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Review article

Research development on gut microbiota and vulnerable atherosclerotic plaque

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ABSTRACT

The relationship between gut microbiota and its metabolites with cardiovascular disease (CVD) has been proven. In this review, we aim to conclude the potential mechanism of gut microbiota and its metabolites on inducing the formation of vulnerable atherosclerotic plaque, and to discuss the effect of intestinal metabolites, including trimethylamine-N-oxide (TMAO), lipopolysaccharide (LPS), phenylacetylglutamine (PAG), short-chain fatty acids (SCFAs) on plaque stability. Finally, we include the impact of gut microbiota and its metabolites on plaque stability, to propose a new therapeutic direction for coronary heart disease. Gut microbiota regulation intervenes the progress of arteriosclerosis, especially on coronary atherosclerosis, by avoiding or reducing the formation of vulnerable plaque, to lower the morbidity rate of myocardial infarction.

1. Introduction

While mortality from cardiovascular events is decreasing with improved medical treatment and hygiene, the burden of cardiovascular events is increasing globally. Today, cardiovascular diseases (CVDs) are the leading cause of human mortality worldwide [1]. According to statistics, the number of deaths due to cardiovascular disease (CVD) was 17.8 million in 2019 and is expected to increase to 23 million in 2030 [2,3]. The statistics also suggest that young people are increasingly suffering from cardiovascular disease, with one in three deaths occurring in the under-70s. The main causes are myocardial infarction and stroke [4]. The discovery of 16S rRNA gene amplicon sequencing and shotgun metagenomic sequencing deepens current understandings towards gut microbiota and its metabolites in diverse field of studies [5], as well as the cardiovascular field. Clinical and laboratory studies have confirmed the importance of gut microbiota and its metabolites in the occurrence and development of CVD [6–18].

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Research has been working on the ability of trimethylamine-N-oxide (TMAO) to accelerate the development of coronary heart disease by promoting coronary atherosclerosis. At the same time, recent studies have shown no correlation between intra-TMAO and atherosclerotic severity [6–11]. TMAO, with its potential to promote plaque formation and activate inflammatory responses, can enhance the vulnerability of coronary atherosclerotic plaques through platelet and inflammatory cell activation. Besides, lipopolysaccharide (LPS) [19–21], phenylacetylglutamine (PAG) [22], short-chain fatty acids (SCFAs) [23–26] are ascertained with direct or indirect influence towards arterial plaque stability.

Among all arterial plaques, vulnerable cardiovascular and cerebrovascular plaques result in the most severe harm to the body, acute coronary syndrome is even known as the "number one killer" of CVD [27]. Based on the fact that the composition and abundance of gut microbiota play an important role in the occurrence and development of CVD, which has been confirmed by previous studies, we hypothesized that gut microbiota and its metabolites may promote the rupture of coronary vulnerable plaques through the aggravation of inflammatory factor and response. Thus, in this paper, our discussion will highlight the influence of gut microbiome and its metabolites on the stabilization of coronary atherosclerotic plaque, and further explore possible pathways of gut microbiome regulation in impeding the progression of coronary atherosclerosis, stabilizing atherosclerotic plaque, and reducing myocardial infarction.

2. Coronary atherosclerosis and plaque susceptibility

Coronary atherosclerosis is the most worrisome and threatening subtype of all atherosclerosis in the human body, as it is considered a precursor to ischemic heart disease. Type 1 myocardial infarction is well known as the typical cause of acute coronary syndrome, which refers to ischemic-related spontaneous myocardial infarction due to primary coronary events (such as plaque erosion and/or rupture, fissuring, or dissection) [28]. Coronary plaque is highlighted as a prominent issue in Type 1 myocardial infarction. The studies concluded about 70 %–80 % of atherosclerotic thrombosis develops as a result of rupture of mild-to-moderate coronary plaque and secondary thrombosis formation, with a minority of thrombosis occurring as a result of plaque erosion, yet fibrous cap rupture remains the primary trigger for plaque rupture. Meanwhile, vulnerable plaque includes far more than plaque rupture, atherosclerosis with thrombosis-inducing tendency and rapid progression towards the formation of criminal plaques (stenosing plaques) should be categorised under plaque susceptibility, too. Naghavi et al. announced the criteria for susceptible plaque morphology, including active inflammatory response, thin fibrous caps with lipid-rich cores, vascular endothelial strippling with surface platelet aggregation, plaque fissures or lesion, and severe stenosis [29]. Its secondary criteria consist of cutaneous calcification, presence of shiny yellowish plaques, intra-plaque haemorrhage, and remodelling of positive vessels. Efficient identification of vulnerable coronary plaques enable atherosclerotic patients to anticipate future complications, such as acute coronary syndrome and cardiogenic shock [30]. Higher discriminative sensitivity and specificity play an important role in clinical practice, as in the future treatment of coronary heart diseases vulnerable plaque management may be required.

