phenotypic characterization of human smooth muscle cells derived from atherosclerotic tibial and peroneal arteries. *J Vasc Surg*. 1996;24(5):883-891. https://doi.org/10.1016/S0741-5214(96)70027-7.
14 Campbell JH, Campbell GR. Smooth muscle phenotypic modulation-a personal experience. *Arterioscler Thromb Vasc Biol*. 2012;32(8):1784-1789. https://doi.org/10.1161/ATVBAHA.111.243212.
15 Zhang DD, Song Y, Kong P, et al. Smooth muscle 22 alpha protein inhibits VSMC foam cell formation by supporting normal LXRα signaling, ameliorating atherosclerosis. *Cell Death Dis*. 2021;12(11):982. https://doi.org/10.1038/s41419-021-04239-w.
16 Orlandi A, Bochaton-Piallat ML, Gabbiani G, et al. Aging, smooth muscle cells and vascular pathobiology: implications for atherosclerosis. *Atherosclerosis*. 2006;188(2):221-230. https://doi.org/10.1016/j.atherosclerosis.2006.01.018.
17 Bashore AC, Chung A, Ibikunle C, et al. Single-cell multimodal profiling of atherosclerosis identifies CD200 as a cell surface lineage marker of vascular smooth muscle cells and their derived cells. *Circulation*. 2024;149(15):1231-1233. https://doi.org/10.1161/CIRCULATIONAHA.123.067092.
18 Liu M, Gomez D. Smooth muscle cell phenotypic diversity. *Arterioscler Thromb Vasc Biol*. 2019;39(9):1715-1723. https://doi.org/10.1161/ATVBAHA.119.312131.
19 Mocci G, Sukhavasi K, Örd T, et al. Single-cell gene-regulatory networks of advanced symptomatic atherosclerosis. *Circ Res*. 2024;134(11):1405-1423. https://doi.org/10.1161/CIRCRESAHA.123.323184.
20 Wirka RC, Wagh D, Paik DT, et al. Atheroprotective roles of smooth muscle cell phenotypic modulation and the TCF21 disease gene as revealed by single-cell analysis. *Nat Med*. 2019;25(8):1280-1289. https://doi.org/10.1038/s41591-019-0512-5.
21 Pan H, Xue C, Auerbach BJ, et al. Single-cell genomics reveals a novel cell state during smooth muscle cell phenotypic switching and potential therapeutic targets for atherosclerosis in mouse and human. *Circulation*. 2020;142(21):2060-2075. https://doi.org/10.1161/CIRCULATIONAHA.120.048378.
22 Rong JX, Shapiro M, Trogan E, et al. Transdifferentiation of mouse aortic smooth muscle cells to a macrophage-like state after cholesterol loading. *Proc Natl Acad Sci U S A*. 2003;100(23):13531-13536. https://doi.org/10.1073/pnas.1735526100.
23 Shankman LS, Gomez D, Cherepanova OA, et al. KLF4-dependent phenotypic modulation of smooth muscle cells has a key role in atherosclerotic plaque pathogenesis. *Nat Med*. 2015;21(6):628-637. https://doi.org/10.1038/nm.3866.
24 Elmarasi M, Elmakaty I, Elsayed B, et al. Phenotypic switching of vascular smooth muscle cells in atherosclerosis, hypertension, and aortic dissection. *J Cell Physiol*. 2024;239(4):e31200. https://doi.org/10.1002/jcp.31200.
25 Hwang AR, Lee HJ, Kim S, et al. Inhibition of p90RSK ameliorates PDGF-BB-ointima. *Int J Mol Sci*. 2023;24(9):8094. https://doi.org/10.3390/ijms24098094.
26 Jiang Y, Qian HY. Transcription factors: key regulatory targets of vascular smooth muscle cell in atherosclerosis. *Mol Med*. 2023;29(1):2. https://doi.org/10.1186/s10020-022-00586-2.
27 Tabas I, García-Cardeña G, Owens GK. Recent insights into the cellular biology of atherosclerosis. *J Cell Biol*. 2015;209(1):13-22. https://doi.org/10.1083/jcb.201412052.
28 Allahverdian S, Chehroudi AC, McManus BM, et al. Contribution of intimal smooth muscle cells to cholesterol accumulation and macrophage-like cells in human atherosclerosis. *Circulation*. 2014;129(15):1551-1559. https://doi.org/10.1161/CIRCULATIONAHA.113.005015.
29 Chen R, McVey DG, Shen D, et al. Phenotypic switching of vascular smooth muscle cells in atherosclerosis. *J Am Heart Assoc*. 2023;12(20):e031121. https://doi.org/10.1161/JAHA.123.031121.
30 Naik V, Leaf EM, Hu JH, et al. Sources of cells that contribute to atherosclerotic intimal calcification: an *in vivo* genetic fate mapping study. *Cardiovasc Res*. 2012;94(3):545-554. https://doi.org/10.1093/cvr/cvs126.
31 Durham AL, Speer MY, Scatena M, et al. Role of smooth muscle cells in vascular calcification: implications in atherosclerosis and arterial stiffness. *Cardiovasc Res*. 2018;114(4):590-600. https://doi.org/10.1093/cvr/cvy010.
32 Lee SJ, Lee IK, Jeon JH. Vascular calcification-new insights into its mechanism. *Int J Mol Sci*. 2020;21(8):2685. https://doi.org/10.3390/ijms21082685.
33 Hu CT, Shao YD, Liu YZ, et al. Oxidative stress in vascular calcification. *Clin Chim Acta*. 2021;519:101-110. https://doi.org/10.1016/j.cca.2021.04.012.
34 Shanahan CM, Cary NR, Metcalfe JC, et al. High expression of genes for calcification-regulating proteins in human atherosclerotic plaques. *J Clin Invest*. 1994;93(6):2393-2402. https://doi.org/10.1172/JCI117246.
35 Shi J, Yang Y, Cheng A, et al. Metabolism of vascular smooth muscle cells in vascular diseases. *Am J Physiol Heart Circ Physiol*. 2020;319(3):H613-h631. https://doi.org/10.1152/ajpheart.00220.2020.
36 Long JZ, Svensson KJ, Tsai L, et al. A smooth muscle-like origin for beige adipocytes. *Cell Metab*. 2014;19(5):810-820. https://doi.org/10.1016/j.cmet.2014.03.025.
37 Davies JD, Carpenter KL, Challis IR, et al. Adipocytic differentiation and liver X receptor pathways regulate the accumulation of triacylglycerols in human vascular smooth muscle cells. *J Biol Chem*. 2005;280(5):3911-3919. https://doi.org/10.1074/jbc.M410075200.
38 Adachi Y, Ueda K, Nomura S, et al. Beiging of perivascular adipose tissue regulates its inflammation and vascular remodeling. *Nat Commun*. 2022;13(1):5117. https://doi.org/10.1038/s41467-022-32658-6.
39 Nguyen DCA, Briones AM, Callera GE, et al. Adipocyte-derived factors regulate vascular smooth muscle cells through mineralocorticoid and glucocorticoid receptors. *Hypertension*. 2011;58(3):479-488. https://doi.org/10.1161/HYPERTENSIONAHA.110.168872.
