

Phytochemical Monomers Derived from Traditional Chinese Medicine May Prevent and Treat Atherosclerosis by Modulating the Macrophage Mitochondrial–Lysosomal Senescence Axis

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Abstract: The pathogenesis of atherosclerosis (AS) is evolving from a lipid-centric view to a paradigm of immunosenescence. Stress-induced senescence of plaque macrophages is associated with inflammation and instability via the senescence-associated secretory phenotype (SASP). Dysfunction of the integrated “mitochondria-lysosome senescence axis” is thought to play a key role in maintaining this senescent state, which correlates with lipid overload, impaired efferocytosis, and fibrous cap degradation. Multi-target monomers from Traditional Chinese Medicine (TCM) such as quercetin, Tanshinone IIA, berberine, and baicalein have been shown to modulate senescent macrophages, potentially via this axis. Proposed mechanisms include inhibiting p38 MAPK/p16 signaling, reducing scavenger receptor-mediated lipid uptake, enhancing cholesterol efflux, suppressing the NF- κ B/NLRP3 inflammasome, promoting efferocytosis via TAM receptors, and restoring metabolic support for lysosomal acidification. This review synthesizes the role of the mitochondria-lysosome axis in AS and highlights the potential of TCM monomers to stabilize plaques, providing a novel framework for therapeutic development.

Keywords: mitochondria-lysosome senescence axis, TCM, atherosclerosis, phytochemical monomers, cardiovascular diseases, macrophage senescence

Introduction

AS has long been regarded as a lipid-driven disorder. In recent years, the intersection of senescence biology and cardiovascular research has contributed to a paradigm shift in understanding: AS, particularly in its advanced complications, represents a classic disease associated with inflammatory senescence or immunosenescence.¹ Immunosenescence refers not merely to the age-related functional decline of the immune system, but more specifically to the premature and accelerated senescence process of immune cells within the atherosclerotic pathological microenvironment, driven by factors such as oxidized lipids and metabolic stress.

Immunosenescence within plaques is not a passive, singular, and homogeneous event. Instead, it manifests as a dynamic and heterogeneous network collaboratively shaped by diverse immune cell populations and their state transitions, playing a pivotal role in sustaining local inflammation, disrupting immune homeostasis, and driving lesion progression.² This system, centered around senescent macrophages and T cells, actively shapes and exacerbates the plaque microenvironment through their distinctive secretome and intercellular communication.³ Senescent immune cells, particularly macrophages, lose their capacity for efferocytosis and homeostasis maintenance, instead adopting

a phenotype characterized by the robust secretion of proteolytic enzymes and proinflammatory mediators. Consequently, immunosenescence is not merely an epiphenomenon of AS but rather a central mechanism directly driving the transition of plaques from a stable to an unstable state.⁴ Elucidating this mechanism, particularly the core organelle-centric pathways driving immune cell senescence, provides novel therapeutic targets for intervening in advanced AS.

The establishment and perpetuation of macrophage immunosenescence are closely linked to the functional integrity of the mitochondria-lysosome senescence axis.⁵ This axis is defined as an integrated, bidirectional organelle stress network in which mitochondrial dysfunction and lysosomal impairment mutually reinforce each other. Mitochondrial dysfunction, characterized by elevated reactive oxygen species (mtROS), reduced ATP production, and impaired mitophagy, compromises lysosomal acidification and degradative capacity.⁶ Conversely, lysosomal membrane permeabilization, pH dysregulation, and hydrolytic enzyme leakage impede the clearance of damaged mitochondria, thereby perpetuating mitochondrial stress. This self-amplifying cycle establishes a “lock-in” state of cellular senescence, culminating in lipid overload, inflammasome activation, senescence-associated secretory phenotype (SASP) secretion, and efferocytosis failure.⁷ Within the atherosclerotic plaque, this axis is thought to serve as a mechanistic hub that integrates metabolic stress, organelle quality control, and inflammatory signaling, offering a conceptual framework for understanding the association between plaque progression and structural instability. Distinct from related concepts such as mitophagy-lysosomal coupling (which focuses on degradative flux) or immunometabolism (which centers on metabolic reprogramming), the mitochondria-lysosome senescence axis uniquely emphasizes the feed-forward nature of organelle crosstalk in driving irreversible senescence and its pathological consequences.

