

# Targeting lipophagy in atherosclerosis: Molecular mechanisms, pathogenesis and therapeutic interventions (Review)

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**Abstract.** Atherosclerosis (AS) is a chronic inflammatory disease characterized by lipid accumulation within the arterial wall. The imbalance between cholesterol influx and efflux, coupled with persistent inflammation, drives the progression of plaque formation. Lipophagy, a selective form of autophagy, specifically targets lipid droplets for lysosomal degradation. Consequently, this process is a notable regulator of cellular lipid homeostasis. In the present review, the core regulatory networks of lipophagy were systematically summarized, including the mechanistic target of rapamycin complex 1/AMP-activated protein kinase, transcription factor EB (TFEB) and farnesoid X receptor/cAMP response element-binding protein signaling axes. The multidimensional roles of lipophagy in key cell types involved in AS are also discussed. For example, in macrophages, lipophagy stabilizes plaques by promoting cholesterol efflux and inhibiting foam cell formation; however, dysregulated lipophagy can exacerbate necrotic core formation. In vascular smooth muscle cells, lipophagy regulates phenotype switching and calcification and in endothelial cells, lipophagy mitigates oxidative stress and inflammation. Advances in therapeutic strategies targeting lipophagy were evaluated, ranging from pharmacological agents (such as statins and metformin) to natural compounds (such as berberine and geniposide) and Traditional Chinese Medicine formulas. In conclusion, targeting lipophagy represents a pivotal therapeutic frontier for stabilizing atherosclerotic plaques;

however, the broad application of autophagy inducers lacks precision. Future strategies should transition from generalized modulation to cell-type specific interventions that precisely calibrate the sirtuin 1-TFEB-lipophagy axis. Furthermore, elucidating the 'double-edged' role of lipophagy in late-stage plaque outcomes is required for developing safe, clinically translatable modulators.

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## 1. Introduction

Atherosclerosis (AS) is a chronic, progressive disease primarily driven by lipid-induced inflammation, predominantly affecting large- and medium-sized arteries. The fundamental mechanism of AS involves a self-perpetuating pathological cycle of dysregulated lipid metabolism and inflammatory responses within the vascular wall that ultimately results in plaque formation, luminal stenosis and thrombotic events. AS, which is a leading global cause of cardiovascular diseases, is characterized by multiple risk factors (such as hyperlipidemia, hypertension, diabetes mellitus and smoking) and a complex pathogenesis that involves various cell types and biological processes (1).

Research has increasingly emphasized the role of lipophagy, a form of cellular autophagy, in AS. Lipophagy is not only involved in the degradation and recycling of intracellular lipids, but it also modulates key pathological processes, including inflammatory cell infiltration (2), foam cell formation (3),

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endothelial cell (EC) damage (4) and the proliferation and migration of vascular smooth muscle cells (VSMCs) (5). Autophagy is a highly conserved self-degradative cellular mechanism in which the dynamic formation and maturation of double-membrane structures are central processes. The key structures implicated in autophagy encompass phagophores, autophagosomes (APs) and autolysosomes (ALs) (2). Lipophagy, as a pivotal subtype of selective autophagy, is distinguished by lysosome-mediated lipid droplet (LD) degradation and is integral to cellular lipid homeostasis regulation. LDs are directed to lysosomes through ubiquitination, which involves the recruitment of lipophagy-specific factors and autophagy receptors (such as ORP8, spartin and p62) (6-8).

Lipophagy markedly affects AS initiation and progression. During AS pathogenesis, abnormal accumulation of LDs (the primary organelles for intracellular neutral lipid storage) is a hallmark of foam cell formation in macrophages and SMCs. LD accumulation is markedly associated with disrupted lipid metabolism and impaired lipophagy function. Lipophagy deficiency can result in excessive intracellular lipid deposition, which promotes AS progression (9). While macroautophagy serves as a bulk degradation system for cytoplasmic components, lipophagy represents a specialized, high-precision defense mechanism against lipotoxicity. Unlike the passive storage of neutral lipids, lipophagy actively mobilizes triglycerides (TGs) and cholesteryl esters (CEs) from LDs for lysosomal hydrolysis. This process is particularly critical in the lipid-rich milieu of AS, in which lipophagic capacity determines whether a macrophage resolves lipid burden or degenerates into a pro-inflammatory foam cell (6,9).

Unlike previous reviews that primarily catalogue individual lipophagic pathways, the present article used established knowledge to propose two novel conceptual frameworks. First, the spatiotemporal 'double-edged sword' model (Fig. 1), highlighting how the net effect of lipophagy depends on the disease stage and the intensity of autotoxic stress in different vascular cell types. Second, the 'convergent therapeutic axis' model (Fig. 2), which systematically categorizes conventional agents, natural compounds and Traditional Chinese Medicine (TCM) formulas based on their capacity to precisely target terminal epigenetic/transcriptional nodes [such as the SIRT-transcription factor EB (TFEB) axis] rather than merely inhibit broad upstream kinases. By bridging microscopic molecular signaling principles with macroscopic clinical and TCM theories, the present review provided original insights to inform the development of next-generation, targeted anti-atherosclerotic therapeutics.

## 2. Literature search strategy

To comprehensively review the role of lipophagy in AS, a systematic literature search was performed using PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Web of Science (<https://www.webofscience.com/>) and Embase (<https://www.embase.com/>). The search covered literature published from database inception to October 2025. The following keywords and combinations were used: i) Lipophagy (Title/Abstract); ii) atherosclerosis (Title/Abstract); iii) and lipophagy and atherosclerosis. Articles written in English, including basic research, clinical studies and high-quality reviews, were independently screened for relevance. Studies primarily focusing

on non-cardiovascular diseases or lacking direct mechanistic links to lipid metabolism in AS were excluded.

## 3. Physiological functions of lipophagy

The core mechanisms of lipophagy encompass lipid uptake, storage and degradation (10). As these processes facilitate the maintenance of cellular lipid homeostasis, lipophagy is integral to the pathogenesis of cardiovascular diseases (such as cardiometabolic syndrome and diabetic cardiomyopathy) (10). Research has concentrated on lipophagy as a notable physiological and pathological process that is particularly relevant within the context of AS (10). Lipophagic degradation releases free fatty acids and glycerol; this mechanism both supports energy acquisition during periods of nutrient deprivation and regulates intracellular lipid homeostasis, thereby mitigating the cytotoxicity associated with excessive lipid accumulation (11). Within ALs, TG-rich LDs are degraded into free fatty acids, which subsequently undergo  $\beta$ -oxidation, producing adenosine triphosphate (ATP) (12,13). Concurrently, LDs enriched with CE are hydrolyzed into free cholesterol via ABCA1-mediated lipophagy, and the free cholesterol is then exported to the extracellular space (14).

Farnesoid X receptor (FXR) and cAMP response element-binding protein (CREB) have been identified as pivotal transcription factors involved in lipophagy regulation, and the FXR/CREB signaling pathway plays a notable role in modulating the initiation of lipophagy (15). At the molecular level, CREB is activated by phosphorylation at the Ser133 residue, which triggers the recruitment of CREB-regulated transcription coactivator 2 (CRTC2), resulting in the formation of a transcriptionally active complex. This complex robustly upregulates autophagy-related genes, including *ATG7* and *ULK1* (16-18). By contrast, FXR exerts an inhibitory effect by competitively binding to CRTC2. This stoichiometric competition physically sequesters CRTC2 from CREB, preventing the assembly of the CREB-CRTC2 transcriptional machinery on the promoters of lysosomal genes. Thus, the dynamic equilibrium between FXR and CREB in competition for CRTC2 binding serves as a molecular switch for lipophagy initiation (19). Notably, PPAR $\alpha$  activation counteracts the suppressive influence of FXR on lipophagy (20,21) (Fig. 1). The disruption of lipophagy may result from excessive lipid accumulation in tissues, as observed in conditions such as AS and hepatic steatosis (11,22,23). Autophagic impairment has been prominently observed in atherosclerotic plaques in both human and animal studies (24,25). Impaired lipophagy, characterized by the suppression of lipid droplet-lysosome fusion and inhibited lysosomal biogenesis, has also been observed in foam cells, suggesting an association between lipophagy and AS (26). During the advanced stages of AS, dysregulation of lipophagy leads to disrupted lipid metabolism. This disturbance subsequently affects macrophage survival and apoptosis, potentially promoting plaque instability. Ultimately, plaque rupture can occur, further exacerbating pathological progression (27).