40 Riascos-Bernal DF, Ressa G, Korrapati A, et al. The FAT1 cadherin drives vascular smooth muscle cell migration. *Cells*. 2023;12(12):1621. https://doi.org/10.3390/cells12121621.
41 Davies MJ, Richardson PD, Woolf N, et al. Risk of thrombosis in human atherosclerotic plaques: role of extracellular lipid, macrophage, and smooth muscle cell content. *Br Heart J*. 1993;69(5):377-381. https://doi.org/10.1136/hrt.69.5.377.
42 Zernecke A. CD98 promotes vascular smooth muscle cell accumulation in atherosclerosis to confer plaque stability. *Atherosclerosis*. 2017;256:128-130. https://doi.org/10.1016/j.atherosclerosis.2016.11.028.
43 Yurdagul AJ. Crosstalk between macrophages and vascular smooth muscle cells in atherosclerotic plaque stability. *Arterioscler Thromb Vasc Biol*. 2022;42(4):372-380. https://doi.org/10.1161/ATVBAHA.121.316233.
44 Nelson AR, Fingleton B, Rothenberg ML, et al. Matrix metalloproteinases: biologic activity and clinical implications. *J Clin Oncol*. 2000;18(5):1135-1149. https://doi.org/10.1200/JCO.2000.18.5.1135.
45 Newby AC. Matrix metalloproteinases regulate migration, proliferation, and death of vascular smooth muscle cells by degrading matrix and non-matrix substrates. *Cardiovasc Res*. 2006;69(3):614-624. https://doi.org/10.1016/j.cardiores.2005.08.002.
46 Braun-Dullaeus RC, Mann MJ, Dzau VJ. Cell cycle progression: new therapeutic target for vascular proliferative disease. *Circulation*. 1998;98(1):82-89. https://doi.org/10.1161/01.CIR.98.1.82.
47 Hofbauer R, Denhardt DT. Cell cycle-regulated and proliferation stimulus-responsive genes. *Crit Rev Eukaryot Gene Expr*. 1991;1(4):247-300.
48 Bennett MR, Evan GI, Schwartz SM. Apoptosis of human vascular smooth muscle cells derived from normal vessels and coronary atherosclerotic plaques. *J Clin Invest*. 1995;95(5):2266-2274. https://doi.org/10.1172/JCI117917.
49 Bennett MR, Macdonald K, Chan SW, et al. Cooperative interactions between RB and p53 regulate cell proliferation, cell senescence, and apoptosis in human vascular smooth muscle cells from atherosclerotic plaques. *Circ Res*. 1998;82(6):704-712. https://doi.org/10.1161/01.RES.82.6.704.
50 Mahmoudi M, Gorenne I, Mercer J, et al. Statins use a novel Nijmegen breakage syndrome-1-dependent pathway to accelerate DNA repair in vascular smooth muscle cells. *Circ Res*. 2008;103(7):717-725. https://doi.org/10.1161/CIRCRESAHA.108.182899.
51 Bredesen DE. Neural apoptosis. *Ann Neurol*. 1995;38(6):839-851. https://doi.org/10.1002/ana.410380604.
52 Li M, Wang ZW, Fang LJ, et al. Programmed cell death in atherosclerosis and vascular calcification. *Cell Death Dis*. 2022;13(5):467. https://doi.org/10.1038/s41419-022-04923-5.
53 Mizushima N, Komatsu M. Autophagy: renovation of cells and tissues. *Cell*. 2011;147(4):728-741. https://doi.org/10.1016/j.cell.2011.10.026.
54 Martinet W, de Meyer GR. Autophagy in atherosclerosis: a cell survival and death phenomenon with therapeutic potential. *Circ Res*. 2009;104(3):304-317. https://doi.org/10.1161/CIRCRESAHA.108.188318.
55 Kiffin R, Bandyopadhyay U, Cuervo AM. Oxidative stress and autophagy. *Antioxid Redox Signal*. 2006;8(1-2):152-162. https://doi.org/10.1089/ars.2006.8.152.
56 Duewell P, Kono H, Rayner KJ, et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. *Nature*. 2010;464(7293):1357-1361. https://doi.org/10.1038/nature08938.
57 Zachari M, Ganley IG. The mammalian ULK1 complex and autophagy initiation. *Essays Biochem*. 2017;61(6):585-596. https://doi.org/10.1042/EBC20170021.
58 Kim J, Kundu M, Viollet B, et al. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nat Cell Biol*. 2011;13(2):132-141. https://doi.org/10.1038/ncb2152.
59 Grootaert MO, da Costa MPA, Bitsch N, et al. Defective autophagy in vascular smooth muscle cells accelerates senescence and promotes neointima formation and atherogenesis. *Autophagy*. 2015;11(11):2014-2032. https://doi.org/10.1080/15548627.2015.1096485.
60 Salabei JK, Hill BG. Implications of autophagy for vascular smooth muscle cell function and plasticity. *Free Radic Biol Med*. 2013;65:693-703. https://doi.org/10.1016/j.freeradbiomed.2013.08.003.
61 Salabei JK, Cummins TD, Singh M, et al. PDGF-mediated autophagy regulates vascular smooth muscle cell phenotype and resistance to oxidative stress. *Biochem J*. 2013;451(3):375-388. https://doi.org/10.1042/BJ20121344.
62 Li J, Zhao L, Yang T, et al. c-Ski inhibits autophagy of vascular smooth muscle cells induced by oxLDL and PDGF. *PLoS One*. 2014;9(6):e98902. https://doi.org/10.1371/journal.pone.0098902.
63 Li H, Li J, Li Y, et al. Sonic hedgehog promotes autophagy of vascular smooth muscle cells. *Am J Physiol Heart Circ Physiol*. 2012;303(11):H1319-1331. https://doi.org/10.1152/ajpheart.00160.2012.
64 García-Miguel M, Riquelme JA, Norambuena-Soto I, et al. Autophagy mediates tumor necrosis factor-α-induced phenotype switching in vascular smooth muscle A7r5 cell line. *PLoS One*. 2018;13(5):e0197210. https://doi.org/10.1371/journal.pone.0197210.
65 Shan R, Liu N, Yan Y, et al. Apoptosis, autophagy and atherosclerosis: relationships and the role of Hsp27. *Pharmacol Res*. 2021;166:105169. https://doi.org/10.1016/j.phrs.2020.105169.
66 Zeng ZL, Li GH, Wu SY, et al. Role of pyroptosis in cardiovascular disease. *Cell Prolif*. 2019;52(2):e12563. https://doi.org/10.1111/cpr.12563.
67 Yin Z, Zhang J, Shen Z, et al. Regulated vascular smooth muscle cell death in vascular diseases. *Cell Prolif*. 2024;57(11):e13688. https://doi.org/10.1111/cpr.13688.
68 Pan J, Han L, Guo J, et al. AIM2 accelerates the atherosclerotic plaque

