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•Review•

Natural products: potential therapeutic agents for atherosclerosis

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[ABSTRACT] Atherosclerosis (AS) is an invisible killer among cardiovascular diseases (CVD), which has seriously threatened the life of quality. The complex pathogenesis of AS involves multiple interrelated events and cell types, such as macrophages, endothelial cells, vascular smooth muscle cells and immune cells. Currently, the efficacy of recommended statin treatment is not satisfactory. Natural products (NPs) have attracted increasing attention with regard to their broad structural diversity and biodiversity, which makes them a promising library in the demand for lead compounds with cardiovascular protective bio-activity. NPs can preclude the development of AS by regulating lipid metabolism, ameliorating inflammation, stabilizing plaques, and remodeling the gut microbiota, which lays a foundation for the application of NPs in clinical therapeutics.

[KEY WORDS] Atherosclerosis; Cardiovascular diseases; Pathogenesis; Target; Natural products
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Introduction

Cardiovascular diseases (CVD) is one of the biggest contributors to the burden of chronic diseases, and has replaced infectious diseases as the leading killer around the world [1]. Data from the *Report on Cardiovascular Health and Disease in China 2019* indicated that 330 million Chinese peoople suffered from CVD with a continuously rising prevalence. Moreover, CVD remained the leading cause of death in 2017, surpassing oncology and other diseases. Atherosclerosis (AS), a chronic inflammatory, immune [2] and epigenetic [3] disease manifested by excessive deposition of low-density lipoprotein (LDL), is a pivotal culprit of ischemic stroke, myocardial infarction and other life-threatening acute cardiovascular events [4]. The development of AS involves multiple events, including oxidation of LDL (ox-LDL), formation of foam cells, migration of vascular smooth muscle cells, activated immune responses, plaque rupture as well as thrombosis. The progress of early AS oftern goes unnoticed. However, once a plaque ruptures and enters the bloodstream, it becomes a time bomb that may threaten life at any time. Although many theoretical studies have been conducted to explain the pathogenesis of AS, such as the classical lipid storage hypothesis [5], the inflammatory hypothesis [6-8] and the emerging bone-vascular axis hypothesis [9], the autoimmune hypothesis [5], and even the human papillomavirus (HPV) infection hypothesis [10], the pathological mechanisms of AS are not completely understood. Currently, statins are recommended as the first-line therapy, supplemented with vasodilators and anticoagulants, both of which however do not exert direct inhibitory effect on the development of atherosclerotic plaques. It should be noted that increasing attention has been drawn on the therapeutic targets of AS [11-14], which lays a foundation for drug exploration based on new mechanisms.

Traditional Chinese medicine is a comprehensive medical system where patients are treated with natural plants, anmials and mineral remedies. In recent decades, due to the increased interests in natural products (NPs), more and more natural compounds have been demonstrated to exhibit anti-AS and other potential cardiovascular activities. Nevertheless, elucidation of the mechanisms of action has just started, based on cellular models for screening anti-atherogenic NP [15]. Potential active NPs against AS have been discussed in terms of modulating foam cell formation [16] and lowering ox-LDL [17, 18]. In the current review, we summarized the key events and potential targets in the pathogenesis of AS, and systematically discussed promising drug candidates from dif-

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ferent aspects related to disease progression.

Pathogenesis of Atherogenic and Potential Therapeutic Targets

AS is a chronic inflammation and epigenetic disease mediated by excessive LDL, monocyte-derived macrophages, arterial wall endothelial cells and immune cells [19]. It may eventually result in the formation and deterioration of plaques, which then protrudes toward the ruptured blood vessel, enters into the bloodstream and finally generates a thrombus [20]. Some risk factors, such as obesity, smoking, hypertension, and diabetes, accelerate AS driven by LDL, though the undelying mechnisms remains elusive [21]. In addition, the molecular mechanism and pathogenesis of plaque formation in the later stage of disease development are not fully understood. However, every event involved in disease progression, comprising excessive accumulation and oxidation of LDL, foam cell formation, activation of inflammatory response, and plaque rupture caused by endothelial cell damage, can provide potential targets for the treatment of AS.

Accumulation of ox-LDL

Oxidative modification of LDL is a crucial factor in the etiology of AS. Many enzymatic systems mediate the production of reactive oxygen species (ROS), including nicotinamide adenine dinucleotide phosphate oxidase (NOX), lipoxygenase (LO), myeloperoxidase (MPO), monooxygenase, cyclooxygenase and xanthine oxidase. The NOX system is the main source of ROS in the vessel wall and endothelial cells [22]. Inhibition of NOX activity by S17834, a benzo(b)pyran-4-one derivative, significantly relieved aortic atherosclerotic lesions [23]. Additionally, LO is closely related to the synthesis of ox-LDL and studies have verified that disruption of the 12/15–LO gene diminishes AS in ApoE$^{-/-}$ mice [24, 25]. MPO is an abundant heme protein secreted from activated phagocytes and has been reported to play a pivotal role in LDL oxidation during AS [26]. It is also believed that MPO contributes to endothelial dysfunction, thereby acting as a potential multifunctional target [27].

Cholesterol uptake and efflux

The maintenance of cholesterol homeostasis in macrophages is essential to prevent the formation of foam cells, which constitutes the predominant source of plaque development, so as to stimulate the generation of fatty streaks and atherosclerotic plaques. Both excessive uptake and obstruction of the elimination process are unfavorable [28]. Scavenger receptors (SRs) on the surface of macrophages mediate the influx of cholesterol in the form of ox-LDL. Nitro-oleic acid (NO_2-OA) specifically interacts with CD36, a high-affinity SR, competitively restricts the uptake of ox-LDL and reverses cholesterol deposition in cells [29]. Except for CD36, SR-A (CD204) and lectin-like ox-LDL receptor-1 (LOX-1) are the other two primary SRs. However, SR-A may act as a double-edged sword. Studies have shown that inhibition of ox-LDL uptake by macrophages through the LOX-1-NF-κB (nuclear factor-kappa B) pathway mitigates AS in ApoE$^{-/-}$ mice [30]. Both free high-density lipoprotein (HDL) in plasma and ATP binding cassette transporter A1 (ABCA1) on the surface of macrophages are vital carriers to facilitate cholesterol reverse transport [31]. The ApoA-I mimetic peptide synthesized by GOU *et al.* has been demonstrated to inhibit AS through promoting the physiological function of HDL [32]. Protein arginine methyltransferase 2 (PRMT2) has been proved to mediate cholesterol efflux through up-regulating ABCA1 expression, thereby inhibiting foam cell formation [33].