## 4. Molecular mechanisms regulating lipophagy in AS

Molecularly, lipophagy involves a sophisticated sequence of recognition and engulfment. Beyond general macroautophagy,

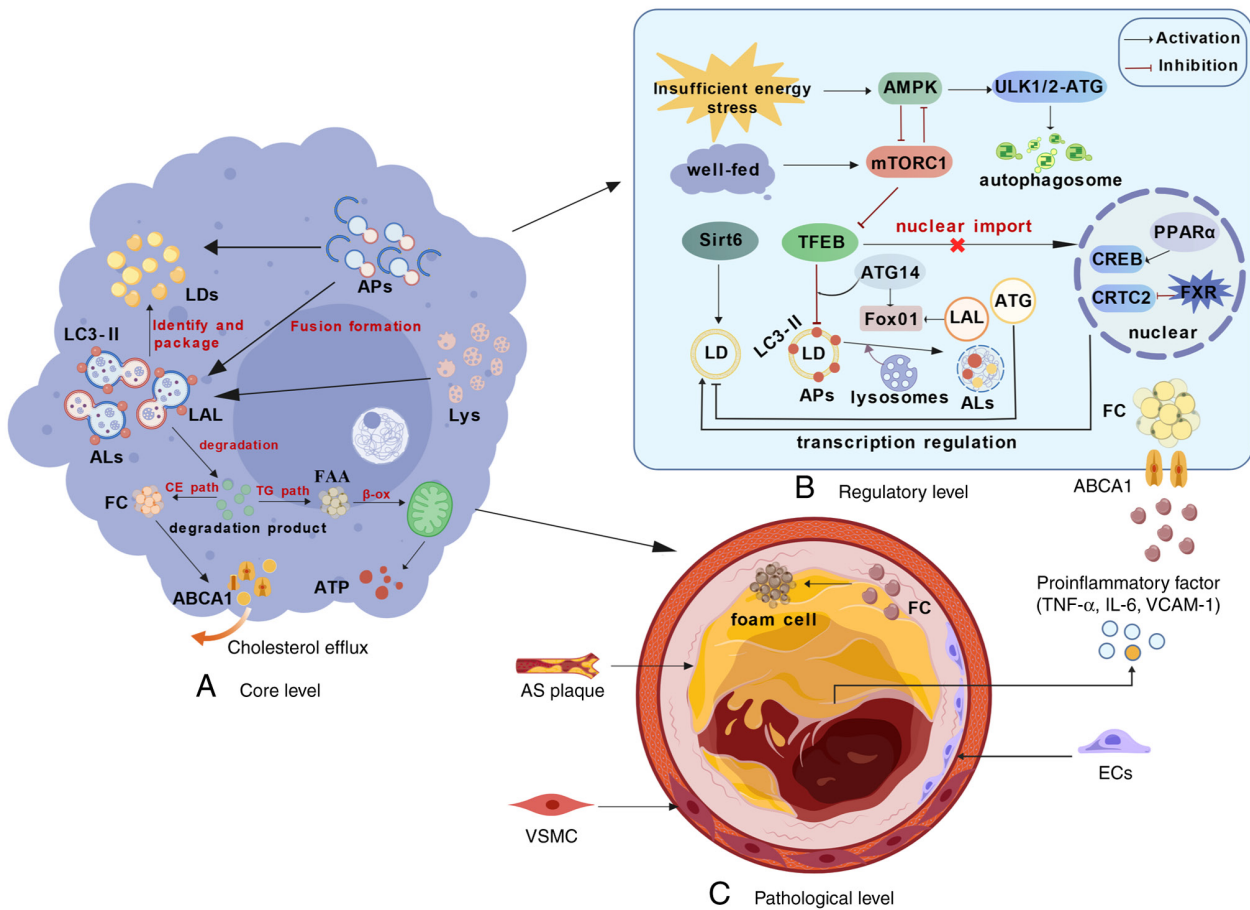


Figure 1. Core mechanisms of lipophagy in AS and therapeutically targetable pathways. Created with BioGDP.com (142). (A) Core execution level: Under lipotoxic stress, intracellular LDs are recognized and sequestered by phagophores decorated with LC3-II, forming APs. These APs subsequently fuse with lysosomes to generate autolysosomes, in which lysosomal acid lipase hydrolyzes LDs. The degradation products (free fatty acids) undergo mitochondrial  $\beta$ -oxidation to produce ATP, while free cholesterol is expelled via the ABCA1 transporter (cholesterol efflux). (B) Upstream regulatory network: The initiation of lipophagy is strictly governed by nutrient-sensing signaling cascades. AMPK activation triggers autophagy by phosphorylating the ULK1/2 complex, whereas the activated mTORC1 pathway suppresses this process. At the transcriptional level, transcription factor EB serves as a master regulator; its dephosphorylation facilitates nuclear translocation to upregulate autophagy-related genes. Additionally, Sirt6 epigenetically promotes lipophagy, and the FXR-CREB axis modulates this process: FXR inhibits the CREB-CRTC2 complex, suppressing lipophagy, while PPAR $\alpha$  counteracts this effect. (C) Pathological manifestation level: In the arterial wall, impaired lipophagic flux leads to massive lipid accumulation in macrophages, driving their transformation into pro-inflammatory foam cells. Concurrently, dysfunctional lipophagy in endothelial cells and vascular smooth muscle cells exacerbates vascular inflammation and pathological remodeling, ultimately accelerating atherosclerotic plaque progression. LDs, lipid droplets; Aps, autophagosomes; ALs, autolysosomes; LALs, lysosomal acid lipase; FFAs, free fatty acids; Lys, lysosome; EC, endothelial cell; VSMC, vascular smooth muscle cell; AS, atherosclerosis; TG, triglyceride; CE, cholesterol ester;  $\beta$ -ox,  $\beta$ -oxidation; FC, free cholesterol.

the specific recruitment of LC3 to the LD surface is facilitated by adapter proteins such as p62 and NBR1, which bind to ubiquitinated perilipins (PLINs) (28). Furthermore, the Rab family of small GTPases (specifically Rab7 and Rab18) is a notable mediator of the physical contact between LDs and the isolation membrane, ensuring the precise sequestration of lipid cargo into nascent autophagosomes (29,30).

Research has uncovered a complex regulatory network governing these processes. Central to this network are several master transcription factors, including TFEB (31), TFE3 (32), PPAR $\alpha$  (33) and forkhead box protein O1 (FoxO1) (34), alongside key epigenetic modulators such as sirtuin 6 (Sirt6) (35). TFEB and Sirt6 are notable protectors against AS progression that enhance lysosomal biogenesis and macrophage lipid clearance, whereas FoxO1 regulates lipophagic flux by activating ATG14 and lysosomal acid lipase (LAL) expression (36,37). These diverse regulatory elements are organized into several core signaling axes.