progressions in ApoE$^{-/-}$ mice. *Biochem Biophys Res Commun*. 2018;498(3):487-494. https://doi.org/10.1016/j.bbrc.2018.03.005.
69 Li Y, Niu X, Xu H, et al. VX-765 attenuates atherosclerosis in ApoE deficient mice by modulating VSMCs pyroptosis. *Exp Cell Res*. 2020;389(1):111847. https://doi.org/10.1016/j.yexcr.2020.111847.
70 Zhou Y, Zhou H, Hua L, et al. Verification of ferroptosis and pyroptosis and identification of PTGS2 as the hub gene in human coronary artery atherosclerosis. *Free Radic Biol Med*. 2021;171:55-68. https://doi.org/10.1016/j.freeradbiomed.2021.05.009.
71 Shimada K, Skouta R, Kaplan A, et al. Global survey of cell death mechanisms reveals metabolic regulation of ferroptosis. *Nat Chem Biol*. 2016;12(7):497-503. https://doi.org/10.1038/nchembio.2079.
72 Zhang Y, Swanda RV, Nie L, et al. mTORC1 couples cyst(e)ine availability with GPX4 protein synthesis and ferroptosis regulation. *Nat Commun*. 2021;12(1):1589. https://doi.org/10.1038/s41467-021-21841-w.
73 Zhang S, Bei Y, Huang Y, et al. Induction of ferroptosis promotes vascular smooth muscle cell phenotypic switching and aggravates neointimal hyperplasia in mice. *Mol Med*. 2022;28(1):121. https://doi.org/10.1186/s10020-022-00549-7.
74 Heldin CH, Westermark B. Mechanism of action and *in vivo* role of platelet-derived growth factor. *Physiol Rev*. 1999;79(4):1283-1316. https://doi.org/10.1152/physrev.1999.79.4.1283.
75 Zhan Y, Kim S, Izumi Y, et al. Role of JNK, p38, and ERK in platelet-derived growth factor-induced vascular proliferation, migration, and gene expression. *Arterioscler Thromb Vasc Biol*. 2003;23(5):795-801. https://doi.org/10.1161/01.ATV.0000066132.32063.F2.
76 Seger R, Krebs EG. The MAPK signaling cascade. *FASEB J*. 1995;9(9):726-735. https://doi.org/10.1096/fasebj.9.9.7601337.
77 Bonizzi G, Karin M. The two NF-κB activation pathways and their role in innate and adaptive immunity. *Trends Immunol*. 2004;25(6):280-288. https://doi.org/10.1016/j.it.2004.03.008.
78 Li ZW, Chu W, Hu Y, et al. The IKKβ subunit of IκB kinase (IKK) is essential for nuclear factor κB activation and prevention of apoptosis. *J Exp Med*. 1999;189(11):1839-1845. https://doi.org/10.1084/jem.189.11.1839.
79 Wang J, Hu K, Cai X, et al. Targeting PI3K/AKT signaling for treatment of idiopathic pulmonary fibrosis. *Acta Pharm Sin B*. 2022;12(1):18-32. https://doi.org/10.1016/j.apsb.2021.07.023.
80 Li QY, Chen L, Fu WH, et al. Ginsenoside Rb1 inhibits proliferation and inflammatory responses in rat aortic smooth muscle cells. *J Agric Food Chem*. 2011;59(11):6312-6318. https://doi.org/10.1021/jf200424k.
81 Huynh DTN, Jin Y, Van Nguyen D, et al. Ginsenoside Rh1 inhibits angiotensin II-induced vascular smooth muscle cell migration and proliferation through suppression of the ROS-mediated ERK1/2/p90RSK/KLF4 signaling pathway. *Antioxidants (Basel)*. 2022;11(4):643. https://doi.org/10.3390/antiox11040643.
82 Moon CY, Ku CR, Cho YH, et al. Protocatechuic aldehyde inhibits migration and proliferation of vascular smooth muscle cells and intravascular thrombosis. *Biochem Biophys Res Commun*. 2012;423(1):116-121. https://doi.org/10.1016/j.bbrc.2012.05.092.
83 Wang K, Wen L, Peng W, et al. Vinpocetine attenuates neointimal hyperplasia in diabetic rat carotid arteries after balloon injury. *PLoS One*. 2014;9(5):e96894. https://doi.org/10.1371/journal.pone.0096894.
84 Li W, Yu J, Xiao X, et al. The inhibitory effect of (−)-epicatechin gallate on the proliferation and migration of vascular smooth muscle cells weakens and stabilizes atherosclerosis. *Eur J Pharmacol*. 2021;891:173761. https://doi.org/10.1016/j.ejphar.2020.173761.
85 Yu J, Song H, Zhou L, et al. (−)-Epicatechin gallate prevented atherosclerosis by reducing abnormal proliferation of VSMCs and oxidative stress of AML 12 cells. *Cell Signal*. 2024;121:111276. https://doi.org/10.1016/j.cellsig.2024.111276.
86 Lin HC, Hsieh MJ, Peng CH, et al. Pterostilbene inhibits vascular smooth muscle cells migration and matrix metalloproteinase-2 through modulation of MAPK pathway. *J Food Sci*. 2015;80(10):H2331-2335. https://doi.org/10.1111/1750-3841.13002.
87 Luo L, Liang H, Liu L. Myristicin regulates proliferation and apoptosis in oxidized low-density lipoprotein-stimulated human vascular smooth muscle cells and human umbilical vein endothelial cells by regulating the PI3K/Akt/NF-κB signalling pathway. *Pharm Biol*. 2022;60(1):56-64. https://doi.org/10.1080/13880209.2021.2010775.
88 Zha Y, Yang Y, Zhou Y, et al. Dietary evodiamine inhibits atherosclerosis-associated changes in vascular smooth muscle cells. *Int J Mol Sci*. 2023;24(7):6653. https://doi.org/10.3390/ijms24076653.
89 Yang TY, Wu YL, Yu MH, et al. Mulberry leaf and neochlorogenic acid alleviates glucolipotoxicity-induced oxidative stress and inhibits proliferation/migration *via* downregulating Ras and FAK signaling pathway in vascular smooth muscle cell. *Nutrients*. 2022;14(15):3006. https://doi.org/10.3390/nu14153006.
90 Li S, Cheng L, An D, et al. *Whitmania Pigra* whitman extracts inhibit lipopolysaccharide induced rat vascular smooth muscle cells migration and their adhesion ability to THP-1 and RAW 264.7 cells. *J Atheroscler Thromb*. 2017;24(3):301-311. https://doi.org/10.5551/jat.36558.
91 Hsuan CF, Lu YC, Tsai IT, et al. *Glossogyne tenuifolia* attenuates proliferation and migration of vascular smooth muscle cells. *Molecules*. 2020;25(24):5832. https://doi.org/10.3390/molecules25245832.
92 Zhang J, Zhao WR, Shi WT, et al. *Tribulus terrestris* L. extract ameliorates atherosclerosis by inhibition of vascular smooth muscle cell proliferation in ApoE$^{-/-}$ mice and A7r5 cells *via* suppression of Akt/MEK/ERK signaling. *J Ethnopharmacol*. 2022;297:115547. https://doi.org/10.1016/j.jep.2022.115547.