Endothelial cell injury

Endothelial injury and dysfunction are considered as the basis and initial steps for AS [4]. Nitric oxide (NO) from endothelial cells exhibt anti-AS effects through dilating the blood vessels, inhibiting platelet adhesion and aggregation and suppressing the proliferation of smooth muscle cells [34]. Therefore, NO synthase disorder will inevitably lead to endothelial cell dysfunction. Endothelial nitric oxide synthase (eNOS) is the most critical subtype enzyme in the process of NO synthesis [35]. It should be noted that the mainstream drug statins also mechanically activate eNOS through phosphatidylinositol-3-kinase (PI3K)/protein kinase B (PKB/Akt) signals [36]. Once endothelial cell apoptosis occurs under the pathological conditions, the function of endothelial cells as a physical barrier to the blood vessel wall will be destroyed [37]. The progression of AS can be restricted by targeting classic apoptosis targets, such as signal transducer and activator of transcription 3 (STAT3) [38-40] and NF-κB [41, 42]. Many other targets in the process of ox-LDL-induced endothelial cell damage have also been elucidated [43-45].

Inflammation and immunity

AS is defined as a chronic inflammatory disease with an autoimmune property [2]. The expression of vascular endothelial cell adhesion molecules, chemokines and cytokines promotes the infiltration of inflammatory cells in the arterial wall [46]. The NOD-like receptor protein 3 (NLRP3) inflammasome, consisting of multiple proteins, is a cell sensor of innate immunity. This complex plays a key role in inflammation activation by secreting IL-1β and IL-18 *via* the caspase-1 dependent pathway [47, 48]. Inhibiting the activation of NLRP3 inflammasome with MCC950 can reduce the development of atherosclerotic lesion in ApoE$^{-/-}$ mice. Pre-clinical studies emphasized that neutralization of IL-1β and IL-18 brought out notable regression of AS [49]. Moreover, blockade of tumor necrosis factor (TNF) comes out to be a valid approach in inhibiting the expression of various inflammatory factors, showing the potential to treat AS [50]. Ox-LDL deposited in atherosclerotic lesions can be recognized by Toll-like receptor 4 (TLR4) and CD36 receptors, followed by induction of the transcription of inflammatory cytokines such as IL-12 and IL-23. $CD4^+$, $CD8^+$ and natural killer T (NKT) cells participate in related inflammation and immune processes through a series of signal transduction cascades [51-53]. Administration of immune checkpoint inhibitors encompassing anti-CTLA-4 and anti-PD-1 antibodies is able to exacerbate T cell-mediated plaque inflammation [54]. On the contrary, stimulation of regulatory T cells can alleviate AS, which was achieved by low-dose IL-2 treatment [55].

Plaque stabilization

Plaque rupture is an immediate flashpoint for the formation of blood clots, blockage of blood vessels, and the ultimate occurrence of acute cardiovascular events. Plaque lipids and tissue factors are exposed to blood components, and initiates the coagulation cascade, before platelet adhesion and thrombosis [20]. Autophagy is extensively involved in the maintenance of plaque homeostasis, which is currently considered to be at least partly beneficial [56]. AMPK inhibits mTORC1 and stimulates ULK1 during glucose deficiency, thus inducing autophagy and slowing down the malignant development of plaques [57]. Autophagy is also a double-edged sword as excessive autophagic death of smooth muscle cells may in turn promote the development of plaques [56]. Additionally, up-regulation of PCSK6 has been probed to elicit extracellular matrix remodeling by enhancing the activity of matrix metalloproteinases (MMPs), eventually leading to plaque instability and rupture [58].

Potential NPs for AS treatment

As the clinical effect of AS is limited by mainstream therapy, we summarized the natural components with potent anti-AS bioactivity. Due to the potential for developing new anti-AS therapies through harnessing natural constituents, we categorize them in four groups based on their mechanisms of action (Table 1). Events associated with AS and related po-

Table 1 Protective effect of individual natural compounds against AS

Biological function toward AS	No.	Compounds	Results	Ref
Regulating lipid metabolism	(**1**)	Vitamin E	Decreasing LDL oxidation 30%−40% in subjects only for five months	[60]
	(**2**)	Vitamin C	Vitamin C intake alleviates the degree of experimental AS induced by periodontitis in rats	[67]
	(**3**)	Quercetin	Quercetin alleviates systemic OS, and reduces plaque area *in vivo*; inhibits ox-LDL induced ROS formation *in vitro*	[68]
	(**4**)	Resveratrol	Anti-inflammation, anti-oxidation, relieving endothelial dysfunction, and remodeling lipid metabolism	[119]
	(**5**)	Epigallocatechin gallate	Reduction of plasma lipid peroxides	[71]
	(**6**)	Fraxetin	Fraxetin induces antioxidant enzymes through Nrf2/ARE activation	[72]
	(**7**)	Neferine	Inhibition of Cu^{2+}-mediated LDL oxidation in mouse peritoneal macrophages	[73]
	(**8**)	Ginkgetin	Ginkgetin attenuates lipid deposition in the aorta of atherosclerotic rats	[74]
	(**9**)	Allicin	Allicin exhibits cholesterol-lowering property in male ICR mice	[75]
	(**10**)	Icariin	Icariin-treatment lowers serum LDL-C levels to 24%	[76]
	(**11**)	Xanthohumol	Reduction of accumulated cholesterol in the aortic arch and up-regulation of HDL-C	[77]
	(**12**)	Guggulsterone	Reduction of total serum lipid and total serum cholesterol	[78]
	(**13**)	Phytanic acid	Induction of hypolipidemia	[79]
	(**14**)	Aegeline 2	Reduction of plasma triglyceride (Tg) levels by 55%, and total cholesterol (TC) by 24%	[80]
	(**15**)	Tanshinone IIA	Inhibition of the mRNA expression of CD36 SR-A and PPARγ in the aorta	[82]
	(**16**)	Chrysin	Chrysin increases the mRNA levels of PPARγ, LXRα, ABCA1 and ABCG1	[84]
	(**17**)	Asperlin	Asperlin inhibits LPS but not ox-LDL-evoked foam cell formation and promotes cholesterol efflux	[85]
	(**18**)	Ginsenoside Compound K	Up-regulation of ABCA1 and ABCG1 expression in macrophages	[86]
	(**19**)	Rutaecarpine	Induction of ABCA1 and SR-BI expression in the liver of $ApoE^{-/-}$ mice	[87]
	(**20**)	Alpinetin	Alpinetin elevates the mRNA levels of PPARγ, LXRα, ABCA1 and ABCG1	[88]
	(**21**)	Baicalin	Stimulation of the PPARγ-LXRα-ABCA1/ABCG1 pathway	[89]
	(**22**)	Lycopene	Stimulation of PPARγ, LXRα and ABCA1 expression	[90]
	(**23**)	1,2,3,4,6-Penta-*O*-galloyl-β-D-glucose	Induction the expression of SR-BI and ABCA1 in J774 and THP-1 macrophages	[91]
	(**24**)	6-Dihydroparadol	Enhancement of ABCA1 and ABCG1 protein levels	[92]
	(**25**)	Paeonol	Paeonol up-regulates the protein stability of ABCA1	[93]