*AMPK-mechanistic target of rapamycin (mTORC1) energy sensing axis.* The AMPK and mTOR signaling pathways are key regulators of lipophagy efficiency owing to their influence on lipid synthesis and oxidation processes (38). Analogous to that of autophagy, the initiation of lipophagy is governed by the inhibition of specific signaling pathways (particularly the PI3K/AKT/mTOR pathway). mTOR predominantly regulates the lipophagic process through its complex, mTORC1 (39). Lipophagy initiation is dictated by the dynamic interplay between AMPK and mTORC1, which are the primary cellular energy sensors (40). mTORC1 activation facilitates ULK1/2 and ATG13 phosphorylation, which in turn inhibits the formation of the ULK1/2-ATG13 complex (41,42). mTORC1 modulates lipophagy via two distinct mechanisms. Initially, lipophagy is inhibited through the modulation of TFEB nuclear translocation, and subsequently, suppression is accomplished by regulation of ATG14 activity (43,44). AMPK activation directly inhibits mTORC1 activity by phosphorylating and

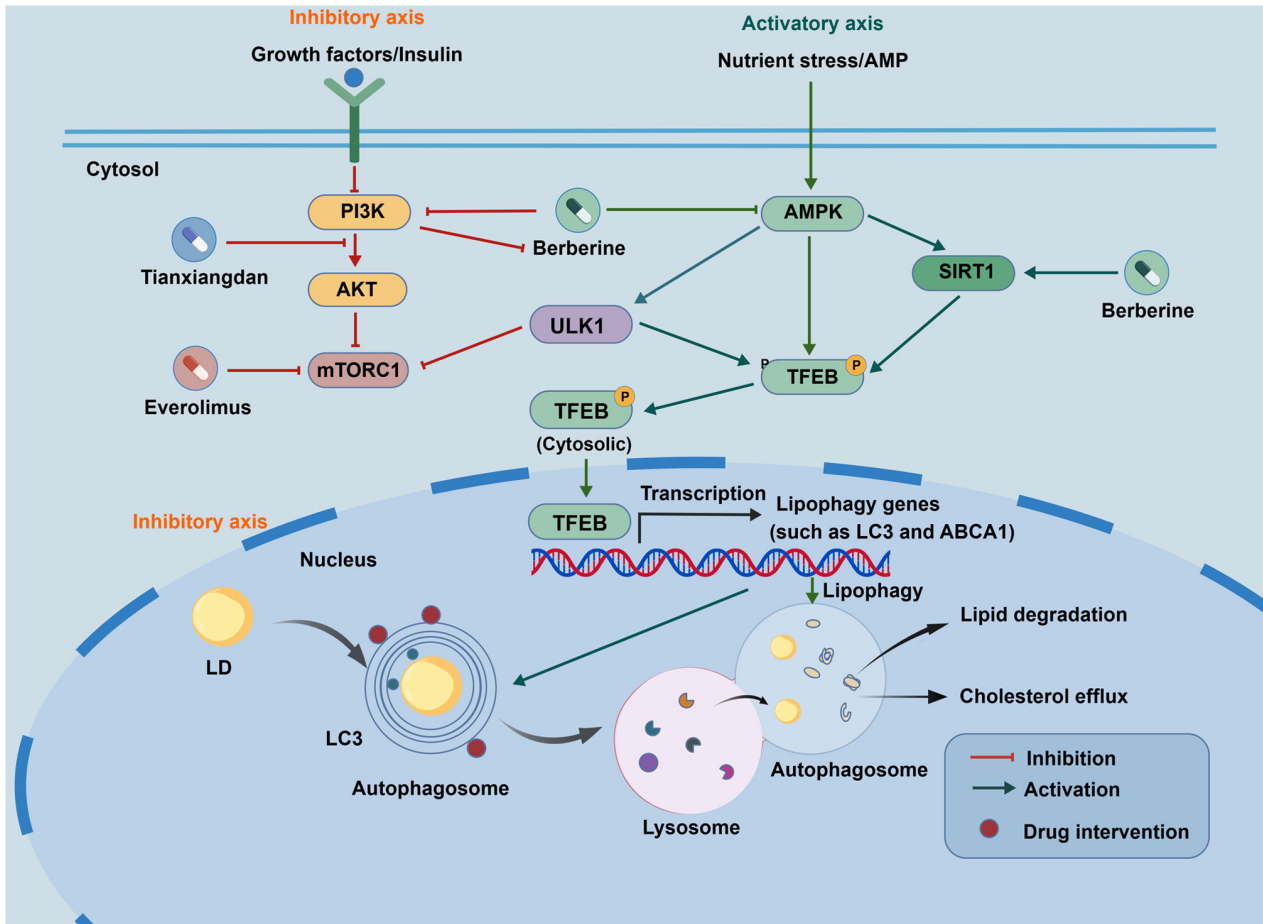


Figure 2. Therapeutic interventions targeting lipophagy signaling pathways in AS. Created with BioGDP.com (29). This schematic diagram highlights how distinct pharmacological agents and TCM formulas mitigate AS by modulating the upstream regulatory axes of lipophagy. Inhibitory axis (red lines): The PI3K/AKT/mTORC1 signaling cascade negatively regulates lipophagy. The TCM formula Tianxiangdan exerts atheroprotective effects by inhibiting upstream PI3K/AKT signaling. Simultaneously, everolimus specifically acts as a direct inhibitor of the mTORC1 complex. mTORC1 suppression relieves its inhibitory phosphorylation of both the ULK1/2 initiation complex and the transcription factor TFEB. Activatory axis (green arrows): Natural compounds effectively trigger lipophagic flux. Berberine demonstrates a dual mechanism by suppressing PI3K while concurrently activating both the AMPK and SIRT1 pathways. SIRT1 activation facilitates the essential deacetylation of TFEB. Convergence and execution: The pharmacological modulation of both axes ultimately converges on the dephosphorylation and deacetylation of TFEB, driving its nuclear translocation. Within the nucleus, TFEB initiates a robust transcriptional program of essential autophagy and lipophagy genes (such as LC3 and ABCA1). This coordinated upregulation enhances autophagosome biogenesis, accelerates LD degradation, and promotes macrophage cholesterol efflux, thereby stabilizing atherosclerotic plaques. TFEB, transcription factor EB; TCM, Traditional Chinese medicine; LD, lipid droplet.

enhancing RHEB GTPase-activating protein activity, as well as by disrupting the stability of the mTORC1 complex through RAPTOR phosphorylation. Simultaneously, mTORC1 exerts negative feedback regulation by phosphorylating the AMPK $\alpha$  subunits at the Ser347 and Ser345 residues. This reciprocal modulation establishes a dynamically balanced metabolic regulatory network (45). In this process, lipophagy regulation is intricately linked to macrophage function as well as the overall status of systemic lipid metabolism. Moreover, disruptions in hepatic lipid metabolism are markedly associated with increased AS risk, underscoring the notable role of lipophagy in maintaining systemic lipid homeostasis (46). Heterogenous nuclear ribonucleoprotein A2/B1 (hnRNPA2B1)-knockout hepatocytes exhibit increased co-localization of APs and LDs and enhanced LD lysosomal degradation, suggesting that lipophagy is crucial for reducing lipid deposition. The absence of hnRNPA2B1 decreases lipid droplet accumulation by preventing Atg5 degradation and boosting autophagy-driven lipophagy (47).