TCM has a long history of application in the prevention and treatment of cardiovascular diseases. Its multi-component and multi-target nature is highly compatible with the complex pathological network of AS.⁸ Accumulating evidence indicates that many bioactive monomers derived from TCM can precisely intervene in specific cellular signaling pathways and organelle functions.⁹ Therefore, investigating how these monomeric constituents regulate the “mitochondria-lysosome senescence axis” in macrophages is of significant scientific value for elucidating the deeper molecular mechanisms of TCM against AS, discovering novel therapeutic targets, and developing innovative drugs.

This article aims to delineate how the functional uncoupling between mitochondria and lysosomes may contribute to the senescence program entrenchment in macrophages and further explores how herbal-derived compounds may serve as a potential strategy for reprogramming senescent macrophages and achieving plaque-stabilizing effects potentially through restoring the integrity of this pivotal axis. [Figure 1](#) illustrates the proposed mechanisms through which active compounds derived from TCM modulate the mitochondria lysosome senescence axis in macrophages.

The Mitochondria-Lysosome Senescence Axis in Macrophages and the Pathogenesis of AS

Lipid Overload

Within the pro-oxidant and pro-inflammatory milieu of the atherosclerotic plaque, macrophages are more prone to acquiring a senescent-like phenotype. These senescence-associated alterations, in turn, prime the cells for a heightened propensity to uptake oxidized lipids and undergo foam cell formation.¹⁰ Evidence from a THP-1 macrophage foam cell model indicates that overexpression of the senescence marker p16INK4a upregulates scavenger receptors CD36 and LOX-1, while concurrently impairing cholesterol efflux capacity. This results in exacerbated intracellular lipid accumulation and enhanced foam cell formation.¹¹ These findings suggest that the upregulation of lipid uptake receptors, driven by senescence markers and leading to increased oxidized lipid internalization, may represent a key mechanism through which senescent macrophages contribute to pathological progression within atherosclerotic plaques. Consequently, therapeutic strategies aimed at attenuating the excessive uptake of oxidized lipids by senescent macrophages may include interventions that either inhibit the core axis driving cellular senescence or directly block the key pathways responsible for oxLDL internalization. Luo et al¹² demonstrated in an ApoE^{-/-} AS model that quercetin alleviates AS by suppressing ox-LDL-induced senescence in plaque macrophages, a mechanism involving inhibition of the p38 MAPK/p16 pathway that may mitigate the aberrant lipid uptake inherent to the senescent phenotype at the level of senescent phenotype. Furthermore,