Continued

Biological function toward AS	No.	Compounds	Results	Ref
Regulating lipid metabolism	(**26**)	Arctigenin	Arctigenin treatment enhances the expression of ABCA1, ABCG1 and ApoE	[94]
	(**27**)	*α*-Asarone	*α*-Asarone treatment blocks the induction of SR-B1 and promotes the induction of ABCA1 and ABCG1	[95]
	(**28**)	Chlorogenic acid	Elevation of the mRNA levels of PPARc, LXR*α*, ABCA1 and ABCG1	[96]
	(**29**)	Berberine	Inhibition of LOX-1 expression; maintainance of intestinal flora homeostasis	[97,123, 154-156]
	(**30**)	Piperine	Piperine up-regulates the expression of ABCA1	[98]
	(**31**)	Leonurine	Up-regulating the expression of PPAR*γ*, LXR*α*, ABCA1 and ABCG1	[99]
Fighting inflammation	(**32**)	Procyanidin B2	Suppressing the activation of NLRP3; and inhibiting caspase-1 activation and IL-1*β* secretion	[102]
	(**33**)	Apigenin	Apigenin inhibits LPS-induced IL-1*β* production by inhibiting caspase-1 activation through disruption of NLRP3	[103]
	(**34**)	Dihydromyricetin	Inhibition of the NLRP3 inflammasome	[104]
	(**35**)	Hematein	Restriction of ROS generation and NF-*κ*B activation	[108]
	(**36**)	7-Hydroxy frullanoide	Inhibition of LPS-induced cytokine production, and the expression of VCAM1, ICAM1 and E-selectin in TNF-*α*-stimulated HUVECs	[109]
	(**37**)	Ginkgolic acid	Reduction of intracellular ROS and ox-LDL-induced NF-*κ*B	[105]
	(**38**)	Juglanin	Juglanin inhibits the inflammatory response by suppressing the expression of IL-1*β*, MCP-1, and HMGB1	[113]
	(**39**)	Policosanol	Reduction of inflammation markers such as sCD40L, sP-selectin, and IFN-*γ*	[114]
	(**40**)	10-Dehydrogingerdione	Reduction of inflammation markers such as sCD40L, sP-selectin, and IFN-*γ*	[114]
	(**41**)	Shikonin	Inhibition of inflammatory activated $CD4^+$ T cells and proinflammatory macrophages in plaques	[115]
	(**42**)	Kaempferol	Modulation of pro-inflammatory enzyme activities and relative genes	[116]
	(**43**)	Morelloflavone	Potent ROS scavengers	[117]
	(**44**)	Volkensiflavone	Effective ROS scavengers	[117]
	(**45**)	Diosgenin	Anti-inflammation, mitigating endothelial dysfunction and remodeling lipid metabolism	[118]
Stabilizing plaques	(**46**)	Cryptotanshinone	Inhibition of the expression of LOX-1 and MMP-9, ROS generation and NF-*κ*B activation.	[122]
	(**47**)	Ginsenoside F1	Reduction of LOX-1 and TLR4 expression, and MPO distribution	[124]
	(**48**)	Ursolic acid	Anti-inflammation and anti-oxidation; restriction of LOX-1	[125-127]
	(**49**)	Hyperoside	Inhibition of oxLDL-induced LOX-1 expression, ERK activation, and cell proliferation	[128]
	(**50**)	Celastrol	Celastrol suppresses atherosclerotic plaque in $ApoE^{-/-}$ mice through inhibiting LOX-1 and OS	[129]
	(**51**)	Trichosanatine	Inhibition of the activated LOX-1/p38 MAPK pathway; protecting HUVECs against ox-LDL-induced injury	[130]
	(**52**)	Dihydrotanshinone I	Inhibition of LOX-1 mediated by the NOX4/NF-*κ*B signaling pathway both *in vitro* and *in vivo*	[131]
	(**53**)	*N*-methylsecoglaucine	Inhibition of rabbit platelet aggregation and the release of ATP induced by arachidonic acid and collagen	[132]
	(**54**)	Gypenoside	The PI3K/Akt/Bad signaling pathway is activated to modulate the apoptosis-related protein expression in the aorta	[133]
	(**55**)	Acacetin	Acacetin activates Sirt1/Sirt3/AMPK signals to protect the vascular endothelium	[134]
	(**56**)	Myricitrin	Reduction of endothelial cell apoptosis *via* the STAT3 and PI3K/Akt/eNOS signaling pathways; prevention of OS injury	[39,135]
	(**57**)	Luteolin	Down-regulation of apoptosis through inhibiting MMP9 and activating the PI3K/Akt signaling pathway	[136]
	(**58**)	Isorhamnetin	Inhibition of macrophage apoptosis by decreasing ROS levels and lipid deposition	[137]

Continued

Biological function toward AS	No.	Compounds	Results	Ref
Stabilizing plaques	(**59**)	Vitexin	Vitexin increases the expression of p-AMPK and decreases the expression of p-mTOR, thus activating autophagy	[138]
	(**60**)	Lupeol	Activation of macrophage autophagy through increasing LC3-II levels and inhibiting p62	[139]
	(**61**)	Curcumin	Inhibition of apoptosis and induction of autophagy *via* the Akt/mTOR pathway.	[140]
	(**62**)	Betulinic acid	Betulinic acid induces eNOS expression, thus preventing endothelial dysfunction	[142]
	(**63**)	Imperatorin	Anti-lesion role in ox-LDL-stimulated VSMCs by inhibiting the PI3K/Akt/mTOR pathway	[145]
	(**64**)	Securinine	Inhibiting the proliferation and migration of aortic smooth muscle cells in a dose-dependent manner	[146]
	(**65**)	Ginsenoside Rg3	Stronger antiproliferative and antimigratory effects due to stronger PPAR activation	[147]
	(**66**)	Artemisinin	Inhibition of MMP-9 expression and activity by suppressing the PKC delta/ERK/p38 cascade	[148]
	(**67**)	Castanospermine	Potential anti-angiogenesis agents	[149]
	(**68**)	Isoliquiritin		
	(**69**)	Radicicol		
Regulating the gut microbiota	(**70**)	Ferulic acid	Modulation of the ratio of Firmicutes to Bacteroidetes	[157]
	(**71**)	Chitin-glucan	Modulation of Lactobacillus and Alistipes, thus ameliorating endothelial and inflammatory dysfunctions	[158]
	(**72**)	Naringin	Modulation of 7α-dehydroxylase-producing bacteria	[159]
	(**73**)	Anthocyanin	Up-regulation of the proportions of Lactobacillus, Akkermansia, Bifidobacterium and Roseburia	[160]
	(**74**)	Trigonelline	Promising gut microbiota regulators	[161]
	(**75**)	2,3,5,4-Tetrahydroxy-stilbene-2-*O*-β-D-glucoside		[162]
	(**76**)	Ginkgolide B		[163]
	(**77**)	Inulin		[164]
	(**78**)	Mannan oligosaccharides		[165]

tential natural products are showed in Fig. 1.

