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Review

Host-microbe co-metabolism system as potential targets: the promising way for natural medicine to treat atherosclerosis

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ABSTRACT

The host-microbe co-metabolism system, generating diverse exogenous and endogenous bioactive molecules that influence the host's immune and metabolic functions, plays a crucial role in the pathogenesis of atherosclerosis. Recent studies have elucidated the interaction between natural medicines and this co-metabolism system. Upon oral administration, natural medicine ingredients can undergo transformation by gut microbiota, potentially enhancing their bioavailability or anti-atherogenic efficacy. Furthermore, natural medicines can exert anti-atherogenic effects *via* modulation of endogenous host-microbe co-metabolism. This review presents an updated understanding of the dual association between natural medicines and host-microbe co-metabolites. It explores the critical function of microbial exogenous metabolites derived from natural medicines and uncovers the mechanisms underlying natural medicines' intervention on key nodes of endogenous host-microbe co-metabolism. These insights may offer new perspectives for cardiovascular disease (CVD) treatment and guide future drug discovery efforts.

1. Introduction

Atherosclerosis, a chronic arterial disease, is the leading cause of vascular mortality worldwide [1]. Its clinical manifestations include ischemic heart disease (IHD), ischemic stroke, and peripheral vascular disease [1]. Coronary heart disease (CHD) is the most prevalent manifestation, presenting as either stable angina pectoris or acute coronary syndromes [2]. In 2022, IHD ranks as the most prevalent cardiovascular disease (CVD) globally, causing the highest number of deaths, followed by ischemic stroke [3]. Large prospective observational studies have identified risk factors for atherosclerosis, including genetic predisposition, blood lipid levels, hypertension, smoking, diabetes, chronic kidney disease (CKD), and adiposity [1]. In recent decades, the gut microbiota has been recognized as a crucial contributor to atherosclerosis pathogenesis. Patients with atherosclerotic CVDs exhibit significant alterations in gut microbial community structure, such as the decreased abundance of *Bacteroides* and *Prevotella* and an increased prevalence of *Streptococcus* and *Escherichia* [4, 5]. The gut microbiota, harboring millions of genes encoding diverse biosynthetic and metabolic enzymes [6], collaborates with host metabolic enzymes to form a complex host-microbe co-metabolic system. This system influences atherosclerosis pathogenesis by producing and eliminating bioactive co-metabolic endogenous molecules. For example, host-microbe endogenous co-metabolites such as trimethylamine-*N*-oxide (TMAO) and phenylacetylglutamine (PAGln) have been associated with increased risk of CVD events [7, 8]. Additionally, human gut *Oscillibacter* isolates, which possess cholesterol glycosylation and dehydrogenation capabilities, demonstrate potential in alleviating hypercholesterolemia and atherosclerosis [9]. Consequently, key nodes in host-microbe endogenous co-metabolism may represent promising novel targets for atherosclerosis intervention.

Natural medicines encompass herbal formulae, herbs, and herbal monomers derived from botanical sources. Guided by traditional Chinese medicine (TCM) theories, natural medicines have demonstrated potent therapeutic efficacy and low toxicity through extensive clinical practice [10]. Furthermore, due to their multi-component and multi-target characteristics, natural medicines exhibit advantages in treating chronic complex diseases, including metabolic syndromes and atherosclerosis [11]. The host-microbe co-metabolic system plays a crucial role in the fermentation or conversion of natural medicines, facilitating the generation of bioactive and bioavailable metabolites [12]. Recent research has also revealed that the host-microbe co-metabolic system serves as a target for natural medicines to exert anti-atherogenic effects [13]. This review examines the relationship between the host-microbe co-metabolism system and atherosclerosis, highlights potential anti-atherogenic exogenous metabolites derived from natural medicines through the host-microbe co-metabolism system, and discusses promising strategies targeting this system using natural medicines to promote cardiovascular health benefits.

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2. Anti-atherogenic bioactive metabolites of natural medicine generated by the host-microbe co-metabolism system

Natural medicines are commonly administered orally or used as dietary supplements. Consequently, their bioactive components, including polysaccharides, flavonoids, and saponins, are typically metabolized by the gut microbiota through processes such as deconjugation, modification, methylation, reduction, oxidation, and hydroxylation [12]. Moreover, these ingredients can be absorbed and transported to the liver, where they undergo metabolism mediated by host cytochrome P450 enzymes [12]. Following hepatic excretion into the gut, these metabolites can be further catalyzed by the gut microbiota to form secondary metabolites [12]. This host-microbe co-metabolism system may enhance the oral bioavailability of natural medicine components or generate new bioactive molecules that exhibit cardioprotective effects (Fig. 1 and Table S1).

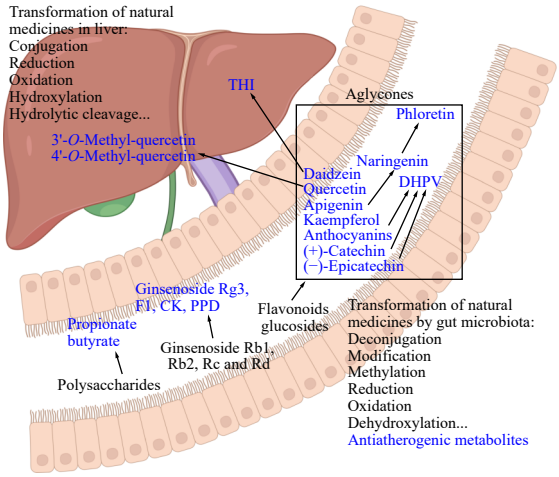

Fig. 1 The anti-atherogenic bioactive metabolites of natural medicine generated by host-microbe co-metabolism system. The terminal metabolites of low-bioavailable polysaccharides are SCFAs, among which propionate and butyrate can effectively attenuate atherosclerosis. Primary ginsenosides, which harbor poor bioavailability, can be hydrolyzed by the gut microbiome to generate secondary ginsenosides, including ginsenoside Rg2, F1, CK, and PPD, which are more bioavailable and also exert anti-atherogenic roles. The gut microbiota hydrolyzes flavonoid glycosides and produces aglycones, among which apigenin, quercetin and kaempferol are anti-atherogenic metabolites. The aglycones undergo further metabolism to generate secondary products such as naringenin, phloretin, and DHPV, which show anti-atherogenic effects. After absorbed, the aglycones and their secondary products were metabolized by hepatic cytochrome P450 to form co-metabolites, such as anti-atherogenic 3'-*O*-methyl-quercetin, 4'-*O*-methyl-quercetin, and THI.