93 Wu Y, Chen M, Chen Z, et al. Theaflavin-3,3'-digallate from black tea inhibits neointima formation through suppression of the PDGFRβ pathway in vascular smooth muscle cells. *Front Pharmacol*. 2022;13:861319. https://doi.org/10.3389/fphar.2022.861319.
94 Fan S, Wang C, Huang K, et al. Myricanol inhibits platelet derived growth factor-BB-induced vascular smooth muscle cells proliferation and migration *in vitro* and intimal hyperplasia *in vivo* by targeting the platelet-derived growth factor receptor-β and NF-κB signaling. *Front Physiol*. 2022;12:790345. https://doi.org/10.3389/fphys.2021.790345.
95 Lee JH, Kim MJ, Woo KJ, et al. Evening primrose extracts inhibit PDGF-BB-induced vascular smooth muscle cell proliferation and migration by regulating cell-cycle-related proteins. *Curr Issues Mol Biol*. 2022;44(5):1928-1940. https://doi.org/10.3390/cimb44050131.
96 Lee GL, Wu JY, Tsai CS, et al. TLR4-activated MAPK-IL-6 axis regulates vascular smooth muscle cell function. *Int J Mol Sci*. 2016;17(9):1394. https://doi.org/10.3390/ijms17091394.
97 Curtiss LK, Tobias PS. Emerging role of Toll-like receptors in atherosclerosis. *J Lipid Res*. 2009;50(Suppl):S340-S345. https://doi.org/10.1194/jlr.R800056-JLR200.
98 Wang Y, Li Y, Chen Y, et al. Corilagin relieves atherosclerosis *via* the toll-like receptor 4 signaling pathway in vascular smooth muscle cells. *Int J Immunopathol Pharmacol*. 2024;38:3946320241254083. https://doi.org/10.1177/03946320241254083.
99 Wu X, Hu Z, Zhou J, et al. Ferulic acid alleviates atherosclerotic plaques by inhibiting VSMC proliferation through the NO/p21 signaling pathway. *J Cardiovasc Transl Res*. 2022;15(4):865-875. https://doi.org/10.1007/s12265-021-10196-8.
100 Song Y, Long L, Zhang N, et al. Inhibitory effects of hydroxysafflor yellow A on PDGF-BB-induced proliferation and migration of vascular smooth muscle cells *via* mediating Akt signaling. *Mol Med Rep*. 2014;10(3):1555-1560. https://doi.org/10.3892/mmr.2014.2336.
101 Gao Y, Zhu P, Xu SF, et al. Ginsenoside Re inhibits PDGF-BB-induced VSMC proliferation *via* the eNOS/NO/cGMP pathway. *Biomed Pharmacother*. 2019;115:108934. https://doi.org/10.1016/j.biopha.2019.108934.
102 Banerjee S, Biehl A, Gadina M, et al. JAK-STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects. *Drugs*. 2017;77(5):521-546. https://doi.org/10.1007/s40265-017-0701-9.
103 Huang Q, Liu X, Yu J, et al. Schisandrin inhibits VSMCs proliferation and migration by arresting cell cycle and targeting JAK2 to regulating the JAK2/STAT3 pathway. *Tissue Cell*. 2024;89:102440. https://doi.org/10.1016/j.tice.2024.102440.
104 Wu Q, Wang W, Li S, et al. American ginseng inhibits vascular smooth muscle cell proliferation *via* suppressing Jak/Stat pathway. *J Ethnopharmacol*. 2012;144(3):782-785. https://doi.org/10.1016/j.jep.2012.09.046.
105 Wang H, Wei Z, Li H, et al. MiR-377-3p inhibits atherosclerosis-associated vascular smooth muscle cell proliferation and migration *via* targeting neuropilin2. *Biosci Rep*. 2020;40(6):BSR20193425. https://doi.org/10.1042/BSR20193425.
106 Sun D, Xiang G, Wang J, et al. miRNA 146b-5p protects against atherosclerosis by inhibiting vascular smooth muscle cell proliferation and migration. *Epigenomics*. 2020;12(24):2189-2204. https://doi.org/10.2217/epi-2020-0155.
107 Huang P, Wang F, Zhang Y, et al. Icariin alleviates atherosclerosis by regulating the miR-205-5p/ERBB4/AKT signaling pathway. *Int Immunopharmacol*. 2023;114:109611. https://doi.org/10.1016/j.intimp.2022.109611.
108 Li J, Li Y, Yuan X, et al. The effective constituent puerarin, from *Pueraria lobata*, inhibits the proliferation and inflammation of vascular smooth muscle in atherosclerosis through the miR-29b-3p/IGF1 pathway. *Pharm Biol*. 2023;61(1):1-11. https://doi.org/10.1080/13880209.2022.2099430.
109 Li Y, Chen F, Guo R, et al. Tanshinone IIA inhibits homocysteine-induced proliferation of vascular smooth muscle cells *via* miR-145/CD40 signaling. *Biochem Biophys Res Commun*. 2020;522(1):157-163. https://doi.org/10.1016/j.bbrc.2019.11.055.
110 Zhang M, Li F, Pokharel S, et al. *Lycium barbarum* polysaccharide protects against homocysteine-induced vascular smooth muscle cell proliferation and phenotypic transformation *via* PI3K/Akt pathway. *J Mol Histol*. 2020;51(6):629-637. https://doi.org/10.1007/s10735-020-09909-1.
111 Chung DJ, Wu YL, Yang MY, et al. *Nelumbo nucifera* leaf polyphenol extract and gallic acid inhibit TNF-α-induced vascular smooth muscle cell proliferation and migration involving the regulation of miR-21, miR-143 and miR-145. *Food Funct*. 2020;11(10):8602-8611. https://doi.org/10.1039/d0fo02135k.
112 Wang K, Zhou Z, Zhang M, et al. Peroxisome proliferator-activated receptor gamma down-regulates receptor for advanced glycation end products and inhibits smooth muscle cell proliferation in a diabetic and nondiabetic rat carotid artery injury model. *J Pharmacol Exp Ther*. 2006;317(1):37-43. https://doi.org/10.1124/jpet.105.095125.
113 Hsueh WA, Jackson S, Law RE. Control of vascular cell proliferation and migration by PPAR-gamma: a new approach to the macrovascular complications of diabetes. *Diabetes Care*. 2001;24(2):392-397. https://doi.org/10.2337/diacare.24.2.392.
114 Guo M, Guo G, Xiao J, et al. Ginsenoside Rg3 stereoisomers differentially inhibit vascular smooth muscle cell proliferation and migration in diabetic atherosclerosis. *J Cell Mol Med*. 2018;22(6):3202-3214. https://doi.org/10.1111/jcmm.13601.
115 Panthiya L, Tocharus J, Chaichompoo W, et al. Hexahydrocurcumin mitigates angiotensin II-induced proliferation, migration, and inflammation in vascular smooth muscle cells. *EXCLI J*. 2023;22:466-481. https://doi.org/10.17179/excli2023-6124.
116 Guo HY, Lu ZY, Zhao B, et al. Effects of Bunao-Fuyuan Decoction serum on proliferation and migration of vascular smooth muscle cells in atherosclerotic. *Chin J Nat Med*. 2021;19(1):36-45. https://doi.org/10.1016/S1875-5364(21)60004-3.