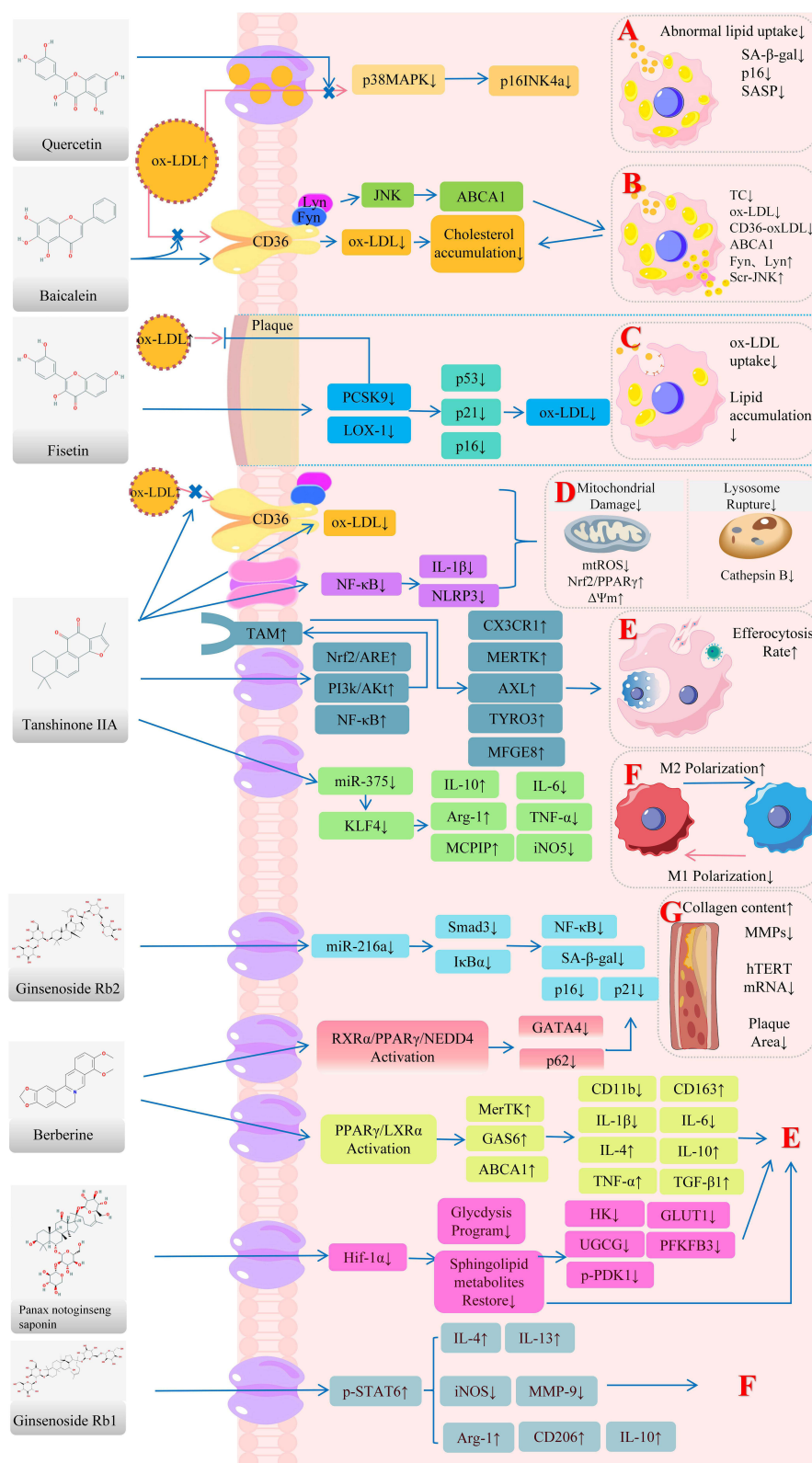


Figure 1 The mechanisms through which active compounds derived from traditional Chinese medicine modulate the mitochondria-lysosome senescence axis in macrophages. In the figure, “↑” indicates an increase in content or activity, while “↓” indicates a decrease. “x” represents blockade. Red arrows denote the oxLDL-mediated pathway, and blue arrows represent the drug intervention pathway. The annotations in the figure are as follows: **(A)** represents the process of Quercetin interfering with abnormal lipid uptake; **(B)** illustrates the competitive inhibition of macrophage-specific epitope receptors by Baicalein; **(C)** depicts the intervention of Fisetin in atherosclerotic plaque formation; **(D)** shows the protective effects of Tanshinone IIA against mitochondrial and lysosomal damage; **(E)** represents the regulation of efferocytosis by Tanshinone IIA, Berberine, and Panax notoginseng saponin; **(F)** illustrates the modulation of macrophage M2 polarization by Tanshinone IIA and Ginsenoside Rb1; and **(G)** represents the regulation of plaque stability by Ginsenoside Rb2 and Berberine.