Regulating lipid metabolism

Serving as the most fundamental inducement, oxidative metabolism and transport of LDL-cholesterol in blood vessels determine the fate of AS. Hypolipidemic statins are still the main approach to treating AS. However, it remains undesirable in severe cases. Natural compounds that regulate lipid metabolism mainly focus on anti-oxidation, lowering blood lipids, and inhibiting macrophages-derived foam cell formation (Fig.2).

Anti-oxidation

According to clinical trials, vitamin E (**1**) exerted certain effect on the reduction of ox-LDL [59, 60]. Ganini and Mason found that α-tocopherol inhibted the production of lipid-radical and protein-derived free-radical caused by Cu^{2+} [61]. Studies of Moser *et al*. suggested that vitamin C (**2**) was involved in the antioxidant process of LDL [62-64]. Better performance can be obtained especially when vitamin C was used in combination with vitamin E (**1**) [65, 66]. An experiment using a rat model of AS caused by periodontitis showed that vitamin C (**2**) alleviated symptoms by decreasing oxidative stress (OS) [67]. Quercetin (**3**) is ubiquitous in our diets and has been proved to protect patients suffering from CVD. Quercetin (**3**) has been reported to suppress the production of ROS through NOX inhibition in the peritoneal macrophages of high-fat diet (HFD) mice [68]. In a male rat model of oxidation damage, quercetin (**3**) up-regulated paraoxonase 1 activity, preventing LDL from oxidative modification [69]. Both resveratrol (**4**) and epigallocatechin gallate (**5**) are potential anti-oxidants with a similar mechanism of action, which have been verified in clinical use [70, 71]. Some compounds that have not been clinically verified such as fraxetin (**6**) and neferine (**7**) also exhibited antioxidant activity in preliminary studies [72, 73].

Lowering blood lipids

Ginkgetin (**8**) has been found to decrease the serum levels of total cholesterol, triglyceride and LDL-cholesterol in atherosclerotic rats [74]. In an experiment exploring the effect of allicin (**9**) on hypercholesterolemia in male ICR mice, decreases in cholesterol, triglyceride and glucose were observed, indicating its potential value in lowering cholesterol [75]. Icariin (**10**), the major bioactive component of *Epimedium brevicornum*, also had similar functions in a rab-

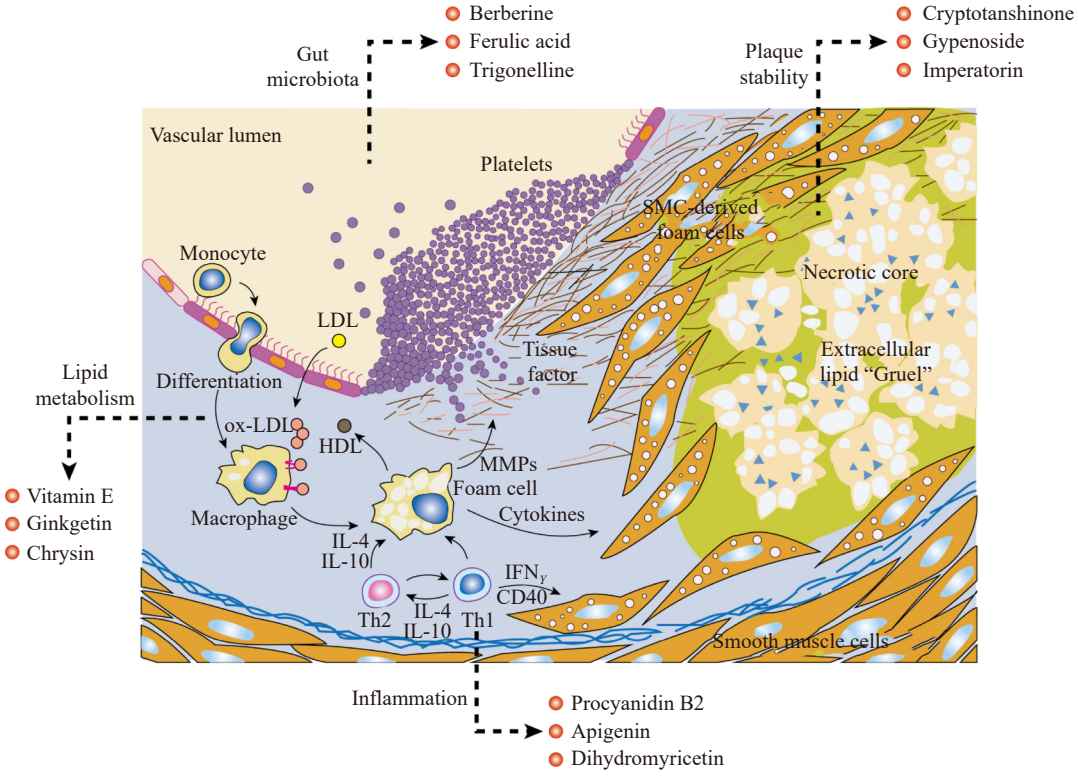


Fig. 1 Events and related potential natural products in AS

bit hyperlipidemia model [76]. Xanthohumol (**11**) has been reported to suppress cholesterol accumulation in lesion areas by HDL-cholesterol metabolism through ApoE enhancement [77]. In addition to those bioactive ingredients mentioned above, more than a dozen of compounds such as guggulsterone (**12**), phytanic acid (**13**) and aegeline 2 (**14**) have been proved in various cell and animal models to be the candidates for lowering blood lipid [78-81].