2.1. Polysaccharides metabolism

Polysaccharides are macromolecular polymers comprising more than ten monosaccharide units, such as glucose, mannose, galactose, and fructose, connected by various glycoside bonds in linear or branched chains [14]. However, some high-molecular-weight or minimally branched polysaccharides exhibit limited absorption following oral administration [15]. Furthermore, due to the low diversity of polysaccharide-metabolizing enzymes encoded by the human genome, certain polysaccharides effectively resist hydrolysis or digestion in human saliva, stomach, and small intestine, subsequently being utilized by the microbiota in the distal gut [16, 17]. The gut microbiota plays a crucial role in enhancing the bioavailability and bioactivity of polysaccharides by catalyzing them into oligosaccharides, disaccharides, and monosaccharides [18]. Microbial degradation of polysaccharides relies on carbohydrate-active enzymes (CAZymes), including glycoside hydrolases (GHs), polysaccharide lyases, glycosyltransferases, glycosaminoglycans, carbohydrate esterases, and auxiliary activity enzymes [18]. *Bifidobacterium* spp. and *Bacteroides* spp. are two primary polysaccharide degraders, which transport polysaccharides using the starch utilization system (Sus)-like system and ABC transport system, respectively, thereby exerting hydrolytic degradation [19, 20]. Importantly, monosaccharides derived from polysaccharides undergo glycolysis and the pentose phosphate pathway, being catalyzed into phosphoenolpyruvate and pyruvate, which are subsequently converted into short chain fatty acids (SCFAs), including acetate, propionate, and butyrate [21]. Most enteric microbiota can synthesize acetate, while microbes including *Bacteroides* spp., *Dialister* spp., *Veillonella* spp., *Megasphaera* spp., *Coprococcus* spp., *Roseburia* spp., and *Ruminococcus* spp. are important propionate producer. Additionally, *Coprococcus* spp., *Anaerostipes* spp., *Eubacterium* spp., *Roseburia* spp. and *Faecalibacterium prausnitzii* can generate butyrate [21]. SCFAs, particularly propionate and butyrate, exert anti-atherogenic effects through their extensive immunoregulatory roles [22]. For instance, propionate can increase small intestinal regulatory T-cell numbers and interleukin (IL)-10 levels, thereby inhibiting intestinal cholesterol absorption and attenuating atherosclerosis [23]. Furthermore, butyrate alleviates atherosclerosis and promotes plaque stability by decreasing cholesterol uptake, proinflammatory cytokine secretion, and macrophage adhesion and migration while relieving endothelial dysfunction and suppressing oxidative stress [24, 25]. These effects are possibly mediated through the activation of G protein-coupled receptor 109A (GPR109A) and GPR41, and the inhibition of histone deacetylases (HDACs) [26]. Moreover, butyrate enhances the anti-inflammatory effects of macrophages and dendritic cells, promoting the differentiation of Treg cells and IL-10-producing T cells [27], which may contribute to its anti-atherogenic effects through the regulation of adaptive immunity.

2.2. Saponins metabolism

Ginsenosides are a class of dammarane-type triterpenoid saponins primarily derived from *Panax ginseng*, *Panax notoginseng*, and *Panax quinquefolius*, which are extensively utilized in clinical practice for CVD treatment. Ginsenosides can be categorized based on their natural abundance into primary ginsenosides (e.g., Rb1, Rb2, Rb3, Rc, Rd, Rg1, Re, and Rd), secondary ginsenosides (e.g., Rg5, Rk1, Rg3, Rh2, F2, F1, Rh1, Rg2, and CK), which constitute less than 0.1% of the herb weight, and sapogenins including protopanaxadiol (PPD) and protopanaxatriol (PPT), *etc* [28, 29]. Secondary ginsenosides and sapogenins are predominantly produced through steaming processes and microbial metabolic transformation of primary saponins following oral administration [28, 30]. Due to their high hydrophilicity, primary ginsenosides are poorly absorbed in the intestines, exhibiting low oral bioavailability below 7% [31, 32]. Gut microbiota encoding α-rhamnosidase, α-arabinofuranosidas and β-glucosidase, including species of *Eubacterium* spp., *Bacteroides* spp., *Bifidobacterium* spp., *Fusobacterium* spp. and *Provotella* spp., mediate the hydrolysis of primary ginsenosides to form lipophilic secondary ginsenosides and sapogenins with enhanced bioavailability [33]. This process results in the formation of ginsenoside Rg3, F2, CK, and PPD from ginsenoside Rb1, Rb2, Rc, and Rd, as well as ginsenoside F1, Rh1, Rg2, and PPT from Re and Rg1 [34, 35]. Secondary ginsenosides such as Rg3, F1, and CK, and the sapogenin 20(*S*)-PPD have demonstrated significant anti-atherogenic effects in animal models [36-39]. In addition to improved oral bioavailability, some secondary ginsenosides and sapogenins exhibit superior efficacy compared to primary ginsenosides. For example, 20(*S*)-PPT demonstrates a more potent anti-inflammatory role in macrophages [40], while CK and ginsenoside Rh1 show stronger effects than ginsenoside Rb1, Rc, and Re in improving endothelial dysfunction [41].

2.3. Flavonoids metabolism

Flavonoids are a class of polyphenolic compounds primarily

categorized into flavones, flavanols, flavanones, flavanonols, isoflavones, anthocyanins, chalcones, dihydrochalcones, and flavanes based on their chemical structure [42]. Following oral consumption, the gut microbiota facilitates the hydrolysis of flavonoid glycosides, including *O*-deglycosylation and the less common *C*-deglycosylation, to produce aglycones in both the small intestine and colon [43]. Microbial species such as *Eubacterium* spp., *Enterococcus* spp., *Bacteroides* spp., *Bifidobacterium* spp., *Parabacteroides* spp., *Lactobacillus* spp., *Lactococcus* spp. and *Escherichia coli* perform the *O*-deglycosylation of flavonoid glycosides, while *Eubacterium* spp. and *Enterococcus* spp. primarily exhibit *C*-deglycosylating effects [44]. Post-hydrolysis, the gut microbiota conducts *C*-ring cleavage, *O*-demethylation, dihydroxylation, and reduction, resulting in the formation of various secondary products [44, 45]. Subsequently, upon intestinal absorption and hepatic transport, the aglycones and their secondary products undergo glucuronidation, methylation, and sulfation by human hepatic cytochrome P450 [46].