*TFEB, the master transcriptional regulator.* TFEB, recognized as a key regulator of autophagy and lysosome biogenesis, is considered to play a marked role in various pathological processes associated with the development of AS (48). TFEB is a marked regulator of lipid metabolism, overseeing transcriptional responses that control lysosomal biogenesis and autophagy. With roles in autophagy regulation, lysosomal formation, fusion and substrate degradation, TFEB promotes lipid breakdown and transport, making it a potential target for regulating lipophagy (49). TFEB has been shown to facilitate LD degradation and enhance lipid metabolic homeostasis by activating the lipophagy pathway. This mechanism may reduce lipid accumulation in macrophages and attenuate inflammatory responses, potentially impeding AS progression (50). TFEB transcriptional activity is tightly regulated by post-translational modifications, primarily phosphorylation and acetylation, which dictate its subcellular localization. Under nutrient-rich conditions, mTORC1 phosphorylates TFEB at specific residues (such as Ser211), promoting its interaction with 14-3-3 proteins

and resulting in its cytosolic sequestration. Conversely, during lipid stress or atherogenic conditions, mTORC1 inhibition or AMPK activation leads to TFEB dephosphorylation (51). Concurrently, NAD<sup>+</sup>-dependent deacetylases, particularly SIRT1, deacetylate TFEB at key lysine residues (such as Lys116) (52). This synergistic dephosphorylation and deacetylation trigger the rapid nuclear translocation of TFEB, where it binds to coordinated lysosomal expression and regulation motifs. This binding markedly upregulates the expression of essential lipophagy and cholesterol efflux genes, including *MAP1LC3B*, *SQSTM1* (p62) and *ABCA1*, thereby accelerating lipid droplet degradation and reducing lipotoxicity (53). TFEB enhances lipid breakdown and cholesterol removal via the autophagy-lysosome pathway and PPAR $\alpha$ -PGC1 $\alpha$  signaling while also stabilizing AS plaques by inhibiting NLRP3 inflammasome activation (38). Although the precise molecular mechanisms by which TFEB regulates AS are not yet fully understood, evidence suggests that TFEB expression levels vary among different cell types (48). These variations may affect AS pathological progression through cell-specific regulatory networks.

**SIRT6 and epigenetic regulation.** Sirt6, a deacetylase enzyme, plays a notable role in lipophagy and lipid metabolism. It has been implicated in the pathogenesis of age-related diseases, cancer and diabetes (54-56), and Sirt6 regulation offers a new strategy for AS treatment. Sirt6 knockout increases plaque area in ApoE<sup>-/-</sup> mice, while its overexpression reduces plaque size and slows AS progression by downregulating MMP-2 and suppressing hypoxia inducible factor-1 $\alpha$ , toll-like receptor-4 and von Willebrand factor. This enhances plaque stability by reducing intraplaque neovascularization (57). In macrophages, increasing Sirt6 expression boosts autophagy, reducing macrophagic interactions with ECs and decreasing adhesion and infiltration. This suppresses macrophage apoptosis and enhances atherosclerotic plaque stability (57). Studies have further highlighted the multifaceted protective roles of SIRT6 in autophagy regulation and inflammation resolution across different vascular cell types. For example, Li *et al* (58) demonstrated that SIRT6 epigenetically enhances macrophage efferocytosis, a specialized phagocytic and autophagic clearance mechanism, by hindering miR-216/217 cluster maturation, which promotes the resolution of chronic inflammation. Furthermore, Zi *et al* (59) showed that the protective role of SIRT6 extends beyond macrophages by revealing that SIRT6-induced autophagy effectively restricts TREM-1-mediated pyroptosis in oxidized low-density lipoprotein (ox-LDL)-treated ECs. This effect notably reduces endothelial damage and inflammatory cell death. These findings collectively underscore that SIRT6 not only prevents macrophage foam cell formation but also globally attenuates vascular inflammation by modulating autophagic flux, reinforcing its potential as a multidimensional epigenetic target for plaque stabilization. Sirt6 also promotes lipophagy by inhibiting the Wnt1 pathway, which reduces the accumulation of LDs and associated proteins, facilitating their degradation. These actions collectively reduce foam cell formation and inhibit AS development (35).

**PLIN family proteins and selective recognition via chaperone-mediated autophagy (CMA).** PLINs, the predominant proteins

on LD surfaces, localize to specific binding sites to modulate lipid storage and hydrolysis (60). As notable surface proteins associated with LDs, PLINs initiate lipophagy by undergoing degradation (61). The PLIN protein family, consisting of PLIN1-5, regulates lipase binding to LDs during lipophagy, influencing both macroautophagy and CAM. PLIN1, required for LD function, plays a notable role in metabolic regulation. In adipocytes, its absence enhances liposome-lysosome fusion and LD-lysosome interactions, accelerating macroautophagy-mediated lipolysis (62). Structurally, the CMA pathway selectively recognizes KFERQ-like motifs within the amino acid sequences of PLIN2 and PLIN3, and the cytosolic chaperone heat shock cognate 70 kDa protein (Hsc70) specifically identifies and binds to these pentapeptide motifs. As a result of this structural interaction, the PLIN-Hsc70 complex is delivered to the lysosomal membrane, where it engages with the lysosome-associated membrane protein 2A (LAMP-2A) receptor for translocation and subsequent degradation. Moreover, PLIN2/3 removal via this process reveals the lipid droplet surface, which is a prerequisite for the macroautophagic machinery to recognize and engulf the lipid cargo. PLIN2 also facilitates AMPK signaling activation by interacting with the HSP70 chaperone protein, effectively coupling lipid droplet sensing to lipophagy upstream modulation (63). Beyond structural interactions, different PLIN family members exert distinct macroscopic effects on AS. Research on human carotid plaques and macrophage models shows that PLIN2 encourages early lipid droplet formation and proinflammatory macrophage behavior, with higher mRNA expression observed in symptomatic plaques (64). By contrast, PLIN1 stabilizes large LDs and supports the anti-inflammatory balance by reducing cholesterol efflux and markedly lowering *TNFA*, *MMP2*, *ABCA1* and *ABCG1* mRNA levels (64). Collectively, these functions demonstrate the pivotal roles of PLIN family proteins in the regulation of lipophagic processes.

**Emerging external regulators: Gut microbiota and metabolites.** Research into metabolites as regulators has confirmed that gut microbiota metabolites directly modulate AS development through lipophagy. Pro-atherogenic substances such as trimethylamine N-oxide promote lipid accumulation by specifically inhibiting macrophage lipophagy. By contrast, beneficial metabolites such as short-chain fatty acids and secondary bile acids improve lipid metabolism by activating the GPCR/FXR signaling pathway (65,66). Additionally, ferulic acid restructures the gut microbiota by specifically reducing the abundance of Firmicutes, Erysipelotrichaceae and *Ileibacterium*, which subsequently modulates fecal metabolites, activating the AMPK/SREBP1/ACC1 signaling pathway (67). Activation of this pathway mitigates lipid accumulation by promoting lipophagy, highlighting a therapeutic mechanism involving the gut-vascular axis (67).

## 5. Role of lipophagy in AS

AS is a complex condition characterized by lipid buildup in arterial walls, which leads to arterial narrowing and plaque formation. Key features of AS include VSMC proliferation and migration, endothelial dysfunction and vascular remodeling.

Lipophagy markedly influences these pathological changes throughout AS development (38).

*Macrophages.* Through lipophagy, LDs in macrophages are transported to lysosomes, where they are hydrolyzed into free cholesterol by LAL. Subsequently, the free cholesterol is exported to the extracellular environment via the cholesterol reverse transport pathway, which is mediated by the ATP-binding cassette transporters ABCA1 and ABCG1 (68). The clearance of excess lipids via macrophagic lipophagy prevents the formation of foam cells, delaying the progression of AS (69). Macrophage ACE expression regulates lipid metabolism by activating PPAR $\alpha$ , which boosts  $\beta$ -oxidation and cholesterol efflux. This increases mitochondrial respiration and ATP production, reducing foam cell formation and promoting M2 polarization and efferocytosis, notably slowing AS progression (70). While lipophagy initially plays an atheroprotective role by promoting cholesterol efflux, its role in advanced AS represents its capacity to act as a 'double-edged sword'. Under conditions of severe lipotoxic stress, excessive or dysregulated lipophagy can overwhelm lysosomal capacity, leading to lysosomal membrane permeabilization, macrophage apoptosis and impaired efferocytosis (71). This transition ultimately contributes to necrotic core expansion and plaque instability. Therefore, understanding the temporal dynamics of lipophagy is required.