Modulating lipid metabolism in macrophages

Cholesterol uptake and excretion by macrophages, which is termed foam cell formation, is a pivotal target of drug intervention. SRs located on the surface of macrophages are responsible for the endocytosis of ox-LDL. TANG *et al.* demonstrated that tanshinone IIA (**15**) down-regulated the expression of CD36 in ApoE$^{-/-}$ mice, thus mitigating AS [82]. Interestingly, vitamin E (**1**) was used as a CD36 inhibitor [83]. Chrysin (**16**), asperlin (**17**), ginsenoside compound K (**18**) and rutaecarpine (**19**) treatments mechanically elevated cholesterol efflux mediated by enhanced ACBA-1 activity [84-87]. Alpinetin (**20**), baicalin (**21**) and other alkaloids have been reported to promote cholesterol efflux *via* the PPARα-LXRα-ABCA1 pathway [88, 89]. Lycopene (**22**) as a typical compound of carotenoids, suppressed cholesterol synthesis and efflux at the concentration of 10 μmol·L^{-1} [90]. Phenolic compounds represented by 1,2,3,4,6-penta-*O*-galloyl-β-d-glucose (**23**), 6-dihydroparadol (**24**) and paeonol (**25**) [91-93], phenylpropanoids represented by arctigenin (**26**), α-asarone (**27**), chlorogenic acid (**28**) [94-96] as well as alkaloids represented by berberine (**29**), piperine (**30**) and leonurine (**31**) [97-99] are all active NP targeting proteins associated with foam cell formation involving ABCA1, ABCG1, HMG-CoA and SR-BI .

Fighting inflammation

Procyanidins is a type of polyphenolic compounds that widely exists in red wine and grape seeds [100, 101]. Procyanidin B2 (**32**) is the major natural procyanidin, which has been reported to suppress the activation of NLRP3 inflammasome *via* the activator protein-1 pathway in human umbilical vein endothelial cells (HUVECs), indicating its cardiovascular protective effect [102]. ZHANG *et al.* found that flavonoid apigenin (**33**) impeded the production of IL-1β and other inflammatory cytokines induced by lipopolysaccharide (LPS) in macrophages. Their further research revealed that the assembly of NLRP3 was destroyed [103]. In addition, dihydromyricetin (**34**) has been proved to reverse the activation of the NLRP3 inflammasome in HUVECs after palmitic acid treatment, thereby preventing AS through inhibiting pyroptosis [104]. NF-κB is also an important signal molecule in inflammation [105-107]. The effect of hematein (**35**) in alleviating AS was evaluated using a hyperlipidemia mouse model and results showed that hematein (**35**) reduced inflammatory mediators by interfering NF-κB activation [108]. 7-Hydroxy frullanoide (**36**), an active ingredient in *Sphaeranthus indicus*, together with quercetin (**3**) and ginkgolic acid (**37**), have been reported to display anti-inflammatory activity through inhibiting the NF-κB pathway [105, 109-112]. Asperlin (**17**) [85], juglanin (**38**) [113], policosanol (**39**) as well as 10-dehydrogingerdione (**40**) [114] down-regulated the level of inflammatory factors such as TNF-α and IL-1β. Immune cells play an

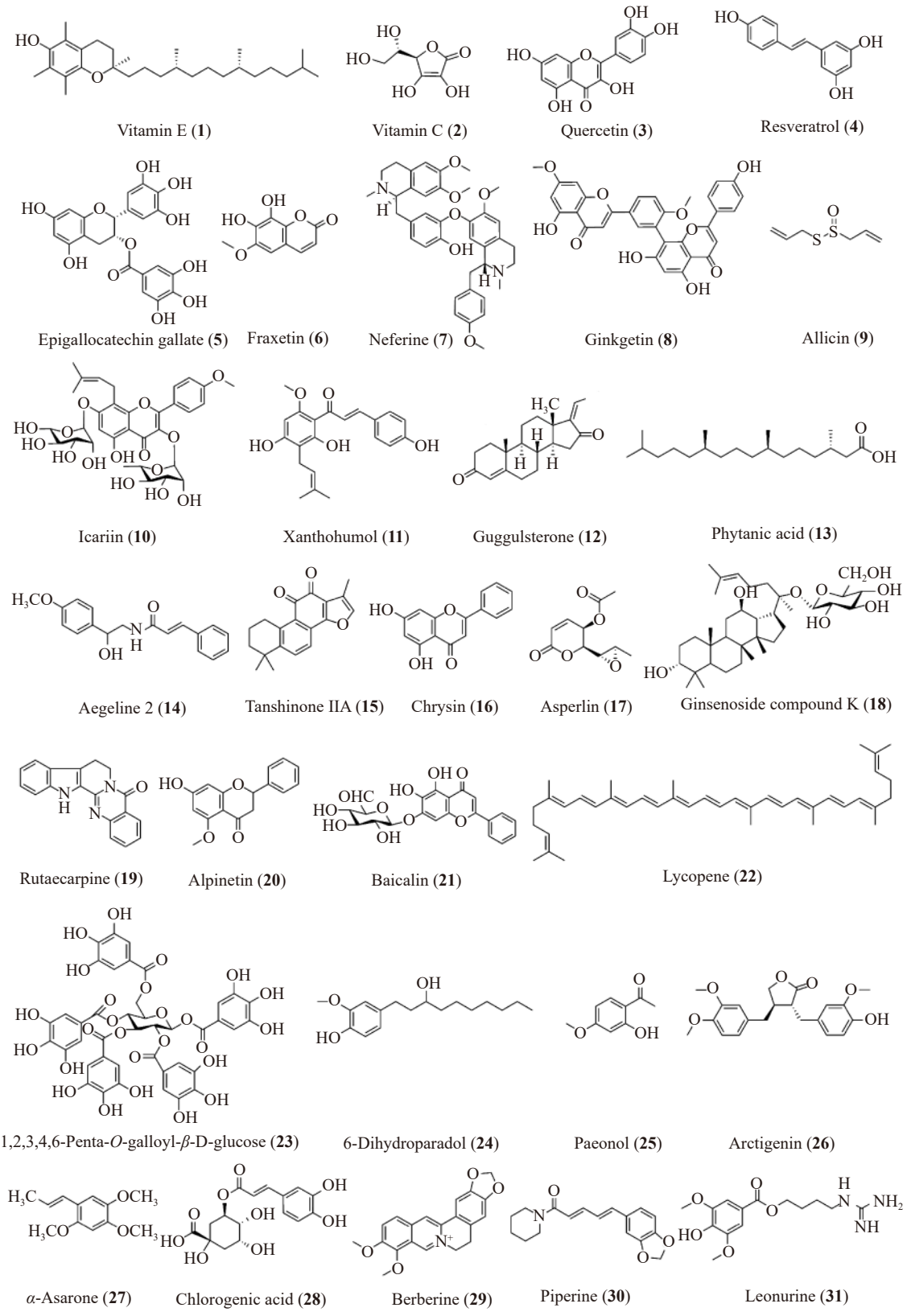


Fig. 2 Natural compounds regulating lipid metabolism against AS

indispensable role in the development of inflammation and are considered to be regulated by shikonin (**41**) [115]. Shikonin (**41**) has been elucidated to repress $CD4^+$ T cell inflammatory activation through inhibiting its essential process of glycolysis and oxidative phosphorylation [115]. Kaempferol (**42**) exerted robust anti-inflammation effects due to multiple mechan-

isms, such as anti-oxidation, modulating pro-inflammatory enzyme activity and relative genes, and reducing adhesion molecule expression [116]. Otherwise, morelloflavone (**43**) and volkensiflavone (**44**) showed atheroprotective effect as ROS scavengers [117]. Both diosgenin (**45**) coupled with resveratrol (**4**), are outstanding natural compounds with huge potential in the treatment of AS, benefiting from multiple functions such as anti-inflammation, relieving endothelial dysfunction, and remodeling lipid metabolism [118, 119]. Nautral constituents displaying anti-inflammatory potential are shown in Fig. 3.