Researchers have proposed different perspectives on the causes and mechanisms of susceptible plaque formation. Alhough the underlying trigger remains unclear, the factors affecting the plaque stability of the patches were identified as: 1. Aging of smooth muscle cells (SMCs) and endothelial cells; 2. Inflammation stimulates local immunity response, activate macrophages, mast cells and T cells, results in the release of both collagen-inhibiting cytokines and proteases which digest fibrous cap in plaque [31]. It promotes the development of vulnerable plaque and acute coronary syndrome. 3. Vascular endothelial invasion. Although neutrophils are rarely found in plaques, it can still induce vascular endothelial erosion through neutrophil traps and proteases secretion in the cellular matrix [32]. Quillard et al. have assured that immune activation of vascular endothelial cells, neutrophils, and neutrophil traps might promote plaque erosion, resulting in thrombosis [33]. A recent study showed that oxidized lipids contributed to neutrophil trap formation and accelerated carotid artery thrombosis in mouse models, where oxidized lipids in the gut can trigger systemic inflammation and atherosclerosis [34,35]. It is thought that the simultaneous production of oxygen radicals or other free radicals during the formation of oxidized lipids attacks vascular endothelial cells. A series of findings can be concluded that the core event of plaque instability is excessive systemic or local inflammation of the blood vessel bed. In atherosclerotic susceptible group, certain factors or substances induce excessive systemic inflammation or local inflammation of the coronary bed, which gradually thins the fibrous cap by activating inflammatory cells that secrete inflammatory factors that attack collagen fibers and smooth muscle cells in atherosclerotic plaque. Moreover, inflammatory cell necrosis, especially in foam cells, increases the burden of lipids in the plaque, which progressively leads to the formation of susceptible plaques.

Lipid-rich and thin-fiber caps are known as the predictors of the rapid progression formatherosclerotic plaques to fragile plaques. The nature of plaques can be clinically evaluated by intravascular imaging (IVUS), intravascular optical imaging (OCT), 18F-FDG scintigraphy, and near-infrared spectroscopy (NIRS). However, high costs, bigger wound and low clinical popularity had required us to include some inflammatory factor indicators to predict the risk of acute vaso-occlusive cardiovascular events and identify high-risk plaques, such as C-reactive protein, interleukin-6, interleukin-18, secreted PLA2, matrix metalloproteinase, TMAO, etc. [36], These indicators have been associated with acute arterial embolic events and plaque rupture in previous studies, but large-scale clinical studies are needed to validate them. If these inflammatory indicators can be used clinically to identify high-risk plaques and predict adverse cardiovascular events in the future, it will not only reduce the incidence and mortality of patients with coronary heart disease complicated by acute coronary syndrome, but also reduce the cost and damage on patients with coronary heart disease.

Until now, the global treatment of coronary heart disease has mostly been based on lipid-lowering and clot-preventing prevention means, without any specific drug for the treatment of vulnerable plaque. Although lipid-lowering drugs, such as statins, can stabilize plaque to some extent by reducing the amount of lipid in the core of the plaque, they do little to prevent plaque from forming in low-lipid areas of the artery wall. Plaques in these sites tend to have a smaller lipid core load, and statins are also less effective at preventing vascular endothelial cell exfoliation and plaque erosion. This urges researchers to better understand the causes and mechanisms of

fragile plaque formation, and to propose more specific treatments to address and prevent acute coronary syndrome [33].

3. Composition of gut microorganisms and vulnerable plaques

The gut microbiome in adults is dominated by five phyla: Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, and Cerrucomicrobia. Together, Bacteroides and Firmicutes make up more than 90 percent of the bacterial species in the gut microbiome of healthy people [37]. As the dominant bacteria in the gut, these two genera are not susceptible to acute disturbances, and fluctuations in the numbers of Bacteroides and Firmicutes are often associated with certain pathological conditions in the human body [38]. Studies have explored an increase in the F/B ratio in certain patients with cardiovascular disease, i.e., an increase in the phylum of Firmicutes and a decrease in the phylum of Bacteroides [39–43]. Emoto et al. also demonstrated a significant increase in the abundance of Firmicutes in the composition of the gut microbiota in patients with coronary artery disease (CAD), while the abundance of Bacteroides decreased [18].