*Lipophagy and VSMC proliferation, migration and apoptosis.* VSMCs are key in maintaining intravascular homeostasis, which includes processes such as contraction, dilation and vascular remodeling. As a result, VSMCs are recognized as cellular determinants in the pathology of arterial walls and are notably associated with cardiovascular diseases, including AS (72). Recent transcriptomic and multi-omics studies (15,57,67) have shown that VSMC proliferation and migration, which occur as a result of a switch from a contractile state to a synthetic state, cause arterial wall thickening. Subsequently, atherosclerotic plaques undergo growth and structural changes driven by the PDGF/BB signaling pathway and lncRNA-ITGA2-related 3D genome interactions, which are key in AS pathology (73). VSMCs are involved in vascular remodeling and markedly contribute to neointimal formation through their proliferative and migratory activities in AS (74). Enhanced lipophagy is intricately associated with VSMC proliferation; this relationship is particularly pronounced under hyperlipidemic conditions, wherein the proliferation of VSMCs and their transformation into foam cells are facilitated by the uptake of lipids, such as ox-LDL (75). Furthermore, peroxidase derived from millet bran markedly inhibits lipid phagocytosis and cell proliferation in human aortic smooth muscle cells (HSMCs). This enzyme facilitates the transition of HSMCs toward a contractile phenotype and concurrently suppresses their migratory capacity. This transition inhibits the phosphorylation of STAT3, which mediates inflammatory responses, reducing aortic plaque formation (76). Concurrently, lipid accumulation and enhanced lipophagy induce VSMC migration. Migration is particularly augmented within inflammatory microenvironments, where VSMCs express specific chemokines and cell adhesion molecules, enabling motility (77).

Lipophagy also plays a notable role in apoptosis regulation in VSMCs. AS progression is often associated with VSMC apoptosis, and the degree of lipophagy markedly affects this process (78). Excessive lipid uptake by VSMCs can initiate cellular clearance by inducing apoptosis. Nonetheless, excessive lipid accumulation and the lipophagy process may further exacerbate cellular death (79). PPAR $\gamma$  coactivator-1 alpha (PGC-1 $\alpha$ ) suppresses glucose-driven VSMC proliferation, migration and inflammation, which are crucial aspects of AS pathology. PGC-1 $\alpha$  encourages VSMCs to differentiate into a macrophage-like form, potentially increasing the quantity of VSMCs-derived foam cells in plaques and aiding plaque stabilization (80). The gelsolin-mediated lipophagy-related signaling pathway is considered a necessary mechanism in safeguarding VSMCs against apoptosis, and this discovery offers new therapeutic insights supporting AS treatment (81).

As a pivotal regulator of VSMC function, lipophagy is a prospective therapeutic target for AS (26,82). The dual role of lipophagy in VSMCs must be considered in the context of overall plaque stability. Specifically, the lipophagic flux in VSMCs serves as a determinant of plaque structural integrity. While physiological lipophagy prevents the transdifferentiation of VSMCs into foam cells by mobilizing intracellular lipids, excessive or dysfunctional autophagic flux can trigger VSMC apoptosis (82). This depletion of VSMCs within the fibrous cap directly compromises its mechanical strength, as these cells are the primary source of the extracellular matrix, particularly interstitial collagen (83). A reduced VSMC population leads to a net loss of collagen fibers and progressive thinning of the fibrous cap, thereby transforming a stable lesion into a vulnerable plaque prone to rupture. Thus, the 'double-edged sword' of lipophagy in VSMCs represents a pivotal link between cellular lipid homeostasis and macroscopic plaque stability (84,85). Thus, the net effect of VSMC lipophagy depends on the disease stage and the intensity of autotoxic stress.

*Association between lipophagy and EC dysfunction.* ECs are notable contributors to AS and serve as regulatory centers throughout the progression of the disease. These cells participate in various physiological processes, such as intracellular signal transduction, cell adhesion, immune response and inflammation (38). EC dysfunction (ECD) involves a compromised endothelial barrier, increased inflammation, oxidative stress imbalance and decreased nitric oxide availability, leading to lipoprotein leakage, monocyte recruitment and plaque formation. As plaques progress, ECD exacerbates inflammation by releasing proinflammatory and prothrombotic factors, contributing to plaque instability (86). Research has elucidated the notable role of lipophagy in preserving EC function, and ECD is acknowledged as an early indicator of AS. Lipophagic deficiency can produce lipid accumulation within ECs, triggering oxidative stress and inflammatory responses, which further aggravates ECD (87). ox-LDL binds to specific receptors on ECs, facilitating EC lipid uptake; this mechanism induces lipid overload and subsequently leads to EC apoptosis (88). Enhanced lipophagy in ECs helps clear excess lipids, improving EC function and vascular health. It also reduces inflammation, a key factor in AS development, by suppressing EC levels of pro-inflammatory cytokines (89). For

example, lipophagy mitigates ox-LDL-induced inflammatory responses in ECs by facilitating intracellular ox-LDL clearance, thus providing protection against EC damage (90,91). Lipophagy mitigates inflammatory responses by facilitating EC repair and regeneration through the modulation of specific autophagy-related signaling pathways, such as the CaMKK $\beta$ /AMPK, SOCE and PI3K/AKT pathways (92,93). The role of lipophagy in EC inflammation extends beyond lipid clearance; it also encompasses regulation of cytokine expression and signaling pathway activity (93,94). Enhanced lipophagy markedly improves EC function and augments resistance to oxidative stress and inflammation. Certain natural compounds, such as naringenin, have been shown to facilitate EC lipophagy, thereby mitigating ox-LDL-induced cellular damage (95). Lipophagy is integral to EC functional recovery; consequently, lipophagy modulation has considerable therapeutic potential in the context of AS.

*Effects of lipophagy on vascular remodeling.* Vascular remodeling is a pathological mechanism critical to AS progression, characterized by structural reorganization of the vascular wall, diminished elasticity, tissue calcification, plaque rupture and luminal narrowing. These phenomena are manifested through a range of pathological processes (70). For example, as a key regulator of lipid metabolism and inflammatory responses, lipophagy is crucial for VSMC remodeling in AS (96). VSMCs not only function as structural support cells but also play a role in lipid metabolism during atherogenesis. By promoting lipid degradation, lipophagy mitigates lipid accumulation within VSMCs, thereby limiting AS progression (97). Macrophages are the primary cells responsible for lipid accumulation within arterial walls. In macrophages, lipophagy mitigates the intracellular accumulation of CEs and TG through LD degradation via lysosomal pathways, thereby preventing foam cell formation and promoting cholesterol efflux (6,68,98). LAL is crucial in the lipophagy pathway, and reduced LAL expression decreases its activity in macrophages, resulting in more LDs, faster foam cell formation and vascular thickening. Conversely, LAL overexpression reduces lipid buildup by boosting the expression of genes such as *Hmgbl*, *Hmgb2*, *Hspa5* and *Scarb2*. This also decreases cholesterol efflux and enhances lipophagy coordination (6,99). Lipophagic deficiency has been shown to expedite the progression of unstable atherosclerotic plaques. Impaired lipophagy within macrophages causes increased lipid core size, diminished collagen content and thinning of the fibrous cap in plaques, collectively enhancing the risk of plaque rupture (66). Vascular endothelial injury triggers vascular remodeling; however, lipophagy shields ECs from ox-LDL and advanced glycation end product damage by maintaining redox balance, clearing damaged mitochondria and lipotoxic products, preventing lipid droplet buildup and reducing lipid deposition. In addition, lipophagy also decreases inflammatory cell secretion, further protecting vascular ECs (100). Preclinical studies indicate that lipophagy activators, including berberine (BBR), decrease the levels of inflammatory factors such as TNF- $\alpha$  and IL-6 through a SIRT3-mediated lipophagy pathway. This mechanism enhances endothelium-dependent vasodilation and attenuates the progression of vascular stiffening (101). Enhancing lipophagic activity may therefore constitute a

pivotal strategy for improving the structural integrity of the vascular wall and preventing AS.