Stabilizing plaques

If foam cell accumulation is the cornerstone of lesion formation, plaque rupture is the last trigger for atherosclerotic deterioration leading to myocardial infarction and stroke, though ischemia caused by end-stage luminal stenosis also represents an underlying factor [120]. NPs that maintain plaque stability by precluding platelet adhesion, inducing macrophage and endothelial cell autophagy rather than apoptosis, counteracting angiogenesis and other ways will display broad cardiovascular benefits in the long term.

Precluding platelet aggregation

LOX-1 is the main receptor in endothelial cells responsible for ox-LDL recognition and internalization [121]. The activation of LOX-1 mediated endothelial dysfunction, leukocyte adhesion, smooth muscle cell proliferation and migration, foam cell formation as well as platelet activation, which constitute the essential events resulting in atherosclerotic plaque rupture [20]. Cryptotanshinone (**46**) is a dominant diterpenoid with bioactivity extracted from *Salvia miltiorrhiza*. One study in ApoE$^{-/-}$ mice pointed out that cryptotanshinone (**46**) significantly down-regulated LOX-1 and MMP-9 expression and inhibited ROS generation, thereby maintaining the stability of plaques [122]. Another study in human macrophage-derived foam cells verified that berberine (**29**) suppressed the elevated expression of LOX-1 caused by ox-LDL in a dose and time-dependent manner [123]. QIN *et al.* investigated that ginsenoside F1 (**47**) attenuated LOX-1 levels and improved endothelial cell viability damaged by ox-

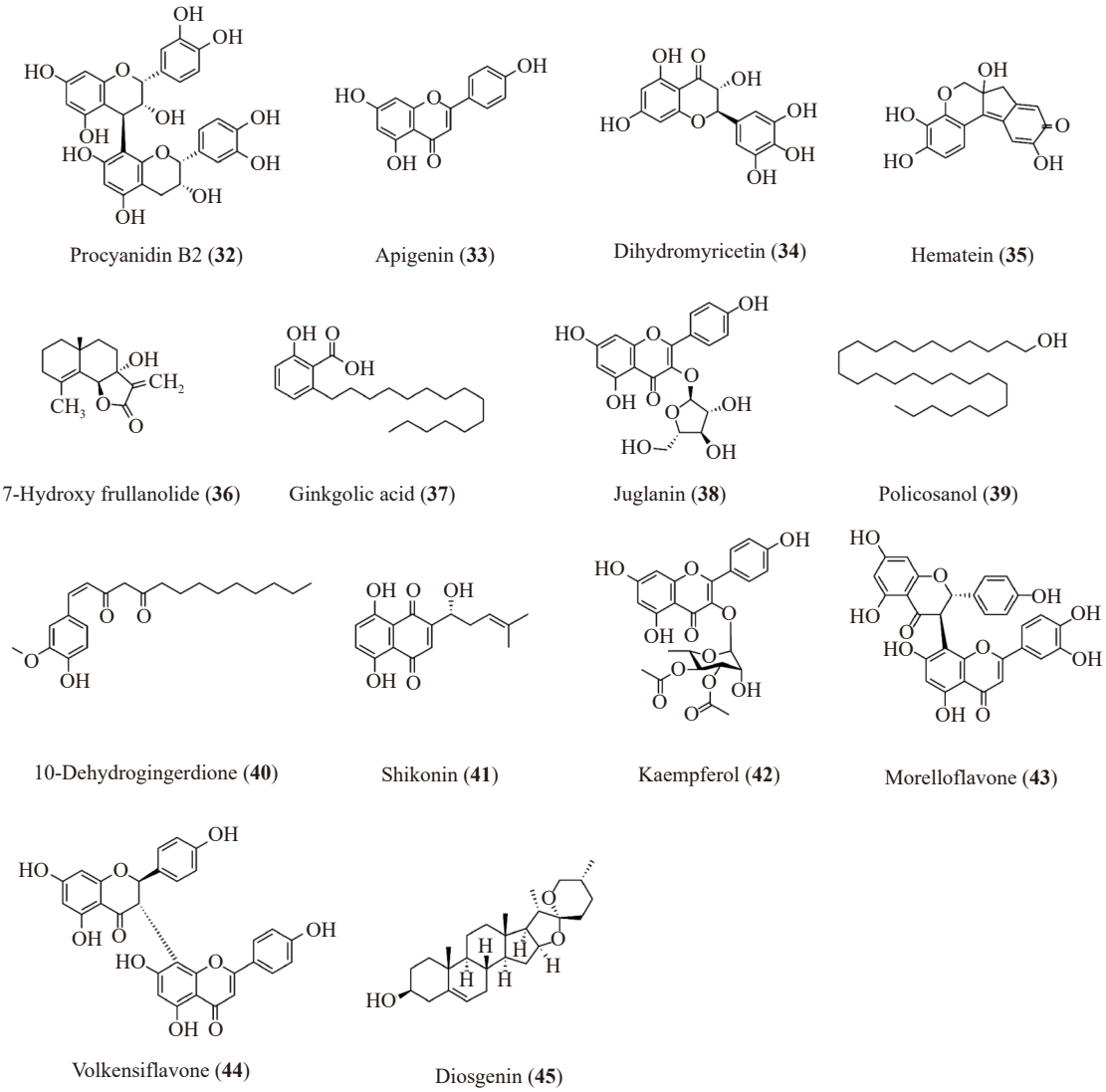


Fig. 3 Natural compounds fighting inflammation in AS

LDL [124]. Ursolic acid (**48**) belonging to the class of phytonutrient has been addressed to play a crucial role in anti-inflammation and anti-oxidation [125, 126]. Ursolic acid (**48**) (100 $mg \cdot kg^{-1} \cdot d^{-1}$) markedly lessened necrotic core sizes dominantly through restricting the role of LOX-1 [127]. An additional study utilizing vascular smooth muscle cells showed that hyperoside (**49**) hampered ox-LDL-induced LOX-1 expression [128]. Compounds with a similar mechanism of action include celastrol (**50**), trichosanatine (**51**) and dihydrotanshinone I (**52**) [129-131]. In addition, five phenanthrene alkaloids represented by *N*-methylsecoglaucine (**53**) inhibited platelet aggregation induced by arachidonic acid, collagen, or some other stimuli, indicating their cardiovascular protective biologic effects [132].