Early sequencing studies by Koren et al. suggest that gut microbes may be associated with atheroplaque, as DNA containing bacteria is found in arterial plaques in humans [39]. Some researchers have found some link between certain gut bacteria and atheroplaque, such as Mycobacterium spp. (a relatively new genus of bacteria that may have a protective effect against cardiovascular disease), Alitipes, Faecal Bacillus, and Bacteroides significantly reduced in atherosclerotic and inflammation-related diseases [44–50].

It has also been found that gut microbes may be linked to atheromatrotic plaque. A randomized, controlled, double-blind interventional exploratory study concluded that mucinous Akkermania promoted plasma LPS reduction in obese individuals with metabolic syndrome, which was shown to be associated with promoting atherosclerosis and the formation of vulnerable plaques [51]. Coincidentally, in another study, the provision of Ackermannia mucinous was able to reduce aortic sclerosis in mice with high cholesterol [52].

Although the relationship between gut microbiota and coronary susceptibility plaque has not been reported, there appears to be some relationship between the two. As early as seven years ago, Mitra et al. demonstrated that the gut microbiota of patients with coronary heart disease with stable plaques differed significantly from that of patients with coronary heart disease with fragile plaques [53]. Some researchers have observed that DNA from gut bacteria can activate macrophages and pass through Toll-like receptor 2 (TLR2) and Toll-like receptor 4 (TLR4) activates the body's immune system, resulting in impaired stability of plaques. In September 2022, a clinical study was conducted in Tokyo, Japan, collecting the feces of 55 patients with acute coronary syndrome (confirmed by

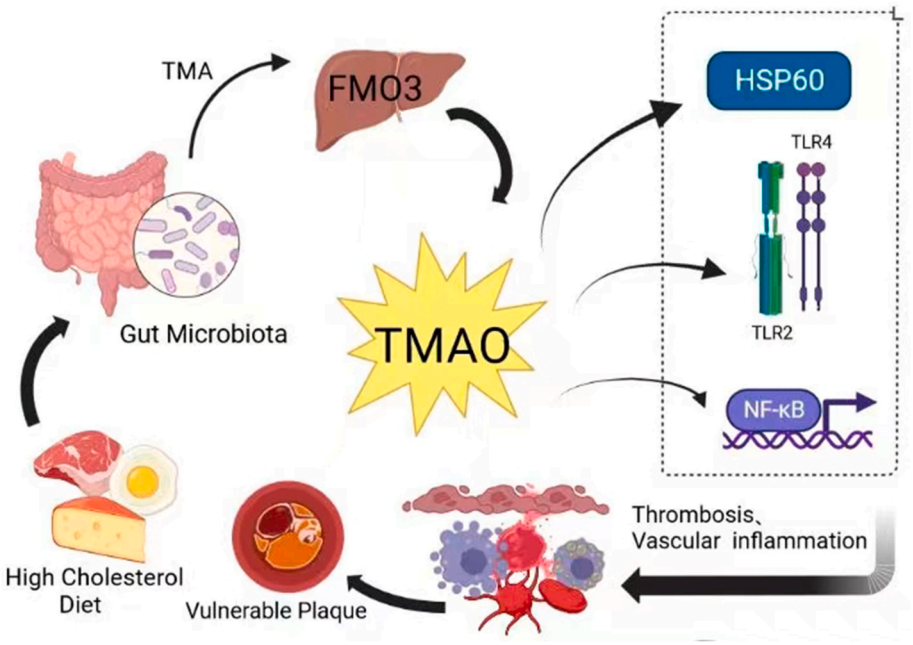

Fig. 1. TMAO increases the vulnerability of atherosclerotic plaques through the molecular mechanisms stated above.
The picture was created with BioRender.com.(biorender.com)
People ingest a large amounts of highly cholinergic substances in the daily diet. These substances are digested and absorbed in gut and decomposed into trimethylamine (TMA) by intestinal bacteria. TMA reaches to the liver through the portal vein and is oxidized into trimethylamine -N-oxide (TMAO) by the flavin monooxygenase 3 (FMO3) secreted by the liver. In the human body, TMAO can activate heat shock protein 60 (HSP60), and also involved in foam cell formation by binding to toll-like receptors, especially TLR2 and TLR4. Besides, TMAO can promote the expression of inflammatory factors such as IL-1, TNF-α, and C-reactive protein through MAPK and NF-κB signaling pathways, thus mediating the inflammatory response of vascular endothelium. In addition, TMAO can induce the activation of NLRP3, promote the expression of IL-18 and IL-1β and lead to vascular endothelial injury, resulting in impaired plaque stability.

coronary angiography), and after extraction, 16 sRNA sequencing was performed [48,54,55]. Intravascular ultrasound (IVUS) and intravascular optical imaging (OCT) to evaluate the nature of plaques found that 2 species of bacteria (Monas succinate and Bacillus) were associated with the presence of atherosclerosis in thin cap fibers, and studies also showed that these two bacteria were also associated with larger plaques in blood vessels [56].