*Other cell types.* Beyond macrophages and VSMCs, emerging evidence suggests that lipophagy serves as a notable metabolic rheostat in other non-canonical cell types, notably T lymphocytes and fibroblasts (102). In T lymphocytes, lipophagy-mediated mobilization of triacylglycerols provides free fatty acids for mitochondrial fatty acid oxidation, an energetic process essential for T-cell activation and the maintenance of regulatory T cell populations. A deficiency in autophagic lipid processing can impair Treg suppressive function and promote a pro-inflammatory Th17 phenotype, thereby intensifying the inflammatory milieu within the plaque. Similarly, in vascular fibroblasts, lipophagy-mediated lipid turnover maintains intracellular lipid proteostasis, thereby suppressing cellular senescence and the pathological fibroblast-to-myofibroblast transition by mitigating oxidative stress (102-104). By governing the availability of lipid-derived signaling molecules, lipophagy influences the production of the extracellular matrix, which is required for the structural integrity of the adventitia and media (105). These emerging insights suggest that lipophagy represents a universal metabolic hub across diverse cell populations in the progression of AS.

## 6. Therapeutics and active compounds for AS prevention and treatment

In terms of clinical applications, targeting lipophagy presents a viable yet complex therapeutic frontier. Current pharmacological strategies can be broadly categorized into two paradigms: Conventional lipid-lowering agents and holistic multi-target modulators (such as natural compounds and TCM) (106,107). While conventional drugs such as statins primarily promote lipophagy indirectly as a secondary consequence of systemic lipid reduction and upstream AMPK activation, TCM formulas and their active botanical monomers (such as BBR) often act directly on intracellular epigenetic and transcriptional networks (such as the SIRT1-TFEB axis) to restore specific autophagic flux. The contrast between these approaches highlights a shift from broad systemic metabolic control toward more nuanced, multi-targeted intracellular regulation. In the following sections, these therapeutic agents are systematically evaluated based on their mechanisms of action.

*Autophagy activators.* Autophagy activators are compounds employed to stimulate or augment autophagy. These agents operate by activating autophagy-related signaling pathways or modulating the expression of notable autophagy-associated proteins. The underlying mechanisms encompass negative regulation of the mTOR signaling pathway and activation of AMPK, among others (108). mTOR is a highly conserved serine/threonine protein kinase with a pivotal role in the regulation of fundamental biological processes such as cell growth, proliferation, protein synthesis, energy metabolism and autophagy (109). Everolimus, the most extensively researched mTOR inhibitor, has been thoroughly investigated to determine its therapeutic potential against AS, owing to its autophagy-inducing properties (110). It notably enhances plaque stability, and the application of everolimus-eluting

cobalt-chromium platforms to cardiac stents facilitates the development of a stable plaque phenotype (110,111). Everolimus has been shown to inhibit AS progression, and its therapeutic efficacy appears to be more pronounced in the early stages of AS than in the advanced stages (112). However, the clinical translation of broad mTOR inhibitors such as everolimus, whose therapeutic efficacy varies between early and advanced lesions in LDL-R-deficient mice and clinical studies, is markedly limited by systemic immunosuppressive effects and metabolic side effects, including treatment-induced hypercholesterolemia, systemic immunosuppressive effects and metabolic side effects, emphasizing the need for cell type-specific delivery systems (109-111).

Metformin (Met) is commonly prescribed as a first-line pharmacological treatment for type 2 diabetes mellitus, and it is acknowledged as an AMPK activator (112). Patients with AS exhibit AMPK and ERK pathway suppression, which contributes to abnormal lipid metabolism and inflammation (113). Met reduces plaque buildup caused by a high-fat diet, exerting a protective effect against AS. Mice fed a high-fat diet exhibit an increased proportion of Ki67-positive proliferating cells and  $\alpha$ -SMA-positive VSMCs within the arterial media. Met decreases abundance of these dual-positive cells and ERK levels while increasing AMPK and Pdlm5 levels. This finding indicates that Met selectively counteracts the pathological VSMC proliferation promoted by a high-fat diet, thereby stabilizing the vascular wall and mitigating AS (112).

Atorvastatin is a primary therapeutic agent for lipid reduction and plaque stabilization that exhibits anti-oxidative, anti-inflammatory, anti-thrombotic and anti-atherosclerotic properties (114). Additionally, it enhances endothelial function and contributes to plaque stabilization (115). It inhibits foam cell formation by promoting lipophagy, marked by increased Atg protein expression, a higher LC3-II/LC3-I ratio and reduced p62 levels. It also enhances LC3 and LD co-localization in treated foam cells, suggesting an ability to induce autophagy in macrophages and reduce intracellular lipid buildup (116). Clinically, while atorvastatin is widely prescribed for systemic lipid-lowering at standard doses of 20-80 mg/d, ongoing clinical evaluations are required to determine whether these conventional regimens are sufficient to optimally induce macrophage lipophagy within the complex plaque microenvironment (117,118). Furthermore, the dose-dependent risk of statin-associated muscle symptoms necessitates the exploration of localized targeted delivery strategies (119,120).

*Herbal monomers.* Increased research into the anti-AS effects of TCM extracts has confirmed the efficacy of numerous herbal monomers against AS. Additionally, synergistic combinations of multiple TCM/natural products (such as multicomponent botanical compositions) demonstrate greater anti-AS activity and fewer side effects than isolated compounds used alone (121). Geniposide (GE), a water-soluble iridoid glycoside also referred to as genipin-1- $\beta$ -gentiobioside, has been identified in >40 plant species, and it exhibits a range of pharmacological effects and biological activities (122). GE boosts lipophagy by inhibiting the PARP1/PI3K/AKT pathway, accelerating LD breakdown and reducing lipid buildup. This slows AS development by preventing apoptosis and foam cell marker expression in VSMC-derived foam cells (123).

Epigallocatechin gallate (EGCG) is the most abundant and biologically active compound in tea polyphenols; it exhibits multiple biological effects, including anti-inflammatory and anti-oxidant (124), anti-obesity (121), as well as anti-infection and anti-tumor activities (125). EGCG activates autophagic flux via the  $Ca^{2+}$ /CaMKK $\beta$ /AMPK pathway, reducing lipid buildup in vascular ECs by promoting lipophagy. EGCG releases  $Ca^{2+}$  from the endoplasmic reticulum, triggering CaMKK $\beta$  and AMPK/ULK1 phosphorylation (bypassing mTOR) and subsequently increasing LC3-II formation and p62 degradation (126). EGCG enhances lysosomal degradation by co-localizing LDs with LC3 and lysosomes, ultimately reducing palmitate-induced lipid accumulation, improving endothelial lipotoxicity and mitigating AS (127,128).