Aglycones derived from flavonoid glycosides, such as apigenin from apigenin-7-*O*-glucoside, quercetin from rutin, and kaempferol from kaempferol-3-*O*-glucoside, have demonstrated significant anti-atherogenic effects in animal models [47-49]. Additionally, various microbial-generated aglycones have been found to alleviate atherosclerosis. Naringenin, metabolized from apigenin by gut microbes encoding flavone reductases like *Flavonifractor plautii* and *Clostridium ljungdahlii*, exhibits anti-atherogenic effects through multiple mechanisms, including suppression of monocyte and macrophage infiltration, reduction of vascular inflammation, inhibition of foam cell formation, and promotion of cholesterol efflux [50-52]. Notably, naringenin shows slightly stronger effects on alleviating endothelial dysfunction than its precursor apigenin [53], suggesting that gut microbiota may contribute to enhancing the efficacy of flavones. Phloretin, a dihydrochalcone produced from naringenin by microbes harboring chalcone isomerase (CHI) and enoate reductase (EnoR/ERED) such as *E. ramulus*, effectively inhibits platelet activation and prevents thrombosis [54, 55]. 5-(3',4'-Dihydroxyphenyl-γ-valerolactone) (DHPV), the major microbial metabolite of flavan-3-ols including proanthocyanidin, anthocyanins, (+)-catechin, and (−)-epicatechin, inhibits the expression of chemokines and adhesive molecules, and alleviates inflammation in monocytes, demonstrating more potent effects than its precursors [56, 57]. *Eggerthella lenta* and *Lactobacillus plantarum* convert (+)-catechin and (−)-epicatechin to an intermediate product, which is further metabolized into DHPV by *F. plautii* [58, 59]. Furthermore, the host liver can metabolize microbial flavonoid metabolites to generate bioactive molecules. For instance, host-methylated metabolites of quercetin, such as 3'-*O*-methyl-quercetin and 4'-*O*-methyl-quercetin, effectively exert anti-inflammatory and anti-oxidant properties in endothelial cells [60]. Additionally, 7,8,4'-trihydroxyisoflavone (THI), the major host metabolite of the isoflavone daidzein, displays stronger inhibitory effects on monocyte-endothelial cell adhesion and higher bioavailability compared to daidzein and its glycoside daidzin [61].

3. Anti-atherogenic effects of natural medicines *via* targeting host-microbe co-metabolism system

The gut microbiota, encoding a diverse array of enzymes, plays a crucial role in the metabolism of dietary and endogenous small molecules, often referred to as the "invisible metabolic organ". It collaborates with host enzymes to mutually expand the structural diversity of metabolites, which in turn shape the host's metabolic and immune homeostasis, including cardiovascular health. However, disturbances in the host-microbe co-metabolism system, particularly in nutrition metabolism, may contribute to CVDs such as atherosclerosis. Notably, the host-microbial co-metabolism of trimethylamine (TMA)/TMAO, bile acids (BAs), and amino acids plays fundamental roles in the occurrence and pathogenesis of atherosclerosis. Recent studies have demonstrated that natural medicines can alter the gut microbial community composition and metabolism by either promoting or suppressing their growth or metabolic activities, thereby potentially alleviating atherosclerosis (Fig. 2 and Table S2).