intervention at critical nodes of oxLDL uptake has been shown to be associated with reduced macrophage lipid loading. Li et al¹³ confirmed in a THP-1-derived macrophage model that baicalein reduces oxLDL uptake and foam cell formation. Mechanistically, its effects are proposed to involve competitive inhibition of the interaction between CD36 and specific epitopes on oxLDL, thereby attenuating intracellular cholesterol accumulation. In addition, Yan et al¹⁴ provided experimental evidence that a study in ApoE^{-/-} mice revealed that fisetin intervention attenuated atherosclerotic plaque formation, improved dyslipidemia and oxidative stress, and downregulated the expression of PCSK9, LOX-1, and cellular senescence markers (p53, p21, p16), suggesting that its effects may involve lipid regulation and anti-senescence effects.

In summary, current evidence indicates that senescence-associated molecules are associated with increased macrophage uptake of oxidized lipids through pathways such as upregulating scavenger receptors. Conversely, herbal medicine compounds show promise in potentially intervening against this aberrant phagocytic clearance, possibly through either inhibiting senescence signaling pathways or directly blocking oxLDL uptake and its upstream regulation, and may thus offer a potential strategy to reduce plaque lipid burden and attenuate disease progression.

Mitochondrial and Lysosomal Dyshomeostasis

Secondary impairment of lysosomal acidification is associated with suppressed hydrolysis of cholesteryl esters (CE). This, in turn, correlates with exacerbated lysosomal swelling and lipid engorgement, thereby which may impair the macrophage's ability to effectively clear and turnover lipids. Furthermore, the oxidation of accumulated LDL within lysosomes has been associated with lysosomal dysfunction and may simultaneously contribute to macrophage senescence (a senescent phenotype) and enhance the secretion of pro-inflammatory factors.¹⁵ Oxidized lipid burden and inflammatory stimuli lead to a sustained elevation of mitochondrial oxidative stress (mtROS). In vivo studies have demonstrated that mtROS in macrophages contributes to AS and amplify the NF-κB-related inflammatory response.¹⁶ Furthermore, lysosomal damage and cholesterol crystals have been shown to be associated with NLRP3 inflammasome activation and may promote IL-1β maturation and release through mechanisms such as phagolysosomal rupture and cathepsin leakage, potentially contributing to an amplification loop. Conversely, insufficient cholesterol efflux—for instance, due to impaired ABCA1/ABCG1-mediated transport—correlates with accelerated foam cell accumulation and may contribute to plaque progression.¹⁷ Consequently, lysosomal lipid overload and mtROS may contribute to plaque inflammation and progression, potentially through mechanisms involving macrophage senescence, amplifying the inflammasome response, and promoting foam cell formation. Regarding pharmacological intervention, Wen et al¹⁸ experimentally confirmed that Tan IIA treatment was associated with reduced the activation of the NLRP3 inflammasome both in an in vivo atherosclerotic model (high-fat diet-fed ApoE^{-/-} mice) and in vitro under ox-LDL-induced conditions. The observed effects were accompanied by reduced NF-κB signaling pathway, downregulates the expression of IL-1β and NLRP3, and reduces the expression of ox-LDL receptors LOX-1 and CD36. Consequently, it was associated with attenuated internalization of ox-LDL, thereby which may mitigate subsequent damage. Li et al¹⁹ demonstrated that quercetin was associated with changes in the expression of reverse cholesterol transport-related proteins, such as ABCA1 and ABCG1, in an ox-LDL-induced RAW264.7 foam cell/injury model. Furthermore, quercetin was associated with reduced cellular senescence markers, as evidenced by β-galactosidase staining. These effects suggesting a potential role in mitigating the vicious cycle triggered by mitochondrial and lysosomal overload.