BBR, an isoquinoline alkaloid derived from *Coptis chinensis* and various *Berberis* species, demonstrates anti-atherosclerotic properties through a range of mechanisms such as lipid regulation, anti-inflammatory effects, oxidative stress reduction, vascular endothelial dysfunction mitigation, modulation of VSMC proliferation and migration and anti-thrombotic activity (129). BBR boosts the intracellular NAD<sup>+</sup>/NADH ratio by activating NAD<sup>+</sup> biosynthesis pathways, enhancing SIRT1 deacetylase activity (130,131). Activated SIRT1 then deacetylates TFEB, increasing the LC3-II/LC3-I ratio and Beclin 1 expression (132). This process promotes autophagosome formation, inducing lipophagy and promoting LD degradation while delaying cell apoptosis. Together, these effects intervene in AS lipid metabolism. Despite these promising *in vitro* mechanisms, the clinical translation of BBR is significantly hindered by its poor oral bioavailability. Achieving sustained therapeutic concentrations specifically within atherosclerotic plaques remains a major challenge, emphasizing the necessity for advanced cell-type-specific delivery systems (130,131). Future clinical applications will likely depend on the development of novel nanoparticle-based delivery systems that enhance lipophagic efficacy *in vivo*.

The therapeutic landscape of natural compounds targeting AS is rapidly expanding beyond traditional signaling pathways to encompass epigenetic regulation and intercellular communication. Recent comprehensive studies have emphasized that natural medicinal active ingredients and TCMs can effectively prevent and treat AS by directly targeting epigenetic modifications (133). For example, intercellular crosstalk via extracellular vesicles (EVs), such as EV-derived miR-146a targeting SMAD4, has recently been identified as a novel pathogenic mechanism in high-fat diet-induced AS (134). Botanical extracts possess a profound capacity to modulate such epigenetic networks, evidenced by their ability to mitigate chronic inflammatory diseases by markedly altering micro RNA expression profiles (135). Consequently, future investigations into natural lipophagy modulators should explore their potential to concurrently regulate EV miRNAs and the epigenetic landscape, which would offer a multi-dimensional, systemic approach to plaque stabilization.

*Chinese herbal formulas.* Research examining the therapeutic effects and underlying mechanisms of TCM interventions in the context of AS has markedly increased in recent years (136,137). TCM formulations demonstrate efficacy in alleviating AS

symptoms and decelerating disease progression, attributed to multi-component actions, multi-target mechanisms and minimal side effects (138). Tianxiangdan enhances lipophagy by inhibiting the PI3K/Akt/mTOR pathway, reducing p85/Akt/mTOR phosphorylation. This activates TFEB and the autophagy proteins ULK1/LC3-II, boosting LD degradation. Tianxiangdan also increases ABCA1 expression and suppresses expression of p62, raising lipophagy levels, reducing foam cell formation, decreasing arterial plaque lipid deposition and slowing AS progression (139). Recent molecular docking and pharmacological analyses indicate that rather than acting as a simple generalized inhibitor, the Huoxue Qutan Formula contains primary active constituents such as specific flavonoids and saponins that directly interact with upstream nutrient-sensing kinases. This targeted interaction persistently suppresses mTORC1 phosphorylation, thereby mechanically uncoupling mTORC1 from TFEB and enhancing TFEB nuclear translocation, increasing LC3-II/I and Beclin1 levels, and reducing p62 levels. This process leads to improved co-localization of LDs with autophagosomes and upregulates the expression of the cholesterol efflux proteins ABCA1 and SCARB1 through TFEB pathways, reducing foam cell formation and lipid deposition in atherosclerotic plaques (140). The Gualou-Xiebai herbal combination inhibits P2RY12 activation, downregulating p62 and Plin2 expression and upregulating LC3II expression. The quantity of autophagosomes is also increased, markedly enhancing lipophagy activity. Consequently, foam cell formation is reduced, and anti-atherosclerotic effects are achieved (141).

In conclusion, accumulating evidence suggests that pharmacological agents and active compounds that modulate lipophagy exhibit notable therapeutic potential for AS prevention and treatment. Research priorities in this domain include autophagy inducers, monomeric TCM components and TCM compounds. Mechanistically, these agents operate by activating autophagy-related signaling pathways, regulating the activity of key autophagy proteins, improving dysregulated lipid metabolism and inflammatory responses, inhibiting foam cell formation, exerting anti-inflammatory and antioxidant effects, ameliorating vascular endothelial dysfunction and modulating VSMC proliferation and migration (Table I). Further investigation is necessary to elucidate the precise mechanisms and assess the clinical feasibility of these pharmacological agents.

*Convergence of therapeutic mechanisms.* As illustrated in the regulatory network (Fig. 2), pharmacological agents modulate lipophagy through two distinct but converging signaling axes. First, in the inhibitory axis, agents such as everolimus and the TCM formula Tianxiangdan function by inhibiting the PI3K/Akt/mTOR pathway. This inhibition suppresses mTORC1 phosphorylation, thereby relieving the suppression of ULK1/2 and TFEB, which subsequently activates autophagy proteins and increases LD degradation. Second, in the activating axis, natural compounds such as BBR and EGCG predominantly target the AMPK-SIRT1 axis. BBR activates NAD<sup>+</sup> biosynthesis, which enhances SIRT1 deacetylase activity and leads to TFEB deacetylation, ultimately increasing the LC3-II/LC3-I ratio. Similarly, EGCG activates the CaMKK $\beta$ /AMPK pathway, bypassing mTOR and directly stimulating autophagic flux. These interventions ultimately

converge to upregulate the expression of cholesterol efflux proteins (ABCA1) and reduce foam cell formation.

## 7. Discussion and future perspectives

AS pathological mechanisms are intricate, involving a multitude of cell types and biomolecules. Lipophagy, a variant of autophagy, has garnered notable attention as a focal point of research. Lipophagy not only plays a pivotal role in modulating inflammatory responses but also directly influences lipid metabolism and cellular functions, contributing to AS initiation and progression (6,14). Recent studies indicate that lipophagy modulates macrophage functionality, either facilitating or inhibiting lipid deposition within arterial walls and thus impacting plaque stability and formation (68,98). Synthesizing these multidimensional findings, our proposed ‘stage-dependent double-edged sword’ model challenges the traditional paradigm that simply views autophagy activation as universally beneficial. Instead, the present model underscores a critical pathogenic threshold where adaptive lipid clearance transitions into maladaptive lysosomal membrane permeabilization and cell death (110). Recognizing this threshold is an original insight that is necessary in order to transition from broad, systemic autophagy inducers to the precise, context-dependent interventions outlined in our therapeutic framework.

To address the existing challenges in the field, future research should prioritize several critical aspects. First, it is imperative to develop more specific lipophagy modulators to enhance therapeutic efficacy and minimize potential side effects. Current agents often possess broad mechanisms of action, which can result in inconsistent effectiveness and safety concerns (110,111). Therefore, precisely targeted lipophagy drugs are required for ensuring therapeutic success. An evaluation of regulatory networks revealed that not all signaling axes hold equal therapeutic promise. While the upstream AMPK-mTORC1 axis acts as the primary cellular energy sensor, its broad influence on global protein synthesis and cell growth makes it susceptible to systemic side effects (114). Consequently, downstream transcriptional and epigenetic regulators, specifically the TFEB and SIRT1/6 axes, are more viable therapeutic targets (82,130). These downstream nodes are well suited for a ‘precision strike’ strategy, which would directly mobilize lysosomal biogenesis and autophagic flux without disrupting fundamental cellular metabolism. Therefore, future drug development should prioritize molecules that specifically calibrate these terminal transcriptional effectors rather than broad upstream kinases.