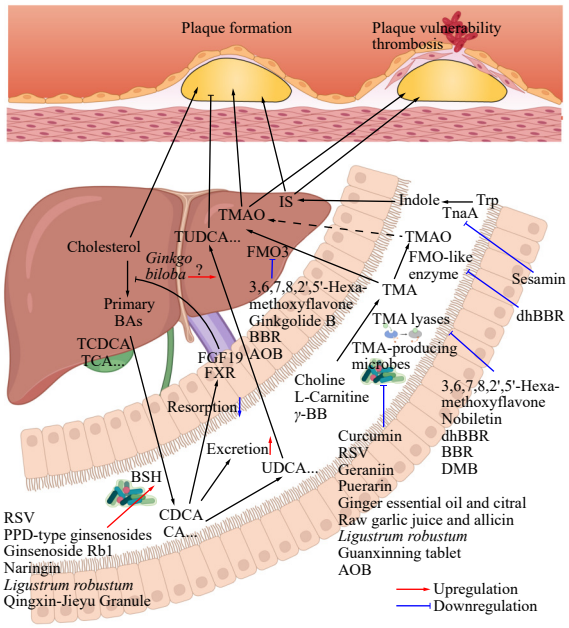

Fig. 2 Anti-atherogenic mechanisms of natural medicines *via* the modulation of host-microbe co-metabolism. Dietary components such as choline and L-carnitine are metabolized by the gut microbiota into TMA, which is subsequently oxidized into TMAO by hepatic FMOs, as well as the microbes encoding FMO-like enzymes. TMAO accelerates atherosclerotic plaque formation, and facilitates plaque vulnerability and thrombosis by enhancing platelet reactivity. Various nature medicines can exert their anti-atherogenic roles by suppressing TMAO production mainly *via* the regulation of the gut microbial community structure, the inhibition of the activity of microbial TMA lyases or FMO3-like enzymes and the suppression of the hepatic FMOs expression. Natural products such as curcumin, RSV, geraniin, puerarin, ginger essential oil and citral, raw garlic juice and allicin, *Ligustrum robustum*, Guanxinning Tablet, and *Alisma orientalis* beverage reduce the abundance of TMA-producing microbes. Compounds including 3,6,7,8,2',5'-hexamethoxyflavone, nobiletin, dhBBR, BBR, and DMB inhibit TMA lyase activity. Notably, dhBBR also suppresses microbial FMO-like enzyme activity. 3,6,7,8,2',5'-Hexamethoxyflavone, ginkgolide B, BBR, DMB downregulate hepatic FMO3. Cholesterol metabolism is regulated by the enterohepatic FXR–FGF19/Fgf15 axis. The enhancement of the gut BSH activity can inhibit enterohepatic FXR–FGF19/Fgf15 axis, which in turn accelerates cholesterol catalyzation and relieves hypercholesterolaemia. RSV, PPD-type ginsenosides including ginsenoside Rb1, naringin, *Ligustrum robustum* and Qingxin-Jieyu Granule enhance the abundance of BSH-encoding microbes. This leads to reduced bile acid reabsorption, increased fecal bile acid excretion, suppression of the FXR–FGF19/Fgf15 axis, and ultimately, attenuation of atherosclerosis. Additionally, the host-microbe co-metabolic secondary bile acids, such as TUDCA and UDCA, can also alleviate atherosclerosis. *Ginkgo biloba* elevates the serum TUDCA level, which might be antiatherogenic. IS is a proatherogenic host-microbe co-metabolite of tyrosine, and sesamin, which is a potent inhibitor of TnaA. Sesamin decreases the formation of indole, a key IS precursor, thereby lowering IS production.

3.1. Enterohepatic TMAO metabolic pathway and atherosclerosis

TMAO is a host-microbe co-metabolite derived from dietary choline, phosphatidylcholine, and L-carnitine [62]. These dietary components are catalyzed by the gut microbiota to generate TMA, which is subsequently converted to TMAO by hepatic flavin monooxygenases (FMOs), specifically FMO1 and FMO3 [7]. A recent study also identified FMO-like enzymes in gut microbes, including *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Peptostreptococcus anaerobius*, and *Enterobacter aerogenes* [63]. The association between TMAO and CVDs was first discovered by Stanley's team at Cleveland Clinic in 2011, when they found that the gut-microbiota-dependent metabolite TMAO derived from dietary phos-

phatidylcholine was a risk factor for CVDs [7]. Subsequent studies have demonstrated that dietary L-carnitine, which is abundant in red meat, could also be metabolized to TMAO and accelerate atherosclerosis [64, 65]. TMA-producing bacterial species are widely distributed across almost every phylum, including *Anaerococcus hydrogenalis*, *C. asparagiforme*, *C. hathewayi*, *C. sporogenes*, *Edwardsiella tarda*, *Lachnoclostridium saccharolyticum*, *E. coli*, *E. fergusonii*, *P. penneri*, *Providencia rettgeri*, *P. mirabilis*, *Shigella boydii* and *B. fragilis* [63, 66-68]. The bacterial enzyme choline TMA-lyase (cutC/D) is responsible for the catalyzation of choline to TMA, while carnitine monooxygenase (cntA/B) mediates the metabolism of carnitine to TMA [69, 70]. The yeaW (dioxygenase)/yeaX (oxidoreductase) complex encoded by *Proteobacteria* species, such as *E. coli*, is another microbial transformation pathway mediating TMA production by using γ-butyrobetaine (γ-BB) as the substrate [71]. A total of 216 bacteria species from 102 genera have been identified as encoding cutC/D, cntA/B, and yeaW/yeaX from databases, with most of these species belonging to *Firmicutes* and *Proteobacteria* [68], the proportion of which is relatively higher in CVD patients [4].

TMAO exerts multiple biological effects on the cardiovascular system. Primarily, it adversely influences lipid metabolism and transport. TMAO accelerates cholesterol uptake by macrophages by upregulating the expression of scavenger receptors, including CD36 and scavenger receptor A1 (SRA1), on the cell surface, promoting foam cell formation [7]. Additionally, TMAO downregulates the expression of hepatic cholesterol catalyzing enzymes 7α-hydroxylase (CYP7A1) and sterol-27-hydroxylase (CYP27A1), as well as BA transporters organic anion transporting polypeptide 1 (OATP1), OATP4, multidrug resistance-associated protein 2 (MRP2), and sodium taurocholate cotransporting polypeptide (NTCP). This downregulation inhibits cholesterol metabolism and reverse cholesterol transport (RCT) [65]. Moreover, TMAO induces endothelial dysfunction, activates the NOD-like receptor pyrin domain containing protein 3 (NLRP3) inflammasome, and promotes M1 macrophage polarization [72-74], demonstrating proinflammatory effects. Furthermore, TMAO enhances platelet hyperreactivity and thrombosis potential in the late stage of atherosclerosis [75].

3.2. Targeting enterohepatic TMAO metabolic pathway using natural medicines

Recent studies have demonstrated that various natural medicines can exhibit anti-atherogenic properties by suppressing TMAO production. This suppression occurs through multiple mechanisms, including the modulation of gut microbial community structure, inhibition of microbial TMA lyase activity, suppression of FMO3-like enzyme activity, and reduction of host FMO expression.

Resveratrol (RSV), a polyphenol derived from grapes and the natural medicine *Polygonum cuspidatum*, is frequently utilized as a dietary supplement for the prevention and alleviation of CVDs. Research has demonstrated that RSV possesses anti-inflammatory, anti-oxidant, anti-proliferative, and angio-regulatory properties effective against CVDs, including atherosclerosis [76]. However, RSV's oral bioavailability is limited, making it challenging to achieve active concentrations in the cardiovascular system through regular dosing [77]. Oral administration of RSV can mitigate atherosclerosis by inhibiting the gut microbial conversion of choline to TMA through modulation of the microbial community structure, thereby suppressing TMAO production [78].

Berberine (BBR), derived from the natural medicine *Coptis chinensis*, significantly reduces blood cholesterol levels and plaque sizes in patients with atherosclerosis [63, 79], despite its low oral bioavailability [80]. Extensive research demonstrates that BBR exerts its anti-atherogenic effects *via* the regulation of the host-microbe co-metabolism system, particularly influencing TMAO formation. BBR notably downregulates hepatic FMO3 expression and reduces the abundance of TMA-producing bacteria, leading to a decrease in blood TMAO levels [81, 82]. Furthermore, dihydroberberine (dhBBR), a microbial metabolite of BBR, also decreases blood TMAO levels by effectively inhibiting the enzymatic activity of CutC and FMO-like enzymes from gut microbiota [63]. Beyond inhibiting TMAO formation, BBR enhances the intestinal expression of tight junction (TJ) proteins, possibly *via* increasing *Akkermansia* levels, and promotes the production of microbial indole derivatives, potentially benefiting cardiovascular health [83, 84].