In summary, current evidence indicates that impaired lysosomal acidification in macrophages is associated with suppressed hydrolysis of CE, which may correlate with lysosomal swelling and lipid accumulation, potentially compromising the cell's lipid-clearance capacity. Concurrently, oxidized lipids accumulated within lysosomes have been linked to sustained mtROS and may act synergistically with other damage-associated signals. Furthermore, impaired cholesterol efflux has been associated with accelerated foam cell formation and plaque progression. Natural compound monomers derived from traditional herbal medicine may target the dysregulated lysosomal-mitochondrial axis and its downstream inflammatory and senescent pathways, thereby potentially offering a therapeutic strategy to attenuate the progression of AS.

Fibrous Cap Degradation

Under conditions of sustained lipid stress and a pro-oxidant inflammatory microenvironment, macrophages within atherosclerotic plaques exhibit an increased tendency toward accumulation of a senescent phenotype and develop a senescence-associated secretory phenotype (SASP), characterized by the hypersecretion of pro-inflammatory cytokines and tissue-remodeling proteases.²⁰ Previous studies have demonstrated that macrophages carrying senescence markers can emerge in atherosclerotic lesions as early as the initial stage and are associated with local amplification of inflammation. In advanced lesions, these senescent cells enhance the secretion of matrix-degrading proteases, such as various MMPs, thereby promoting the destruction of elastic fibers and the extracellular matrix (ECM). This process consequently which may contribute to structural weakening and thinning of the fibrous cap and may ultimately contribute to the transition of plaques toward an unstable phenotype and increasing the risk of rupture.^{10,11,21} Correspondingly, clearance or inhibition of the senescent cell burden within plaques has been associated with restoration of the number of repair-associated smooth muscle cells and the composition of matrix components in the fibrous cap, which may improve stability indicators such as cap thickness.²² In the ApoE^{-/-} model, Wang et al²³ assessed plaque stability and reported an increase in collagen content accompanied by a reduction in MMP-9 positive area. In macrophage models, these changes were accompanied by a decrease in SA- β -gal-positive cells and downregulated expression of senescence-associated genes such as p16 and p21, suggesting that the intervention may improve plaque stability by attenuating macrophage senescence burden and modulating the inflammation-protease axis. Additionally, Zheng et al²⁴ demonstrated that berberine was associated with suppression of SASP-associated proteins potentially through promoting the ubiquitination and degradation of relevant complexes via the RXR α /PPAR γ /NEDD4 pathway, and observed morphological improvements in atherosclerotic plaques in atherosclerotic plaques in ApoE^{-/-} mice.

In summary, sustained lipid stress and a pro-oxidant inflammatory microenvironment are associated with the acquisition of a senescent phenotype by plaque macrophages and the development of a SASP. During early stages, SASP has been linked to amplification of local inflammation, while in advanced lesions, it may be associated with upregulation of matrix-degrading enzymes such as MMPs, potentially contributing to elastic fiber and ECM disruption, fibrous cap thinning, and increased plaque vulnerability and rupture risk. Extracts derived from TCM hold significant therapeutic potential for atherosclerotic plaque stabilization possibly by targeting the macrophage senescence-inflammation-protease axis.

Efferocytosis

Under physiological conditions, macrophage efferocytosis in atherosclerotic plaques proceeds through a regulated program of recognition, phagocytosis, degradation, and immune reprogramming.²⁵ Impairment of this process, however, can lead to accumulation of apoptotic cells, their progression to secondary necrosis, and subsequent necrotic core enlargement, which may ultimately contribute to plaque destabilization by degrading the fibrous cap.²⁶ Hence, strategies aimed at rescuing efferocytic capacity and fostering inflammation resolution may represent a pivotal direction for stabilizing vulnerable plaques.