Second, there should be an emphasis on optimizing combination therapies. Single-drug treatments are often inadequate for addressing complex pathological conditions, whereas rationally designed multi-drug regimens have the potential to improve therapeutic outcomes and reduce the risk of drug resistance. Through systematic clinical trials and personalized strategies, drugs with complementary mechanisms can be strategically combined to achieve enhanced efficacy. Furthermore, advancing translational research is a key priority. While basic studies provide a theoretical foundation for lipophagy-based therapies, further work is needed to translate these discoveries into clinical practice. The integration of multidisciplinary approaches, such as molecular biology, is essential to facilitate this transition.

Table I. Pharmacological agents and active compounds targeting lipophagy for the prevention and treatment of AS.

A, Autophagy activator						
Drug ingredients	Mechanism of action	Method	Model	Targets	Actions (Refs.)	
Everolimus	<ol style="list-style-type: none"> <li>Inhibits mTORC1 signaling.</li> <li>Induces foam cell apoptosis and autophagy.</li> <li>Suppresses matrix degradation and pro-inflammatory cytokine secretion.</li> </ol>	<p><i>In vivo</i> and <i>In vitro</i></p>	<p><i>In vitro</i>:</p> <ol style="list-style-type: none"> <li>Human THP-1 macrophage-derived foam cells</li> <li>HCASMCs</li> <li>HUVECs</li> </ol> <p><i>In vivo</i>:</p> <ol style="list-style-type: none"> <li>Hypercholesterolemic rabbit iliac artery model</li> </ol>	mTORC1, Survivin, Clusterin, MAP1LC3, MMP1 and MCP-1	<ol style="list-style-type: none"> <li>Selectively reduced foam cell viability.</li> <li>Induced autophagy</li> <li>Inhibited matrix degradation.</li> <li>Reduced pro-inflammatory secretion.</li> <li>Decreased macrophage infiltration <i>in vivo</i>.</li> </ol>	(108-110)
Metformin	<ol style="list-style-type: none"> <li>Activates the AMPK pathway.</li> <li>Inhibits the ERK pathway.</li> </ol>	<i>In vivo</i>	C57/B6 mice	AMPK, ERK and Pdlim5	<ol style="list-style-type: none"> <li>Attenuated atherosclerotic deposition.</li> <li>Inhibited VSMC proliferation and migration.</li> </ol>	(111,112)
Atorvastatin	<ol style="list-style-type: none"> <li>Upregulates phosphorylation of AMPK.</li> <li>Downregulates phosphorylation of the mTOR.</li> <li>Promotes lipophagy.</li> </ol>	<i>In vitro</i>	Macrophages	Atg, LC3-II/LC3-I and p62	<ol style="list-style-type: none"> <li>Inhibited foam cell formation.</li> <li>Reduced lipid droplet accumulation.</li> </ol>	(114)
B, Herbal monomers						
Drug ingredients	Mechanism of action	Method	Model	Targets	Actions (Refs.)	
Geniposide	Inhibits the PARP1/PI3K/AKT signaling pathway	<i>In vivo</i> and <i>In vitro</i>	<p><i>In vitro</i>: High-fat diet-fed ApoE<sup>-/-</sup>-mice.</p> <p><i>In vivo</i>: VSMCs</p>	PARP1, PI3K, AKT	<ol style="list-style-type: none"> <li>Inhibited lipid accumulation, apoptosis, and foam cell marker expression.</li> <li>Accelerated lipid droplet degradation.</li> <li>Suppressed VSMC-derived foam cell formation.</li> </ol>	(123)
Epigallocatechin gallate	Activates the CaMKK $\beta$ /AMPK pathway	<i>In vitro</i>	Primary bovine aortic endothelial cells.	CaMKK $\beta$ , AMPK, ULK1 and LC3-II.	<ol style="list-style-type: none"> <li>Promoted autophagic flux and lipophagy.</li> <li>Inhibited lipid droplet accumulation and clearance of ectopic lipid deposits.</li> <li>Ameliorated lipotoxicity in vascular endothelial cells.</li> </ol>	(126-128)

Table I. Continued.

B, Herbal monomers							(Refs.)
Drug ingredients	Mechanism of action	Method	Model	Targets	Actions	(Refs.)	
Berberine	1. Inhibits the PI3K/AKT/mTOR signaling pathway. 2. Activates the SIRT1/TFEB pathway. 3. Upregulates the NAD <sup>+</sup> /NADH ratio.	<i>In vitro</i>	Peritoneal macrophages	SIRT1, TFEB, LC3-II/LC3-I and Beclin1.	1. Induced lipophagy. 2. Promoted lipid droplet degradation. 3. Delayed cellular apoptosis.	(130,131)	
C, Chinese herbal formula							
Drug ingredients	Mechanism of action	Method	Model	Targets	Actions	(Refs.)	
Tianxiangdan	Suppresses the PI3K/Akt/mTOR pathway and activates TFEB	<i>In vivo</i>	High-fat diet-fed ApoE <sup>-/-</sup> mice	PI3K, Akt, mTOR, TFEB, LC3II/I, ULK1, ABCA1 and p62	1. Activated lipophagy. 2. Promoted lipid droplet degradation. 3. Reduced foam cell formation and intra-plaque lipid deposition.	(139)	
Huayu Qutan Recipe	1. Regulates the mTORC1/TFEB signaling pathway. 2. Inhibits the PI3K/Akt/mTOR pathway and activates TFEB.	<i>In vivo</i> and <i>in vitro</i>	<i>In vivo</i> : ApoE <sup>-/-</sup> mice <i>In vitro</i> : RAW 264.7 cells	mTORC1, TFEB, LC3-II/I, Beclin1 and p62	1. Activated lipophagy. 2. Upregulated ABCA1 and SCARB1. 3. Modulated serum lipid profiles. 4. Reduced lipid accumulation in macrophages. 5. Inhibited foam cell formation. 6. Promoted autophagosome formation. 7. Facilitated lipid degradation in foam cells via the autophagic-lysosomal pathway.	(140)	
Gualou-Xiebai herb pair	1. Downregulates P2RY12, p62 and Plin2. 2. Upregulates LC3-II protein expression	<i>In vivo</i>	High-fat diet-fed ApoE <sup>-/-</sup> mice	P2RY12, LC3II, p62 and PLIN2	1. Enhanced lipophagy. 2. Increased the number of autophagosomes. 3. Reduced foam cell formation.	(141)	

TFEB, transcription factor EB; VSMC, vascular smooth muscle cell.

From a translational perspective, the molecular mechanism of lipophagy aligns well with the TCM principle of resolving phlegm (Qutan). Formulas such as Huoxue Qutan and Gualou-Xiebai promote lipophagy by upregulating LC3-II and reducing p62/Plin2 levels. By facilitating the lysosomal degradation of 'turbid' lipids (LDs) (140,141), these herbal pairs effectively reduce the necrotic core and stabilize plaques. This intricate molecular crosstalk provides a compelling modern biological basis for classical TCM therapies, highlighting their potential as multi-targeted modulators for AS.

Lipophagy has been established as a critical process in AS development and progression that is characterized by complex and dual regulatory mechanisms. Future research should aim to elucidate the specific functions of lipophagy and its interactions with other biological processes. The therapeutic potential of targeting lipophagy for clinical management warrants further scientifically rigorous research to facilitate the development of novel therapeutic strategies and provide new approaches for AS prevention and treatment.

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### Authors' contributions

SN drafted the manuscript and prepared the figures. CP, XM, JJ and FZ conducted the literature search and contributed to the writing and editing of the manuscript. YC proposed the research design, supervised the study and critically revised the manuscript for important intellectual content. Data authentication is not applicable. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

Not applicable.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

### Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the

manuscript. Subsequently, the authors thoroughly reviewed and edited the content produced by the artificial intelligence tools as necessary, and the manuscript was further refined by professional native-speaking editors from LetPub. The authors take full responsibility for the integrity and ultimate content of the present manuscript.

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