Furthermore, various herbal monomers demonstrate the ability to reduce systemic TMAO levels by inhibiting the growth of microorganisms that produce γ-BB or TMA. These include allicin found in raw garlic, curcumin extracted from *Curcuma longa*, geraniin derived from *Geranium thunbergia*, puerarin obtained from *Pueraria lobata*, ginger essential oil and citral from ginger, and water extract from *Ligustrum robustum* [85-90].

In addition to reducing TMA-producing bacteria abundance, various herbs and herbal compounds can directly inhibit the activity of microbial TMA lyases and/or host FMO3. For instance, 3,3-dimethyl-L-butanol (DMB), commonly found in extra virgin olive oils and grapeseed oils, inhibits cutC/D and partially yeaW/X enzymatic activity, thereby reducing TMAO production [91]. Moreover, polymethoxyflavones from orange peel, including nobiletin and 3,6,7,8,2',5'-hexamethoxyflavone, significantly inhibit cntA/B and cutC/D *in vitro*, with 3,6,7,8,2',5'-hexamethoxyflavone also downregulating FMO3 mRNA expression in HepG2 cells [92]. Virtual screening analysis reveals that natural flavonoids such as baicalein, fisetin, acacetin, myricetin, baicalin, naringin, and hesperidin demonstrate good binding effects on cutC/D [93], suggesting potential inhibitory effects on TMA synthesis. Polyphenols from the hickory nut, including corilagin, (−)-gallocatechin gallate, and epigallocatechin gallate (EGCG), have the potential to directly hinder CutC enzyme activity, while casuariin and cinnamtannin B2 also show potential inhibitive effects on both CutC and FMO3 enzymatic activities [94]. The terpene lactone ginkgolide B, derived from *Ginkgo biloba*, can inhibit the transcriptional and protein expressions of FMO3, thus reducing blood TMAO levels and alleviating atherosclerosis [95].

Herbal formulations, comprising multiple herbs, have demonstrated anti-atherogenic effects through modulation of the host-microbial co-metabolic system, potentially in a more comprehensive manner than single herbs or herbal monomers. The Guanxinning Tablet not only reduces the level of proatherogenic TMAO but also elevates the levels of microbe-derived SCFAs, including propionic acid and butyric acid, which exhibit anti-atherogenic properties [96]. Additionally, *Alisma orientalis* beverage (AOB) has been shown to decrease serum TMAO concentration *via* downregulation of hepatic FMO3 expression and alleviate circulating chronic inflammation associated with perturbed gut microbiota [97].

3.3. Enterohepatic cholesterol and BA metabolism and atherosclerosis

BAs are host-microbe co-metabolites derived from cholesterol. The primary pathway for cholesterol metabolism involves hepatic CYP7A1 and 12α-hydroxylase (CYP8B1), forming primary BAs such as CA and chenodeoxycholic acid (CDCA) [98]. An alternative pathway, mediated by CYP27A1 and subsequent hydroxylation by oxysterol 7α-hydroxylase (CYP7B1), also contributes to the transformation of cholesterol to primary BAs, predominantly CDCA [98]. In humans and pigs, CYP3A4 further 6α-hydroxylates CDCA to hyocholic acid (HCA) [99]. In rodents, Cyp2c70 6β-hydroxylates CDCA and ursodeoxycholic acid (UDCA) to α-muricholic acid (α-MCA) and β-muricholic acid (β-MCA), respectively [100].

BAs are subsequently conjugated with glycine or taurine at position C-24 by BA coA: amino acid *N*-acyltransferase (BAAT), then transported into bile *via* the bile salt export pump (BSEP), a member of the ATP-binding cassette transporter family B11 (ABCB11), and stored in the gallbladder until secretion after a meal [101]. Approximately 95% of conjugated BAs are actively reabsorbed at the ileum terminus *via* the apical sodium-dependent bile acid transporter (ASBT), entering the portal blood to the liver in a process called enterohepatic circulation [102, 103]. The remaining BAs are catalyzed into unconjugated BAs by microbial bile salt hydrolase (BSH), then dehydroxylated or 7*α/β*-epimerized by gut microbiota to form secondary BAs [104]. BSH, an abundant enzyme found in all major gut microbiota phyla, including *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria* [105], can be classified into eight major phylotypes with diverse gene sequences, substrate selectivity, and enzymatic activity [106]. Post-deconjugation, BAs can be converted to secondary BAs through dehydroxylation, oxidation, and epimerization [107]. Major bile salt modifications include 6*β*-epimerization, 7*α/β*-oxidation deconjugation, oxidation of hydroxy groups at C-3, C-7, and C-12, and 7*α/β*-dehydroxylation [108]. The transformation of CA to deoxycholic acid (DCA) and CDCA to lithocholic acid (LCA) is mediated by 7*α*-dehydroxylase, encoded by the BA-inducible (bai) manipulator, comprising eight genes: *baiB*, *baiCD*, *baiE*, *baiA*, *baiF*, *baiG*, *baiH*, and *baiI* [109]. The *bai* gene cluster, present in most individuals, is detectable in a small fraction of total gut bacteria (< 1%), primarily incorporating uncultured members of the order *Clostridiales* and a small fraction of the families *Lachnospiraceae* and *Peptostreptococcaceae* [110, 111]. Additionally, UDCA can be dehydroxylated to LCA by 7*β*-dehydroxylase expressed by *C. scindens* [112]. Hyodeoxycholic acid (HDCA) is derived from *β*-MCA through microbial 6*β*-epimerization and additional 7*β*-dehydroxylation in microbes such as the HDCA-1 strain [113]. Pyridine nucleotide-dependent hydroxysteroid dehydrogenases (HSDH), encoded by gut microbiota, perform hydroxyl oxidation/reduction at the C-3, C-7, and C-12 positions of BAs [114]. For instance, 7*α*-HSDH expressed in *E. lenta*, *C. scindens*, and *E. coli* mediates the metabolism of CDCA to the intermediate 7-oxo-LCA, while 7*β*-HSDH in *R. gnavus* and *R. torques* subsequently converts 7-oxo-LCA into UDCA [108, 115].