117 Lu Q, Hong W. Bcl2 enhances c-Myc-mediated MMP-2 expression of vascular smooth muscle cells. *Cell Signal*. 2009;21(7):1054-1059. https://doi.org/10.1016/j.cellsig.2009.02.020.

118 Luo Z, Deng H, Fang Z, et al. Ligustilide inhibited rat vascular smooth muscle cells migration *via* c-Myc/MMP2 and ROCK/JNK signaling pathway. *J Food Sci*. 2019;84(12):3573-3583. https://doi.org/10.1111/1750-3841.14936.

119 Chen CP, Wu YL, Chan KC, et al. Mulberry polyphenols ameliorate atherogenic migration and proliferation by degradation of K-Ras and downregulation of its signals in vascular smooth muscle cell. *Int J Med Sci*. 2022;19(10):1557-1566. https://doi.org/10.7150/ijms.76006.

120 Hao Y, Baker D, Ten Dijke P. TGF-β-mediated epithelial-mesenchymal transition and cancer metastasis. *Int J Mol Sci*. 2019;20(11):2767. https://doi.org/10.3390/ijms20112767.

121 Derynck R, Budi EH. Specificity, versatility, and control of TGF-β family signaling. *Sci Signal*. 2019;12(570):eaav5183. https://doi.org/10.1126/scisignal.aav5183.

122 Zhou Y, Little PJ, Xu S, et al. Curcumin inhibits lysophosphatidic acid mediated MCP-1 expression *via* blocking ROCK signalling. *Molecules*. 2021;26(8):2320. https://doi.org/10.3390/molecules26082320.

123 Chen G, Xu H, Wu Y, et al. Myricetin suppresses the proliferation and migration of vascular smooth muscle cells and inhibits neointimal hyperplasia *via* suppressing TGFBR1 signaling pathways. *Phytomedicine*. 2021;92:153719. https://doi.org/10.1016/j.phymed.2021.153719.

124 Sasaki Y, Ikeda Y, Miyauchi T, et al. Estrogen-SIRT1 axis plays a pivotal role in protecting arteries against menopause-induced senescence and atherosclerosis. *J Atheroscler Thromb*. 2020;27(1):47-59. https://doi.org/10.5551/jat.47993.

125 Yuan L, Wang D, Wu C. Protective effect of liquiritin on coronary heart disease through regulating the proliferation of human vascular smooth muscle cells *via* upregulation of sirtuin1. *Bioengineered*. 2022;13(2):2840-2850. https://doi.org/10.1080/21655979.2021.2024687.

126 He JH, Li XJ, Wang SP, et al. Eugenol inhibits Ox-LDL-induced proliferation and migration of human vascular smooth muscle cells by inhibiting the Ang II/MFG-E8/MCP-1 signaling cascade. *J Inflamm Res*. 2024;17:641-653. https://doi.org/10.2147/JIR.S446960.

127 He Y, Wang R, Zhang P, et al. Curcumin inhibits the proliferation and migration of vascular smooth muscle cells by targeting the chemerin/CMKLR1/LCN2 axis. *Aging (Albany NY)*. 2021;13(10):13859-13875. https://doi.org/10.18632/aging.202980.

128 Huo YB, Gao X, Peng Q, et al. Dihydroartemisinin alleviates Ang II-induced vascular smooth muscle cell proliferation and inflammatory response by blocking the FTO/NR4A3 axis. *Inflamm Res*. 2022;71(2):243-253. https://doi.org/10.1007/s00011-021-01533-3.

129 Lee JJ, Yi H, Kim IS, et al. (2*S*)-naringenin from *Typha angustata* inhibits vascular smooth muscle cell proliferation *via* a G_0/G_1 arrest. *J Ethnopharmacol*. 2012;139(3):873-878. https://doi.org/10.1016/j.jep.2011.12.038.

130 Gubanova E, Issaeva N, Gokturk C, et al. SMG-1 suppresses CDK2 and tumor growth by regulating both the p53 and Cdc25A signaling pathways. *Cell Cycle*. 2013;12(24):3770-3780. https://doi.org/10.4161/cc.26660.