4. Intestinal microorganisms and their metabolites promote the formation of vulnerable plaques

Scientists shared diverse views on how gut flora affects the stability of atherosclerotic plaque, leading to the formation of vulnerable plaques.

It has far been announced that the metabolites of gut microorganisms TMAO and LPS can cause vascular endothelial damage, resulting in impaired plaque stability and promote thrombosis [57,58]. In the mouse model of plaque instability (tandem-stenosis mouse), TMAO has been shown to come with inflammatory reactors, thrombosis, etc., which are the common reasons affecting plaque stability in atherosclerotic patients. As a major product of gut bacteria, especially gram-negative bacilli, LPS can impair plaque stability by promoting a systemic inflammatory response and activating inflammatory cells. However, short-chain fatty acids (SCFAs), metabolites of intestinal flora, stabilize coronary atherosclerotic plaques. These research outcomes certainly provide a new direction for the prevention and treatment of coronary heart disease and the reduction of acute myocardial infarction events.

4.1. TMAO increases the instability of atheromatoid plaques

About a decade ago, Koeth et al. revealed a potential causal relationship between the gut microbiome and coronary heart disease (CHD), with a focus on trimethylamine N-oxide (TMAO) [59]. TMAO is a metabolite secreted by the liver (mainly flavin monooxygenase3) that is metabolized by intestinal microorganisms after ingesting more dietary nutrients from the Western diet (e.g., lecithin, choline, carnitine), and finally secreted by the liver (mainly flavin monooxygenase3, FMO3) is the product formed by oxidation (Fig. 1). TMAO has been shown to predict the risk of coronary heart disease in multiple clinical cohorts and can accelerate atherosclerosis in animal models [60–63]. However, recent studies have shown no association between TMAO and the severity of atherosclerosis. In the Framingham heart study, it was confirmed that TMAO was not associated with the severity of atherosclerosis, i.e., as a measure of atherosclerosis in human subjects, namely the coronary artery calcification score (CAS). and carotid intimamedial thickness (cIMT) was not correlated with plasma TMAO levels [6]. There have also been reports that do not support an association between TMAO levels and the degree of atherosclerosis, suggesting that plasma TMAO levels are actually negatively or independently correlated with atherosclerosis and thrombosis [7–11].

Although the relationship between TMAO levels and the severity of atherosclerosis is controversial. However, a large number of studies have confirmed that TMAO formed by cleavage and oxidation of choline precursors (including choline, carnitine, lecithin, etc.) can promote thrombosis and aggravate the inflammatory response of blood vessels [64–70]. In a large community cohort study in the United States, researchers followed 5580 patients with atherosclerotic vascular disease (ASCVD) for 7 years. TMAO levels were found to be positively correlated with ASCVD recurrence, especially if renal function was impaired [71].The risk of recurrence of ASCVD is significantly increased because TMAO is metabolized via the kidneys. Liu et al. showed that atheroplaques in patients with coronary heart disease with higher TMAO levels exhibited more unstable features, and these plaques had thinner fibrous caps [72]. That is, the presence of thin cap fibrous atherosclerosis (TCFA) is higher in patients with CAD with high TMAO levels [72]. Meanwhile, in one experiment, researchers found that feeding ApoE mice on a high-fat diet ultimately increased the chance of intraplaque bleeding without altering the burden of atheroplaques or the composition of plaques [73]. This means that TMAO in the plasma can contribute to the rupture or bleeding of atherosclerotic plaques in the coronary arteries to some extent. In addition, TMAO can also induce macrophage-mediated increased lipid uptake, and oxidized LDL is a prerequisite for atherosclerosis and a risk factor for vulnerable plaque formation [60].