BAs regulate glucose and lipid metabolism primarily through BA receptors, including the nuclear receptor farnesoid X receptor (FXR) and the plasma membrane receptor Takeda G protein-coupled receptor 5 (TGR5) [116]. Hepatic cholesterol metabolism and BA synthesis are tightly regulated by negative feedback inhibition *via* hepatic and intestinal FXR. In the liver, FXR activation upregulates the expression of small heterodimer partner (SHP), which binds to liver receptor homolog-1 (LRH-1), subsequently inhibiting *CYP7A1* transcriptional expression and cholesterol metabolism [117]. Beyond hepatic FXR effects, FXR activation in the distal ileum induces fibroblast growth factor 19 (FGF19, Fgf15 in mice) expression, which inhibits *CYP7A1* transcriptional expression by binding to the FGF receptor 4 (FGFR4)/b-klotho heterodimer complex after reaching the liver *via* the portal vein, known as the enterohepatic FXR-FGF19/Fgf15 signaling axis [118]. Hepatic FXR activation may be athero-protective, as it suppresses intestinal cholesterol absorption by altering BA pool size and composition, enhancing RCT [119]. However, intestinal FXR signal activation might be proatherogenic. Serum FGF19 levels are elevated in hypercholesterolemic patients, and inhibiting ileal FXR signaling effectively promotes cholesterol excretion and alleviates atherosclerosis [120, 121]. Moreover, suppressing intestinal FXR signaling downregulates ceramide synthesis enzyme expression [122], which attenuates atherosclerosis [120, 122]. TGR5 is considered protective during atherosclerosis, as its activation alleviates macrophage inflammation and reduces lipid loading [123]. BAs exhibit diverse effects on FXR and TGR5. For instance, CDCA most potently agonizes FXR, followed by DCA and LCA [124]. Conversely, tauro-*β*-muricholic acid (T*β*-MCA), glycoursodeoxycholic acid (GUDCA), HCA, and HDCA are FXR antagonists [125, 126]. TGR5 agonists include LCA, TLCA, DCA, CDCA, CA, HCA, HDCA, glycohyocholic acid (GHCA), taurohyocholic acid, glycohyodeoxycholic acid (GHDCA), and taurohyodeoxycholic acid (THDCA) [126, 127]. TGR5 signal activation regulates glucose homeostasis and reduces obesity by inducing glucagon-like peptide-1 (GLP-1) release from intestinal L cells [128]. Recent studies reveal that GLP-1 receptor activation inhibits leukocyte-endothelial interactions, relieves inflammation, and reduces carotid intima-media thickness in diabetic patients, demonstrating multiple anti-atherogenic functions [129]. In addition to suppressing intestinal FXR, GUDCA retards atherosclerosis by inhibiting foam cell formation *via* SRA1 expression downregulation and regulating gut microbial structure [120, 130]. Furthermore, HDCA lowers plasma cholesterol levels and improves HDL function, thereby inhibiting atherosclerotic plaque formation [131, 132], potentially resulting from its inhibition of intestinal FXR and activation of TGR5.

Recent studies have revealed that BAs also possess immune-regulatory properties. For instance, 3-oxoLCA and isoLCA have been shown to inhibit Th17 cell differentiation, while isoalloLCA and isoDCA promote the generation of Treg cells [133, 134]. Furthermore, our previous research has elucidated the role of DCA and CDCA in activating both the classical NLRP3 and nonclassical apoptotic protease activating factor-1 (Apaf-1)/caspase-4 pyroptosome pathways [135, 136], both of which can induce proatherogenic inflammation. Additionally, DCA and CDCA have been identified as endogenous activators of mitofusin 2 (MFN2), which can modulate innate immune responses [137]. These BAs also inhibit T cell activation by disrupting intracellular calcium homeostasis, specifically by suppressing mitochondrial calcium uptake and increasing cytoplasmic Ca^{2+} concentration [138]. Moreover, UDCA has been found to reduce proinflammatory cytokine expression by interfering with receptor of advanced glycation endproducts (RAGE) signaling [139]. Both tauroursodeoxycholate acid (TUDCA) and UDCA have demonstrated the ability to inhibit endoplasmic reticulum stress and inflammation, thereby alleviating atherosclerosis [140].

3.4. Targeting enterohepatic cholesterol and BA metabolism using nature medicines

Ginsenosides, the active triterpenoid saponins derived from *Panax ginseng* and *Panax notoginseng*, have been extensively utilized in treating various CVDs, including atherosclerosis, for millennia in China. *Panax ginseng* has demonstrated the ability to reduce plasma total cholesterol and triglyceride levels while increasing HDL-cholesterol (HDL-c) levels in patients with hyperlipidemia and hypercholesterolemia [141]. Due to their low oral bioavailability [31, 32], ginsenosides are postulated to exert their anti-atherogenic effects partially through the modulation of the host-microbe co-metabolism system. PPD-type ginsenosides, such as ginsenoside Rb1, can increase the abundance of *Lactobacillus* and its BSH, leading to enhanced intestinal conjugated BA hydrolysis and decreased intestinal BA resorption. This, in turn, inhibits the enterohepatic FXR-FGF15 axis and alleviates hypercholesterolemia [142]. *L. brevis*, which is enriched following oral ginsenoside Rb1 administration [143], effectively ameliorates hypercholesterolemia *via* LDLR overexpression and elevation of HDL-c levels [144]. Furthermore, compound K stimulates the production of microbe-derived secondary BAs, including DCA and LCA, which subsequently enhance GLP-1 secretion *via* TGR5 on L-cells, reducing obesity and benefiting cardiovascular health [145]. Ginseng extract also promotes the growth of *Enterococcus faecalis*, which further exerts anti-obesity effects through its metabolite myristoleic acid [146], and may play an anti-hypercholesterolemic role by accelerating cholesterol efflux in the intestine and liver [147].