131 Zhang DQ, Li JS, Zhang YM, et al. Astragaloside IV inhibits angiotensin II-stimulated proliferation of rat vascular smooth muscle cells *via* the regulation of CDK2 activity. *Life Sci*. 2018;200:105-109. https://doi.org/10.1016/j.lfs.2018.03.036.

132 Lin HH, Hsieh MC, Wang CP, et al. Anti-atherosclerotic effect of gossypetin on abnormal vascular smooth muscle cell proliferation and migration. *Antioxidants (Basel)*. 2021;10(9):1357. https://doi.org/10.3390/antiox10091357.

133 Hou L, Zou Z, Wang Y, et al. Exploring the anti-atherosclerosis mechanism of ginsenoside Rb1 by integrating network pharmacology and experimental verification. *Aging (Albany NY)*. 2024;16(8):6745-6756. https://doi.org/10.18632/aging.205680.

134 Kahl CR, Means AR. Regulation of cell cycle progression by calcium/calmodulin-dependent pathways. *Endocr Rev*. 2003;24(6):719-736. https://doi.org/10.1210/er.2003-0008.

135 Ginty DD. Calcium regulation of gene expression: isn't that spatial? *Neuron*. 1997;18(2):183-186. https://doi.org/10.1016/S0896-6273(00)80258-5.

136 Graef IA, Chen F, Chen L, et al. Signals transduced by $Ca^{(2+)}$/calcineurin and NFATc3/c4 pattern the developing vasculature. *Cell*. 2001;105(7):863-875. https://doi.org/10.1016/S0092-8674(01)00396-8.

137 Xiao M, Xian C, Wang Y, et al. Nuciferine attenuates atherosclerosis by regulating the proliferation and migration of VSMCs through the Calm4/MMP12/AKT pathway in $ApoE^{(-/-)}$ mice fed with high-fat-diet. *Phytomedicine*. 2023;108:154536. https://doi.org/10.1016/j.phymed.2022.154536.

138 Zhang W, Zhang L, Zhang X. Anti-atherosclerotic effects of genistein in preventing ox-low-density lipoprotein-induced smooth muscle-derived foam cell formation *via* inhibiting SRC expression and L-Ca channel currents. *Ann Transl Med*. 2022;10(12):700. https://doi.org/10.21037/atm-22-2113.

139 Qi J, Cui J, Mi B, et al. Isoliquiritigenin inhibits atherosclerosis by blocking TRPC5 channel expression. *Cardiovasc Ther*. 2020;2020:1926249. https://doi.org/10.1155/2020/1926249.

140 Byon CH, Javed A, Dai Q, et al. Oxidative stress induces vascular calcification through modulation of the osteogenic transcription factor Runx2 by AKT signaling. *J Biol Chem*. 2008;283(22):15319-15327. https://doi.org/10.1074/jbc.M800021200.

141 Tang FT, Chen SR, Wu XQ, et al. Hypercholesterolemia accelerates vascular calcification induced by excessive vitamin D *via* oxidative stress. *Calcif Tissue Int*. 2006;79(5):326-339. https://doi.org/10.1007/s00223-006-0004-8.

142 Iacobini C, Fassino V, Mazzaferro S, et al. *In vitro* evaluation of the calcification inhibitory properties of policosanol, genistein, and vitamin D (Reduplaxin®) either alone or in combination. *Kidney Blood Press Res*. 2024;49(1):137-143. https://doi.org/10.1159/000535810.

143 Zheng G, Zhao Y, Li Z, et al. GLSP and GLSP-derived triterpenes attenuate atherosclerosis and aortic calcification by stimulating ABCA1/G1-mediated macrophage cholesterol efflux and inactivating RUNX2-mediated VSMC osteogenesis. *Theranostics*. 2023;13(4):1325-1341. https://doi.org/10.7150/thno.80250.

144 Pei YQ, Zheng YQ, Ding YD, et al. Triptolide attenuates vascular calcification by upregulating expression of miRNA-204. *Front Pharmacol*. 2020;11:581230. https://doi.org/10.3389/fphar.2020.581230.

145 Li Q, Zhou Q, Li S, et al. Target analysis and identification of curcumin against vascular calcification. *Sci Rep*. 2024;14(1):17344. https://doi.org/10.1038/s41598-024-67776-2.

146 Zhong H, Li DY, Wang SY, et al. Tanshinone IIA attenuates vascular calcification through inhibition of NF-κB and *β*-catenin signaling pathways. *Acta Physiol Sin*. 2022;74(6):949-958. https://doi.org/10.13294/j.aps.2022.0086.

147 Liou SF, Nguyen TTN, Hsu JH, et al. The preventive effects of xanthohumol on vascular calcification induced by vitamin D(3) plus nicotine. *Antioxidants (Basel)*. 2020;9(10):956. https://doi.org/10.3390/antiox9100956.

148 Sulistyowati E, Hsu JH, Lee SJ, et al. Potential actions of baicalein for preventing vascular calcification of smooth muscle cells *in vitro* and *in vivo*. *Int J Mol Sci*. 2022;23(10):5673. https://doi.org/10.3390/ijms23105673.

149 Wei X, Shen Z, Zhu M, et al. The pterostilbene-dihydropyrazole derivative Ptd-1 ameliorates vascular calcification by regulating inflammation. *Int Immunopharmacol*. 2023;125(Pt B):111198. https://doi.org/10.1016/j.intimp.2023.111198.

150 Cui X, Zhang L, Lin L, et al. Notoginsenoside R1-protocatechuic aldehyde reduces vascular inflammation and calcification through increasing the release of nitric oxide to inhibit TGFβR1-YAP/TAZ pathway in vascular smooth muscle cells. *Int Immunopharmacol*. 2024;143(Pt 3):113574. https://doi.org/10.1016/j.intimp.2024.113574.

151 Du H, Zhao Q, Zang H, et al. Artemisinin attenuates the development of atherosclerotic lesions by the regulation of vascular smooth muscle cell phenotype switching. *Life Sci*. 2019;237:116943. https://doi.org/10.1016/j.lfs.2019.116943.

152 Sun SY, Cao YM, Huo YJ, et al. Nicotinate-curcumin inhibits Ang II-induced vascular smooth muscle cell phenotype switching by upregulating Daxx expression. *Cell Adh Migr*. 2021;15(1):116-125. https://doi.org/10.1080/19336918.2021.1909899.

153 Zhao L, Cai H, Tang Z, et al. Matrine suppresses advanced glycation end products-induced human coronary smooth muscle cells phenotype conversion by regulating endoplasmic reticulum stress-dependent Notch signaling. *Eur J Pharmacol*. 2020;882:173257. https://doi.org/10.1016/j.ejphar.2020.173257.