Regulating apoptosis/autophagy in endothelial cells and macrophages

Apoptosis of either endothelial cells or macrophages can promote the development of plaques, while autophagy acts the opposite role. Gypenoside (**54**) has been reported to abolish the apoptosis of endothelial cells by regulating the mitochondria *via* the PI3K/Akt/Bad axis [133]. Acacetin (**55**) was reported to protect HUVECs against apoptosis in an *in vitro* endothelial injury model stimulated by high glucose [134]. Myricitrin (**56**) is a natural flavonoid isolated from the root bark of *Myrica cerifera*. Myricitrin (**56**) treatment has been proved to effectively reduce endothelial cell apoptosis through the STAT3 and PI3K/Akt/eNOS signaling pathways [39] or prevention of OS injury [135]. Relevant studies have shown that luteolin (**57**) and isorhamnetin (**58**) interfered with macrophage apoptosis, thus reducing plaque instability [136, 137]. One study in HUVECs designed to address the effect of vitexin (**59**) on endothelial dysfunction revealed that vitexin (**59**) induced autophagy, while inhibiting apoptosis [138]. Lupeol (**60**) treatment remarkably activated the autophagy of macrophages as indicated by increased LC3-II levels and inhibition of p62 [139]. Curcumin (**61**) and quercetin (**3**) were also considered to be autophagy activators of macrophages [140, 141]. Betulinic acid (**62**), a natural pentacyclic triterpenoid, has been reported to prevent endothelial dysfunction by promoting eNOS expression through stimulating the HDACS/ERKS/KLF2 pathway [142].

Inhibiting angiogenesis by targeting MMP-2/9

The proliferation and migration of vascular smooth muscle cells (VSMCs) due to MMP-2 and MMP-9 overexpression are crucial steps in the pathogenesis of intimal thickening and plaque instability [143, 144]. A recent study has demonstrated that angelica dahurica-derived imperatorin (**63**) precluded the migration of VSMCs induced by ox-LDL through repressing MMP-2 [145]. Securinine (**64**) was also identified to attenuate the proliferation and migration of smooth muscle cells by abating the expression of both adhesion molecules and MMP-2/9 [146]. Similar observations were reported after treatment with ginsenoside Rg3 (**65**), which however worked by activating PPARγ [147]. Artemisinin (**66**), a classic antimalarial drug, has been explored to decrease MMP-9 expression in phorbol myristate acetate-stimulated macrophages, thus exhibiting potential anti-atherosclerotic biologic effects [148].

With regard to the prevention and treatment of angiogenesis associated with AS, natural angiogenesis inhibitors exhibit markedly high potency [149]. Castanospermine (**67**), isoliquiritin (**68**), radicicol (**69**) and others have been reported to be potentially active compounds. Nevertheless, the specific inhibitory mechanisms of action remain to be explored [149]. Natural compounds for plaque stability are shown in Fig.4.

Regulating the gut microbiota

The gut microbiota is partially involved in the progression of AS at least by interfering with lipid metabolism and inducing systemic inflammation [150, 151]. Gut microbiota metabolites such as trimethylamine-*N*-oxide can cause platelet overactivation, dyslipidemia, OS and endothelial dysfunction, which are the key factors to aggravate AS [152]. Therefore, the gut microbiota becomes an important target in the treatment of AS [153]. Related active natural compounds are displayed in Fig.5.

Berberine (**29**) is the main active component of *Rhizoma coptidis*, whose anti-inflammatory and endothelial cell-protective effects in the treatment of AS have been widely investigated [154]. In HFD-fed $ApoE^{-/-}$ mice, berberine (**29**) significantly increased the abundance of *Akkermansiain* in the gut [155]. Moreover, further studies showed that berberine (**29**) significantly changed the composition of the gut microbiota, which varies from different dosages. Alistipes and roseburia were enriched in the high-dose group while blautia and allobaculum were enriched in the low-dose group. The microbiota exhibited excellent anti-inflammatory effects, thanks to glucolipid metabolism and the synthesis of short-chain fatty acids [156]. Ferulic acid (**70**) is a phenolic acid widely distributed in plants, which has been proved to reverse gut dysbiosis through turning the ratio of Firmicutes/Bacteroidetes to the normal [157]. Chitin-glucan (**71**) and pomegranate peel extract were shown to decrease the relative abundance of Alistipes and Lactobacillus, thus abating endothelial and inflammatory disorders in a mouse CVD model [158]. As a major flavonoid in Citrus species, naringin (**72**) has been found to lower cholesterol content in the serum and liver by adjusting the abundance of 7α-dehydroxylase-producing bacteria [159]. Anthocyanin (**73**) significantly up-regulated the proportions of Lactobacillus, Akkermansia, Bifidobacterium and Roseburia, thus reversing the "pro-atherogenic" gut microbiota community [160]. Aside from trigonelline (**74**), 2,3,5,4′-tetrahydroxy-stilbene-2-*O*-β-D-glucoside (**75**) and ginkgolide B (**76**), polysaccharides such as inulin (**77**) and mannan oligosaccharides (**78**) are also potential anti-AS ingredients in modulating the gut microbiota [161-165].

Concluding Remarks and Future Perspectives

AS is the main risk factor of thrombosis, which is the dominating culprit of death worldwide. Despite great progress achieved during the diagnosis and treatment of AS in the past decades, AS is still a global problem threatening hu-