In addition to their potential regulatory effects on the TMAO metabolic pathway, RSV, naringin, and *Ligustrum robustum* play significant roles in modulating cholesterol and BA metabolism. RSV enhances gut-microbe-mediated conjugated BA hydrolysis, thereby inhibiting the enterohepatic FXR-FGF15 axis, leading to the mitigation of hypercholesterolemia and atherosclerosis [78]. Moreover, RSV reverses HFD-induced gut microbial dysbiosis, including restoring the *Bacteroidetes/Firmicutes* ratio, and upregulates the expression of intestinal TJ proteins, maintaining gut barrier integrity [148]. This may partially explain the anti-inflammatory properties of RSV. The water extract of *Ligustrumrobustum* promotes *Bifidobacterium*-mediated conjugated BA hydrolysis, thereby enhancing fecal cholesterol and BA excretion [89]. Naringin alleviates atherosclerosis by downregulating proprotein convertase subtilisin/kexin type 9 (PCSK9) and enriching bacteria that encode BSH and 7α-dehydroxylase, which promote conjugated BA hydrolysis and secondary BA production, subsequently suppressing the intestinal FXR/FGF15 pathway [149, 150].

Ganoderma lucidum, a medicinal mushroom in TCM, exhibits anti-depressant, anti-cancer, anti-diabetic, anti-hyperglycemic, hypolipidemic, and anti-atherogenic properties [151-153]. Extracts from Mexican *Ganoderma lucidum* can alleviate hypercholesterolemia, partially by enriching gut *Lactobacillus* [154]. Furthermore, *Ganoderma* meroterpene derivative (GMD) demonstrates therapeutic effects on atherosclerosis by increasing the abundance of *Parabacteroides merdae*, which can eliminate branched-chain amino acids, known risk factors for atherosclerosis [155]. Additionally, *Ganoderma lucidum* water extract and its high-molecular-weight polysaccharides function as prebiotic agents, ameliorating HFD-induced gut microbial dysbiosis by reducing the *Firmicutes*/*Bacteroidetes* ratio and *Proteobacteria* abundance while elevating levels of beneficial bacteria such as *Parabacteroides* and *Roseburia* [156]. These bacteria exert an anti-atherogenic role through the production of their metabolite, butyrate [157]. Moreover, *Ginkgo biloba* extract ameliorates atherosclerosis by remodeling the composition and metabolic profiles of the gut microbiota and increasing circulating TUDCA and THDCA levels, which are potentially beneficial [158]. The herbal formula Qingxin-Jieyu Granule can restore gut microbial BA metabolism, subsequently inhibiting ileal FGF15 expression and enhancing hepatic cholesterol metabolism [159].

3.5. Enterohepatic aromatic amino acid metabolic pathway and atherosclerosis and nature medicine intervention

The gut microbiota collaborates with the host to convert dietary aromatic amino acids, including phenylalanine, tyrosine, and tryptophan, into endogenous proatherogenic metabolites [160]. PAGln derived from phenylalanine, *p*-cresol glucuronide, and *p*-cresol sulfate (PCS) from tyrosine, and indole glucuronide and indoxyl sulfate (IS) from tryptophan have demonstrated positive associations with major adverse cardiovascular event risks [160].

Microbial aromatic amino acids aminotransaminase (ArAT) can convert dietary tyrosine to 4-hydroxyphenylpyruvate (4-HPA) [161]. Phenylpyruvate oxidoreductase (PorA) then transforms 4-HPA into 4-hydroxyphenylacetate, which is subsequently converted to *p*-cresol by *p*-hydroxyphenylacetate decarboxylase (Hpd) [161]. The metabolic cascade from tyrosine to *p*-cresol involves collaboration among various microbes [162]. Following absorption, sulphotransferase (SULT)-1A1 in the intestinal mucosa and liver metabolizes the majority of *p*-cresol to PCS, while UDP-glucuronyltransferases convert the remaining portion to *p*-cresyl glucuronide [163]. Unconjugated *p*-cresol enhances LDL uptake by macrophages through micropinocytosis activation [164]. PCS exhibits proatherogenic effects by increasing inflammatory cytokine and adhesion molecule expression in endothelial cells and macrophages and by intensifying oxidative stress in endothelial cells, mononuclear cells, and vascular smooth muscle cells (VSMCs) [165, 166]. Furthermore, PCS promotes plaque vulnerability by stimulating aortic VSMC migration and proliferation and disrupting the balance between matrix metalloproteinases and tissue inhibitors of metalloproteinases [167].

Tryptophan can also be metabolized into indole derivatives through bacterial conversion. Specifically, microbes expressing tryptophanase (TnaA), such as *Alistipes putridinis*, *Butyricicoccus* sp. BIOML-A1, *B. thetaiotamicron*, *E. coli*, *Flavonifractor* sp. An52, and *Fusobacterium varium*, catalyze the conversion of tryptophan to indole [168]. Subsequently, indole is further transformed into IS by hepatic CYP2E1 and SULT-1A1 [163]. IS has been shown to induce vascular endothelial dysfunction, promote proinflammatory macrophage activation, increase oxidative stress, enhance vascular calcification, stimulate platelet hyperactivity, and inhibit cholesterol efflux by macrophages, thereby exacerbating atherosclerosis [169-171].

The gut microbiota can convert dietary phenylalanine to phenylacetic acid (PAA), which is subsequently transformed in the liver by hepatic phenylacetyltransferase and glycine *N*-phenylacetyltransferase to produce PAGln, a known risk factor for CVD events [172, 173]. Two distinct gut microbial metabolic pathways are responsible for PAA synthesis: the phenylpyruvate ferredoxin oxidoreductase (PPFOR) pathway and the phenylpyruvate decarboxylase (PPDC) pathway [172]. Specifically, *B. thetaiotaomicron* mediates the pathways including the PPFOR pathway, while *P. mirabilis* mediates the PPDC pathway to generate PAA [172]. Research indicates that PAGln can enhance platelet reactivity and thrombosis potential through adrenergic receptor signaling [8].