154 Meng Q, Yu X, Chen Q, et al. Liuwei Dihuang Soft Capsules inhibits the phenotypic conversion of VSMC to prevent the menopausal atherosclerosis by up-regulating the expression of myocardin. *J Ethnopharmacol*. 2020;246:112207. https://doi.org/10.1016/j.jep.2019.112207.

155 Xiang L, Wang Y, Liu S, et al. Quercetin attenuates KLF4-mediated phenotypic switch of VSMCs to macrophage-like cells in atherosclerosis: a critical role for the JAK2/STAT3 pathway. *Int J Mol Sci*. 2024;25(14):7755. https://doi.org/10.3390/ijms25147755.

156 Li Y, Qin R, Yan H, et al. Inhibition of vascular smooth muscle cells premature senescence with rutin attenuates and stabilizes diabetic atherosclerosis. *J Nutr Biochem*. 2018;51:91-98. https://doi.org/10.1016/j.jnutbio.2017.09.012.

157 Zhou M, Ma X, Gao M, et al. Paeonol attenuates atherosclerosis by inhibiting vascular smooth muscle cells senescence *via* SIRT1/P53/TRF2 signaling pathway. *Molecules*. 2024;29(1):261. https://doi.org/10.3390/molecules29010261.

158 Liu K, Czaja MJ. Regulation of lipid stores and metabolism by lipophagy. *Cell Death Differ*. 2013;20(1):3-11. https://doi.org/10.1038/cdd.2012.63.

159 Ouimet M, Franklin V, Mak E, et al. Autophagy regulates cholesterol efflux from macrophage foam cells *via* lysosomal acid lipase. *Cell Metab*. 2011;13(6):655-667. https://doi.org/10.1016/j.cmet.2011.03.023.

160 Zuo J, Guo S, Qin X. Bisdemethoxycurcumin suppresses the progression of atherosclerosis and VSMC-derived foam cell formation by promoting lipophagy. *Naunyn Schmiedebergs Arch Pharmacol*. 2023;396(12):3659-3670. https://doi.org/10.1007/s00210-023-02558-7.

161 Gao WC, Yang TH, Wang BB, et al. Scutellarin inhibits oleic acid induced vascular smooth muscle foam cell formation *via* activating autophagy and inhibiting NLRP3 inflammasome activation. *Clin Exp Pharmacol Physiol*. 2024;51(4):e13845. https://doi.org/10.1111/1440-1681.13845.

162 Shi Y, Jiang S, Zhao T, et al. Celastrol suppresses lipid accumulation through LXRα/ABCA1 signaling pathway and autophagy in vascular smooth muscle cells. *Biochem Biophys Res Commun*. 2020;532(3):466-474. https://doi.org/10.1016/j.bbrc.2020.08.076.

163 Wang G, Zhu Y, Li K, et al. Curcumin-mediated photodynamic therapy inhibits the phenotypic transformation, migration, and foaming of oxidized low-density lipoprotein-treated vascular smooth muscle cells by promoting autophagy. *J Cardiovasc Pharmacol*. 2021;78(2):308-318. https://doi.org/10.1097/FJC.0000000000001069.

164 Pi S, Mao L, Chen J, et al. The P2RY12 receptor promotes VSMC-derived foam cell formation by inhibiting autophagy in advanced atherosclerosis. *Autophagy*. 2021;17(4):980-1000. https://doi.org/10.1080/15548627.2020.1741202.

165 Bao Y, Zhu L, Wang Y, et al. Gualou-Xiebai herb pair and its active ingredients act against atherosclerosis by suppressing VSMC-derived foam cell formation *via* regulating P2RY12-mediated lipophagy. *Phytomedicine*.