During the initiation of senescence, macrophages exhibit a hallmark alteration in the surface expression and activity of TAM family receptors, particularly MerTK and AXL.^{27,28} Wang et al²⁹ reported that in LDLR^{-/-} atherosclerotic mice, the impaired efferocytic signaling was associated with restoration of TIIA administration. This restoration was associated with concurrent upregulation in the expression of TAM receptors (TYRO3, MERTK, and AXL), suggesting a potential mechanism through which TIIA may promote efferocytosis to clear lipids and ameliorate AS. Shen et al³⁰ demonstrated that berberine (BBR) is associated with modulation of the PPAR γ /LXR α signaling pathway, enhancing cholesterol efflux, modulating macrophage polarization, suppressing the production of pro-inflammatory cytokines, and promoting the release of pro-resolving mediators, and may thus exhibit anti-atherosclerotic activity.

During the phagocytic and degradative phase, impaired efficiency in senescence has been linked to dysfunctions in cytoskeletal reorganization and diminished lysosomal acidification and degradative capacity. These processes are critically dependent on sufficient ATP supply, in which SLC2A1 (glucose transporter 1)-mediated reprogramming of glucose metabolism is considered a rate-limiting step for ATP generation.^{31,32} The acidic intraluminal environment of

lysosomes is not passively established but is actively generated and maintained by the V-type ATPase (V-ATPase), a multisubunit transmembrane protein complex. This proton pump utilizes energy derived from ATP hydrolysis to transport protons (H^+) from the cytosol into the lysosomal lumen against their concentration gradient, thereby establishing and sustaining the low pH required for optimal lysosomal function.¹⁵ Li et al³³ demonstrated, through both in vivo and in vitro experiments, that total saponins of *Panax notoginseng* (PNS) AS the underlying mechanisms involve the suppression of HIF-1 α expression, which was accompanied by downregulation of key glycolytic regulators (PFKFB3, GLUT1, HK2) and subsequent inhibition of glycolysis. Concurrently, PNS was associated with increased expression of MRC1 and iNOS potentially contributing to restrained M1 macrophage polarization and upregulation of sphingosine-1-phosphate (S1P) which may modulate sphingolipid metabolism, thereby potentially contributing to the alleviation of AS.

Phase of Immune Reprogramming

When the microenvironment of M1 macrophages shifts from being dominated by mediators such as IFN- γ and LPS to one rich in IL-4, IL-13, immune complexes, or apoptotic cells, signaling pathways including STAT6 and PI3K/Akt become activated. This activation is associated with suppression of pro-inflammatory pathways such as NF- κ B and subsequent expression of genes associated with the M2 polarization program.³⁴ Conversely, when M2 macrophages within atherosclerotic plaques are exposed to stimuli such as IFN- γ , TLR ligands, or GM-CSF, they undergo repolarization characterized by the reactivation of the STAT1, NF- κ B, and MAPK signaling pathways which correlates with upregulation of iNOS, MHC-II, and pro-inflammatory cytokines.^{35,36} The maintenance of macrophage immunophenotype following reprogramming is precisely governed by a multi-tiered epigenetic regulatory network. Central to this regulation are dynamic histone modifications. Loci of M1-related genes are predominantly characterized by the presence of activating histone marks like H3K4me3 and H3K27ac, in contrast to M2-related genes, which frequently harbor repressive marks such as H3K27me3.³⁷ Concurrently, a hypomethylation state at the promoters of specific genes is closely associated with their transcriptional activation and the maintenance of the resulting phenotype. Furthermore, non-coding RNAs (such as the pro-M1 miR-155, and the pro-M2 miR-124 and miR-223) are thought to consolidate the reprogrammed cellular state by targeting and suppressing key signaling molecules involved in the opposite polarization direction. Zhang et al³⁸ demonstrated both in vitro and in vivo that ginsenoside Rb1 was associated with promotion macrophage polarization towards the M2 phenotype accompanied by enhanced secretion of IL-4 and IL-13 and activating STAT6 phosphorylation. This M2 polarization was subsequently associated with enhanced atherosclerotic plaque stability, as evidenced by an increase in M2 macrophages and a decrease in MMP-9 expression. Using an ApoE^{-/-} mouse model of high-fat diet-induced AS, Chen³⁹ demonstrated a significant upregulation of miR-375 among inflammation-related miRNAs compared to wild-type and TNA-treated groups. Investigations in plaque-derived macrophages and an ox-LDL-induced in vitro model further indicated alterations in autophagic pathway proteins and macrophage phenotype, suggesting Krüppel-like factor 4 (KLF4) as a potential key target of miR-375 in mediating macrophage polarization. Collectively, their findings suggest that TNA may suppress AS progression through modulation of miR-375, which is associated with upregulation of KLF4, enhances autophagic flux, and promotes a pro-repair M2 macrophage polarization.