Certain natural medicines have demonstrated potential inhibitory effects on the production of proatherogenic aromatic amino acid metabolites. Sesamin, a potent inhibitor of TnaA in *E. coli*, effectively suppresses the lyase of tryptophan to form indole, thereby decreasing the substrate for IS formation [174]. Polyphenolic compounds, including EGCG, (−)-epicatechin gallate, and (−)-gallocatechin gallate, effectively inhibit PAA generation by *Porphyromonas gingivalis in vitro* [175], potentially leading to a subsequent reduction in PAGln. However, the regulatory effects of natural medicines on the host-microbe co-metabolism of aromatic amino acids have not been thoroughly elucidated. Future research may focus on discovering novel bioactive natural medicines that potently inhibit microbial or host metabolic enzymes mediating the production of proatherogenic aromatic amino acid metabolites.

4. Future perspectives

The host-microbe co-metabolic system generates diverse bioactive metabolites from natural medicines and small molecular endogenous metabolites, which are subsequently delivered into circulation to exert effects throughout the body. Currently, strategies to reconstruct the intestinal micro-ecological system and intervene in microbial metabolic pathways include fecal materials transplantation (FMT) and prebiotics/probiotics usage. These approaches have been widely applied in clinical practice, particularly in patients with inflammatory bowel disease (IBD) and *Clostridiodes difficile* infection (CDI) [176, 177]. However, colonization resistance from the local gut microbiota limits the persistent colonization of exogenous live microorganisms in the host [178]. This resistance impairs the therapeutic effects of probiotics or other live microorganisms and restricts the application of FMT or probiotics [178].

Natural medicines, characterized by their diverse bioactive constituents and multi-target mechanisms, offer unique therapeutic advantages in the management of chronic and multifactorial diseases such as atherosclerosis [179]. The host-microbe co-metabolism system catalyzes the ingredients of natural medicines to generate diverse secondary metabolites. Among these, those with enhanced bioavailability and demonstrated anti-ath-

erogenic properties hold promise as novel lead compounds for the development of anti-atherosclerotic therapies. Furthermore, the combined use of natural medicines and microbes that mediate the production of bioavailable and anti-atherogenic metabolites may enhance the efficacy of natural medicines by promoting the generation of bioactive metabolites, presenting a promising avenue for synbiotic development.

The host-microbe co-metabolism system presents a promising target for natural medicines in atherosclerosis treatment. Components of natural medicines, including polysaccharides, monosaccharides, glycosides, phenolic acids, and fibers, may function as nutrients that stimulate the growth of microbes with specific nutritional preferences, subsequently conferring advantages to these microbes in the gut [180]. For example, polysaccharides such as *β*-glucan, laminarin, and levan specifically support the growth of *B. ovatus*, *B. uniformis*, and *B. thetaiotaomicron*, respectively, while they cannot be utilized by some common human microbes belonging to *Firmicutes*, *Actinobacteria*, *Proteobacteria* and *Verrucomicrobia* [181]. The monosaccharide fucose is preferentially used by *E. coli* and *A. muciniphila*, while rhamnose and ribose specifically promote the proliferation of *Bacteroidetes*, *Collinsella aerofaciens*, and *E. coli*. In contrast, galactose and glucose can be utilized by almost all common human microbes [181]. Furthermore, numerous compounds derived from natural medicines demonstrate relatively specific anti-microbial effects, particularly against pathogens and opportunistic pathogens [182]. Additionally, some compounds from natural medicine, such as DMB and dhBBR, may act as potent inhibitors of metabolic enzymes mediating the formation of proatherogenic metabolites [63, 91]. Consequently, natural medicines may effectively regulate the host-microbe co-metabolic system by rebuilding the gut ecosystem and/or modulating microbial and host metabolic activity. However, the molecular targets of natural medicines on key proteins determining bacterial growth and microbial metabolic enzymes remain unclear, leading to a lack of guidelines for clinical intervention in the host-microbe metabolic system using natural medicines. Future research should focus on elucidating the precise molecular mechanisms underlying the regulatory effects of natural medicines on microbial growth and metabolic function.

While the specific roles of endogenous host-microbe co-metabolic metabolites, such as TMAO, in atherosclerosis have been established, and interventions targeting these metabolic pathways have shown significant improvements in animal models, there is limited clinical research demonstrating the efficacy of regulating these pathways to alleviate atherosclerosis in human subjects. Future clinical studies are necessary to confirm whether drugs targeting host-microbe co-metabolic pathways can provide tangible clinical benefits. Furthermore, the comprehensive mapping of connections between the host-microbe co-metabolic system and cardiovascular health remains incomplete. Additional research is required to identify crucial endogenous host-microbial-derived bioactive molecules and to elucidate their biological functions and underlying mechanisms.

Multi-omic analyses represent crucial approaches for identifying key functional microbes, genes, proteins, and metabolites in the host-microbe co-metabolism system that contribute to the anti-atherogenic efficacy of natural medicines. Untargeted and targeted metabolomics on animal models and population-based cohorts can identify and quantify potentially effective exogenous metabolites derived from natural medicines and differential endogenous host-microbe co-metabolites or cohort-specific molecules. Comprehensive microbiome analyses, including 16S rRNA sequencing, metagenomics, and transcriptomics, are employed to discover differential taxa and genes encoding functional metabolic enzymes. Culturomics is valuable for identifying and obtaining specific microbes responsible for alterations in metabolomic profiles. Metaproteomics contributes to the discovery of differential metabolic enzymes and functional proteins, which may serve as potential drug targets for atherosclerosis treatment. The validation of target genes or proteins responsible for differences in the metabolome and CVD phenotype relies on protein binding assays, catalytic function detection, and the construction of microbial mutant (knockout or knockdown) strains through gene editing [6].

In conclusion, the host-microbe co-metabolism system facilitates the production of bioactive microbial exogenous metabolites from natural medicines and provides numerous endogenous metabolic targets influencing the pathogenesis of atherosclerosis, establishing a promising new avenue for drug targets and drug-like molecules. Mechanistic research elucidating the interaction between natural medicines and the host-microbe co-metabolism system will provide the foundation for metabolic therapeutic strategies in the clinical treatment of CVDs.

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Supporting Information

Supporting information for this work can be obtained by contacting the corresponding authors *via* E-mail.

Declaration of competing interest

These authors have no conflict of interest to declare.

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