2024;128:155341. https://doi.org/10.1016/j.phymed.2024.155341.
166 Lin J, Gu M, Wang X, et al. Huanglian Jiedu Decoction inhibits vascular smooth muscle cell-derived foam cell formation by activating autophagy *via* suppressing P2RY12. *J Ethnopharmacol*. 2024;328:118125. https://doi.org/10.1016/j.jep.2024.118125.
167 Zhou Z, Li Y, Jiang W, et al. Molecular mechanism of calycosin inhibited vascular calcification. *Nutrients*. 2023;16(1):99. https://doi.org/10.3390/nu16010099.
168 He HQ, Law BYK, Zhang N, et al. Bavachin protects human aortic smooth muscle cells against *β*-glycerophosphate-mediated vascular calcification and apoptosis *via* activation of mTOR-dependent autophagy and suppression of *β*-catenin signaling. *Front Pharmacol*. 2019;10:1427. https://doi.org/10.3389/fphar.2019.01427.
169 Yu X, Xu L, Su C, et al. Luteolin protects against vascular calcification by modulating SIRT1/CXCR4 signaling pathway and promoting autophagy. *AAPS J*. 2024;26(6):111. https://doi.org/10.1208/s12248-024-00982-y.
170 Song Z, Wei D, Chen Y, et al. Association of astragaloside IV-inhibited autophagy and mineralization in vascular smooth muscle cells with lncRNA H19 and DUSP5-mediated ERK signaling. *ToxicolAppl Pharmacol*. 2019;364:45-54. https://doi.org/10.1016/j.taap.2018.12.002.
171 Liu Y, Song A, Wu H, et al. Paeonol inhibits apoptosis of vascular smooth muscle cells *via* up-regulation of autophagy by activating class III PI3K/Beclin-1 signaling pathway. *Life Sci*. 2021;264:118714. https://doi.org/10.1016/j.lfs.2020.118714.
172 Liang Y, Dong L, Yan J, et al. Paeonol attenuates atherosclerosis by regulating vascular smooth muscle cells apoptosis and modulating immune cells infiltration through reducing LTβR expression. *Phytomedicine*. 2024;135:156196. https://doi.org/10.1016/j.phymed.2024.156196.
173 Yang HL, Korivi M, Chen CH, et al. *Antrodia camphorata* attenuates cigarette smoke-induced ROS production, DNA damage, apoptosis, and inflammation in vascular smooth muscle cells, and atherosclerosis in ApoE-deficient mice. *Environ Toxicol*. 2017;32(8):2070-2084. https://doi.org/10.1002/tox.22422.
174 Yang H, Xu G, Li Q, et al. Ligustrazine alleviates the progression of coronary artery calcification by nhibiting caspase-3/GSDME mediated pyroptosis. *Biosci Trends*. 2024;18(5):482-491. https://doi.org/10.5582/bst.2024.01096.
175 Zhang J, Xie SA, Wang J, et al. Echinatin maintains glutathione homeostasis in vascular smooth muscle cells to protect against matrix remodeling and arterial stiffening. *Matrix Biol*. 2023;119:1-18. https://doi.org/10.1016/j.matbio.2023.03.007.
176 Zhang J, Yan J. Protective effect of ginkgolic acid in attenuating LDL induced inflammation human peripheral blood mononuclear cells *via* altering the NF-κB signaling pathway. *Front Pharmacol*. 2019;10:1241. https://doi.org/10.3389/fphar.2019.01241.
177 Förstermann U, Xia N, Li H. Roles of vascular oxidative stress and nitric oxide in the pathogenesis of atherosclerosis. *Circ Res*. 2017;120(4):713-735. https://doi.org/10.1161/CIRCRESAHA.116.309326.
178 Lee KP, Sudjarwo GW, Jung SH, et al. Carvacrol inhibits atherosclerotic neointima formation by downregulating reactive oxygen species production in vascular smooth muscle cells. *Atherosclerosis*. 2015;240(2):367-373. https://doi.org/10.1016/j.atherosclerosis.2015.03.038.
179 Wang YL, Sun GY, Zhang Y, et al. Tormentic acid inhibits H2O2-induced oxidative stress and inflammation in rat vascular smooth muscle cells *via* inhibition of the NF-κB signaling pathway. *Mol Med Rep*. 2016;14(4):3559-3564. https://doi.org/10.3892/mmr.2016.5690.
180 Hu Y, Li H, Li R, et al. Puerarin protects vascular smooth muscle cells from oxidized low-density lipoprotein-induced reductions in viability *via* inhibition of the p38 MAPK and JNK signaling pathways. *Exp Ther Med*. 2020;20(6):270. https://doi.org/10.3892/etm.2020.9400.
181 Zheng X, Wang P, Jia M, et al. Baicalin alleviates thrombin-induced inflammation in vascular smooth muscle cells. *Biomed Res Int*. 2022;2022:5799308. https://doi.org/10.1155/2022/5799308.
182 Zhang X, Qin Y, Ruan W, et al. Targeting inflammation-associated AMPK/Mfn-2/MAPKs signaling pathways by baicalein exerts anti-atherosclerotic action. *Phytother Res*. 2021;35(8):4442-4455. https://doi.org/10.1002/ptr.7149.
183 Meng L, Yan D, Xu W, et al. Emodin inhibits tumor necrosis factor-α-induced migration and inflammatory responses in rat aortic smooth muscle cells. *Int J Mol Med*. 2012;29(6):999-1006. https://doi.org/10.3892/ijmm.2012.940.
184 Li Y, Guo Y, Chen Y, et al. Establishment of an interleukin-1β-induced inflammation-activated endothelial cell-smooth muscle cell-mononuclear cell co-culture model and evaluation of the anti-inflammatory effects of tanshinone IIA on atherosclerosis. *Mol Med Rep*. 2015;12(2):1665-1676. https://doi.org/10.3892/mmr.2015.3668.
185 Quesada I, de Paola M, Alvarez MS, et al. Antioxidant and anti-atherogenic properties of *Prosopis strombulifera* and *Tessaria absinthioides* aqueous extracts: modulation of NADPH oxidase-derived reactive oxygen species. *Front Physiol*. 2021;12:662833. https://doi.org/10.3389/fphys.2021.662833.
186 Lee AS, Kim Y, Hur HJ, et al. *Chrysanthemum coronarium* L. extract attenuates homocysteine-induced vascular inflammation in vascular smooth muscle cells. *J Med Food*. 2023;26(12):869-876. https://doi.org/10.1089/jmf.2023.K.0058.
187 Wang YS, Lin RT, Cheng HY, et al. Anti-atherogenic effect of San-Huang-Xie-Xin-Tang, a traditional Chinese medicine, in cultured human aortic smooth muscle cells. *J Ethnopharmacol*. 2011;133(2):442-447. https://doi.org/10.1016/j.jep.2010.10.018.
188 Guo H, Li Y, Qiu L, et al. Gua-Lou Er-Chen Decoction attenuates atherosclerosis by reducing proteoglycans accumulation and inflammation. *Phytomedicine*. 2023;115:154811. https://doi.org/10.1016/j.phymed.2023.154811.
189 Wei JM, Yuan H, Liu CX, et al. The Chinese medicine Xin-Tong-Tai Granule protects atherosclerosis by regulating oxidative stress through NOX/ROS/NF-κB signal pathway. *Biomed Pharmacother*. 2023;165:115200. https://doi.org/10.1016/j.biopha.2023.115200.
190 Zhou J, Zhang L, Zheng B, et al. *Salvia miltiorrhiza* bunge exerts anti-oxidative effects through inhibiting KLF10 expression in vascular smooth muscle cells exposed to high glucose. *J Ethnopharmacol*. 2020;262:113208. https://doi.org/10.1016/j.jep.2020.113208.
191 Gong X, Liu Y, Liu H, et al. Re-analysis of single-cell transcriptomics reveals a critical role of macrophage-like smooth muscle cells in advanced atherosclerotic plaque. *Theranostics*. 2024;14(4):1450-1463. https://doi.org/10.7150/thno.87201.
192 Xue Y, Luo M, Hu X, et al. Macrophages regulate vascular smooth muscle cell function during atherosclerosis progression through IL-1β/STAT3 signaling. *Commun Biol*. 2022;5(1):1316. https://doi.org/10.1038/s42003-022-04255-2.
193 Adhikari N, Shekar KC, Staggs R, et al. Guidelines for the isolation and characterization of murine vascular smooth muscle cells. *A report from the International Society of Cardiovascular Translational Research. J Cardiovasc Transl Res*. 2015;8(3):158-163. https://doi.org/10.1007/s12265-015-9616-6.
194 Wang D, Yang Y, Lei Y, et al. Targeting foam cell formation in atherosclerosis: therapeutic potential of natural products. *Pharmacol Rev*. 2019;71(4):596-670. https://doi.org/10.1124/pr.118.017178.
195 Maguire EM, Pearce SWA, Xiao Q. Foam cell formation: a new target for fighting atherosclerosis and cardiovascular disease. *Vascul Pharmacol*. 2019;112:54-71. https://doi.org/10.1016/j.vph.2018.08.002.
196 Chistiakov DA, Melnichenko AA, Myasoedova VA, et al. Mechanisms of foam cell formation in atherosclerosis. *J Mol Med (Berl)*. 2017;95(11):1153-1165. https://doi.org/10.1007/s00109-017-1575-8.