Conclusion and Perspective

In summary, bioactive components derived from TCM exert pleiotropic effects associated with modulation of senescence in AS through multi-target and multi-pathway mechanisms, offering novel insights and potential avenues for the development of therapeutic agents against AS. Emerging evidence suggests that immunosenescence within plaques may represent an active, prematurely triggered state—influenced by a synergistic pathological milieu of oxidized lipids, mtROS, and lysosomal compromise, and potentially perpetuated in a self-reinforcing manner. At the core of this process, macrophage senescence, mediated through multiple coupled pathways, is associated with the evolution of lesions from a lipid-centric phase toward a state marked by profound inflammatory imbalance and structural instability. Senescence-associated signals such as p16 and p21 can upregulate scavenger receptors including CD36 and LOX-1 and impair cholesterol efflux, which may render macrophages within plaques more prone to lipid overload.^{40,41} Impaired lysosomal

acidification is associated with suppressed cholesteryl ester hydrolysis and swelling of both lipid droplets and lysosomes. Compounded by membrane damage induced by intralysosomal LDL oxidation and cholesterol crystallization which can trigger cathepsin leakage and NLRP3 inflammasome activation this cascade may further amplify inflammatory axes such as IL-1 β . Ultimately, it may form a cross-organelle inflammatory amplification loop with the mitochondrial ROS/NF- κ B pathway.⁴² The SASP of senescent macrophages is associated with sustained upregulation of proteolytic enzymes, such as MMPs, which mediate the degradation of fibrous cap collagen, elastin fibers, and the ECM. This cascade may culminate in plaque destabilization, thereby potentially providing a mechanistic explanation for why the “inflammation-protease axis”, rather than lipid burden alone, may better account for the vulnerable plaque phenotype observed in advanced AS.^{43,44} Furthermore, senescence has been associated with impaired efferocytosis—potentially via attenuated TAM receptor signaling (eg., MerTK/AXL), insufficient cytoskeletal remodeling, and reduced lysosomal acidification and degradation capacity linked to limited ATP supply, which may promote secondary necrosis and necrotic core expansion, events that could collectively exacerbate plaque destabilization and increase the risk of rupture.^{45–47} Thus, the functional uncoupling of the “mitochondria-lysosome senescence axis” likely represents a critical hub that may drive macrophages from metabolic stress into a senescence lock-in state. It not only underlie an interconnected cascade involving lipid overload, inflammasome activation, SASP secretion, fibrous cap degradation, and failed apoptotic cell clearance but also provide a more mechanistically grounded intervention point for targeting advanced complications.⁴⁸

The multitarget, multipathway pharmacology of TCM and its bioactive monomers aligns closely with the networked pathology embodied by the mitochondria-lysosome senescence axis. This review synthesizes available evidence indicating that distinct monomers may contribute to senescent macrophage reprogramming through several interrelated mechanisms, including: (1) attenuation of senescence signaling nodes such as p38 MAPK and p16^{INK4a}; (2) limitation of CD36/LOX-1-dependent oxLDL uptake; (3) enhancement of ABCA1/ABCG1-mediated cholesterol efflux; (4) suppression of the NF- κ B/NLRP3 inflammatory circuitry; (5) promotion of TAM receptor expression and the production of pro-resolving mediators; and (6) restoration of glycolysis-ATP coupling to sustain V-ATPase-dependent lysosomal acidification. Collectively, these coordinated actions may help mitigate the homeostatic entrenchment of senescent macrophages, potentially contributing to reduced lipid burden, attenuated inflammatory amplification, and improved plaque stability. Nevertheless, the current body of evidence is dominated by associative observations and phenotypic improvements, with a relative paucity of causal, mechanistic validation.