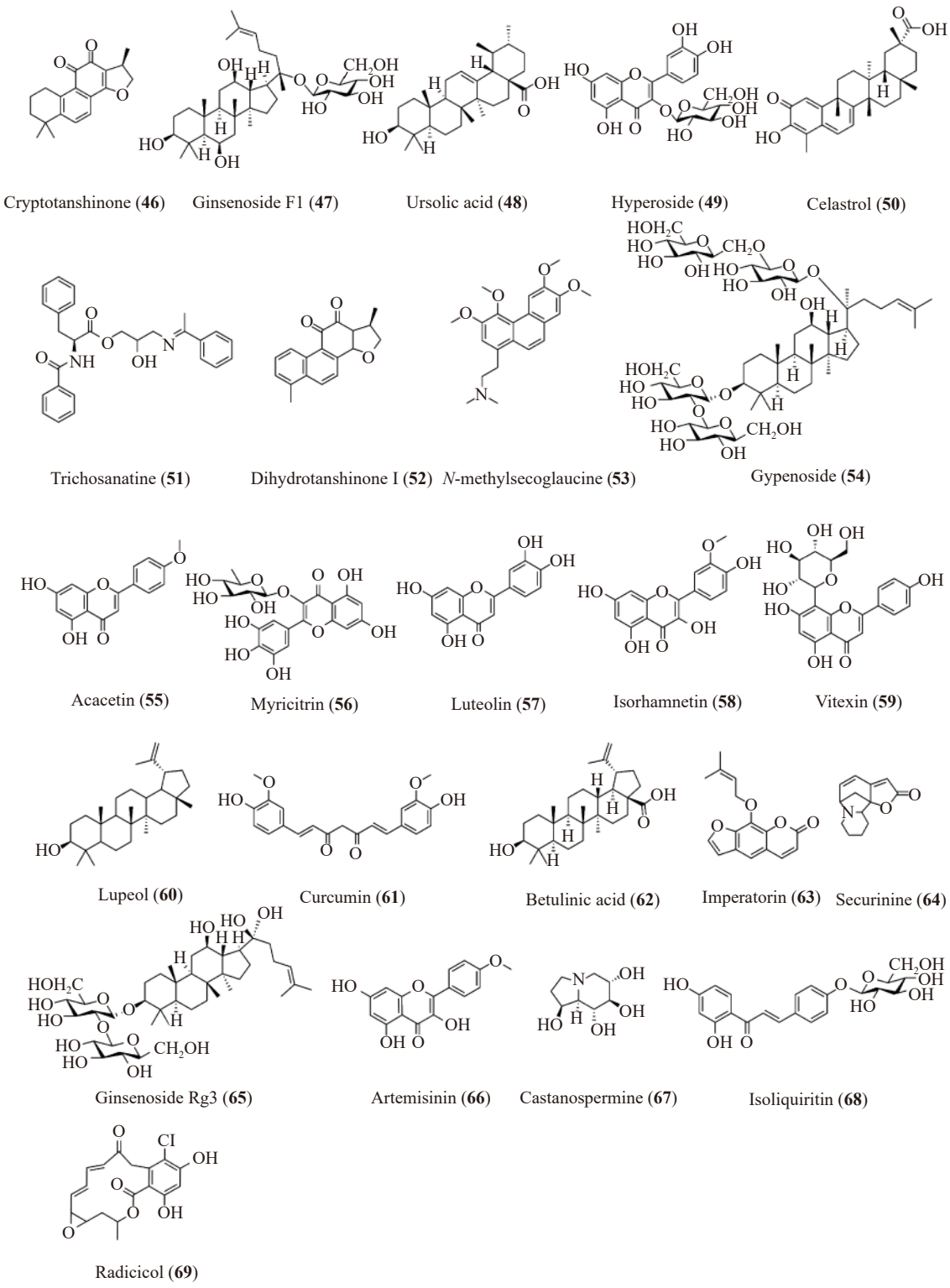
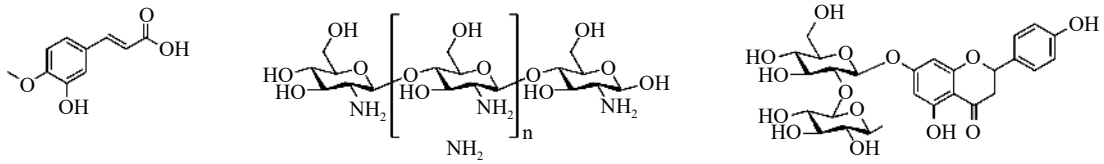


Fig. 4 Natural compounds for atherosclerotic plaque stability

man health. With the deepening of research, the development of a variety of diagnostic and detection technologies has allowed us understand the pathogenesis and treatment targets of AS in a more comprehensive manner. For instance, metabolomics and proteomics are leveraged to investigate the changes of plasma metabolites in animal models of AS, thus helping to predict biomarkers [166-169]. The application of network pharmacology and bioinformatics has improved our comprehension of the mechanism of action of drugs [170, 171].

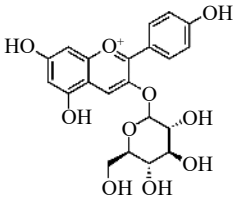
NPs with medicinal values are treasures bestowed by nature. The source and structure diversity render them more potent in treating AS and plenty of compounds have been re-



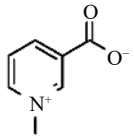
Ferulic acid (**70**)

Chitin-glucan (**71**)

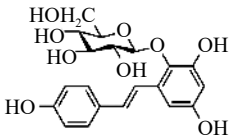
Naringin (**72**)



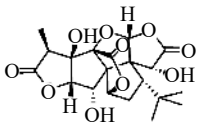
Anthocyanin (**73**)



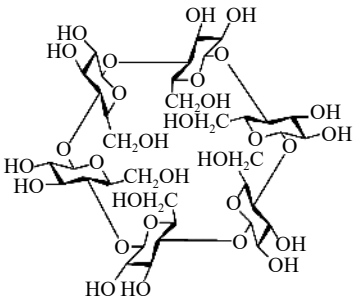
Trigonelline (**74**)



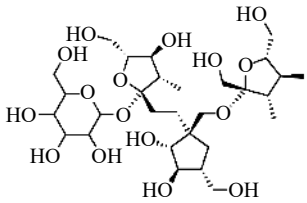
2,3,5,4-Tetrahydroxy-stilbene -2-*O*-b-D-glucoside (**75**)



Ginkgolide B (**76**)



Inulin (**77**)



Mannan oligosaccharides (**78**)

Fig. 5 Natural products for gut microbiota homeostasis

ported to be potent. With regard to the complex and non-independent pathogenesis and development of AS, multi-drug combination based on multiple targets will be of great significance. Such therapy can not only achieve synergistic efficacy but also reduce the untoward effects of certain drugs. Clinical trials have shown that the combination of low-dose rivaroxaban and acetylsalicylic acid to prevent thrombosis is an effective option to treat AS [172]. New technical methods such as microbiology and metabolomics have been utilized to investigate the anti-AS mechanism of natural products and traditional Chinese medicines, encouraging pharmaceutical researchers to energetically screen active ingredients from natural product libraries and explain the target of action of drugs [173]. Moreover, great success has been seen in expanding nanomedicine to the treatment of cardiovascular diseases such as AS [174-176], which also provide a new and powerful approach for the targeted delivery of NPs to the sites of atherosclerotic lesion in the near future.

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