Future studies should aim to establish more stringent causal evidence at the level of inter-organelle crosstalk. (1) A priority will be genetically and pharmacologically stratified interventions along a mitochondria ROS-lysosomal acidification-inflammasome axis, aiming to enabling stepwise dissection of hierarchy and directionality within this pathway. (2) These efforts should ideally be integrated with single-cell and spatial omics to characterize intraplaque senescent macrophage subpopulations and to map state-transition trajectories that accompany disease progression or therapeutic perturbation. (3) In vivo lineage tracing integrated with functional readouts—such as efferocytosis capacity and fibrous-cap biomechanical metrics—would be valuable for determining whether “senescence reprogramming” translates into bona fide, clinically meaningful gains in plaque stabilization.

Although this review systematically summarizes the potential mechanisms by which phytochemical monomers derived from traditional Chinese medicine modulate atherosclerotic plaque stability through the macrophage mitochondrial-lysosomal senescence axis, it is important to acknowledge several limitations inherent to the current research landscape and the literature upon which this review is based. These limitations also delineate critical directions for future fundamental and translational research.

① The preponderance of associative evidence and insufficient causal validation. The majority of current studies have focused on observing changes in senescence markers (eg., p16/p21 expression) or improvements in plaque phenotype. There is a notable lack of direct causal evidence established through approaches such as genetic manipulation (eg., macrophage-specific gene knockout), organelle-targeted interventions, or functional flux assays (eg., dynamic monitoring of lysosomal pH, quantification of mitophagy flux). Consequently, the proposed regulatory network centered on the “senescence axis” necessitates more rigorous mechanistic dissection and validation.

② Multiple pharmacokinetic and safety barriers to clinical translation. The phytochemical monomers reviewed herein, such as quercetin, tanshinone IIA, and berberine, commonly exhibit challenges including low oral bioavailability,

rapid in vivo metabolism, and unclear tissue distribution. Currently, data regarding their achievable plasma concentrations in humans, effective exposure doses, and long-term safety profiles remain scarce. Furthermore, systematic investigations into their potential pharmacokinetic interactions and pharmacodynamic synergistic or antagonistic effects with standard cardiovascular therapies, such as statins or PCSK9 inhibitors, are lacking. Future research should prioritize the integration of advanced drug delivery systems (eg., nanoformulations, phospholipid complexes) and the conduct of rigorous pharmacokinetic/pharmacodynamic (PK/PD) modeling studies in preclinical models to rigorously assess their translational potential.

③ The necessity to contextualize single-organelle targeting within the broader framework of organelle crosstalk. Mitochondrial and lysosomal dysfunction do not occur in isolation; they are engaged in complex reciprocal regulation with other cellular processes, including endoplasmic reticulum stress, Golgi apparatus dysfunction, and peroxisomal metabolic dysregulation. Therefore, future investigations should expand from a “single-organelle” perspective to a “multi-organelle network” viewpoint, exploring whether these monomers exert their protective effects by reshaping inter-organelle communication.

Overall, integrating the regulatory effects of Chinese medicine monomers on organelle homeostasis and immunosenescence into the conceptual framework of the “mitochondria-lysosome senescence axis” not only facilitates a deeper elucidation of the mechanistic underpinnings and target networks underlying their anti-atherosclerotic effects but also provides a clear and testable theoretical roadmap for developing innovative interventional strategies aimed at mitigating advanced plaque vulnerability.

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Disclosure

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