Zhu et al. found that TMAO can alter the conduction of calcium signaling in human platelets and improve platelet response to agonists (e.g., thrombin, ADP, collagen), as increased thrombosis can be observed in both whole blood and in vivo arterial injury models [64,74]. In subsequent human-level studies, healthy volunteers given oral choline showed higher TMAO levels, accompanied by increased platelet responsiveness and aggregation. This may indicate that once plaque rupture occurs in atherosclerotic patients on a high cholinergic diet, the rate and chance of thrombosis and infarction is faster and higher than in atherosclerotic patients on a low cholinergicgic diet. Higher TMAO levels were dose-dependent with increased platelet aggregation responsiveness, even in subjects with low doses of aspirin. This suggests that aspirin's antiplatelet effect may be diminished in subjects with elevated TMAO, suggesting that TMAO may be involved in the so-called "aspirin resistance" that occurs in the treatment of coronary heart disease. Therefore, patients with coronary heart disease who develop "aspirin resistance" may be able to improve by reducing the level of TMAO in plasma. In addition to affecting platelet function, TMAO can also induce the expression of tissue factor (TF) in endothelial cells, which is the initiator of exogenous coagulation in the human body and has the potential to promote TMAO thrombosis and inflammation, and this potential risk can be specifically blocked by TMA lyase [75,76].

TMAO's increased plaque instability may also involve a molecular mechanism, TMAO can activate heat shock protein 60 (HSP60), activation of which has been shown to be the initiating event of atherosclerosis. TMAO can be involved in the formation of foam cells via Toll-like receptors, specifically TLR2 and TLR4 [77–80]. TMAO can also promote IL-1, TNF- through the MAPK and NF-κB signaling pathways α, the expression of C-reactive protein (CRP), thereby mediating the inflammatory response of the vascular endothelium, and can induce NLRP3 activation, promoting expression of IL-18 and IL-1β results in vascular endothelial damage, resulting in impaired plaque stability (Fig. 1) [81–87].

TMAO levels can also be used to distinguish between plaque rupture and plaque erosion, which are completely different in patients with acute myocardial infarction. Given the differences in coronary response to coronary intervention (PCI) following plaque rupture and plaque erosion, and to avoid the potential risks of stent thrombosis, stent restenosis, and long-term dual antiplatelet therapy, treatment that focuses on antithrombotic drugs rather than coronary intervention is recommended in plaque erosion [88,89]. Therefore, it is important to distinguish plaque rupture from plaque erosion to determine individualized treatment strategies. Tan et al. concluded that the cut-off threshold for TMAO to distinguish plaque erosion and plaque rupture with maximum sensitivity and specificity is 1.95 μM [90].

While there is controversy about whether the level of TMAO is positively correlated with the degree of atherosclerosis, there is no doubt that TMAO increases the vulnerability of coronary atherosclerotic plaques by promoting platelet activation and thrombosis, as well as the activation of inflammatory cells and inflammatory factors.

4.2. *LPS promotes the formation of vulnerable plaques*

In recent years, several studies have suggested that there may be some relationship between LPS and vulnerable plaques [19, 91–94].

LPS is a cell wall component of Gram-negative bacilli. Because 90 % of the human gut microbiome is composed of Bacteroides and Firmicutes, when these Gram-negative bacilli die, endotoxin is released into the gut lumen. In some situations, the permeability of the intestinal barrier increases, and LPS can be translocated from the intestinal lumen to the bloodstream through the intestinal mucosa, which plays an effect on the development of atherosclerosis as blood circulates [91,92].

The composition of the intestinal barrier is inextricably linked to the gut microbe. In a healthy gut, a screen of the intestinal epithelium can prevent most LPS from activating the intestinal immune system, whereas unhealthy gut flora can cause increased intestinal permeability, the so-called "leaky gut," in which more LPS enters the blood circulation and triggers excessive inflammation of the vascular endothelium [95]. A large number of studies have shown that LPS can change the stability of plaques and make them more likely to rupture [19,96–101].

In one study, LPS levels were found to be much higher in people with carotid plaque than in controls without carotid plaque, suggesting that levels of LPS may be positively correlated with atherosclerosis [96]. In a latest study of LPS and vulnerable plaques by S Nooti et al., intracavitary injection of LPS at the site of injury caused by blocking carotid blood flow in hypercholesterolemic Yucatan microswine resulted in, compared with controls, local administration of LPS induces the formation of vulnerable plaques [19]. In addition, Carnevale et al. also found that macrophages, which are closely related to atherosclerotic formation and plaque stability, had larger volumes in LPS and TLR4-positive carotid plaque profiles than in LPS and TLR4-negative carotid plaque profiles. In this study,

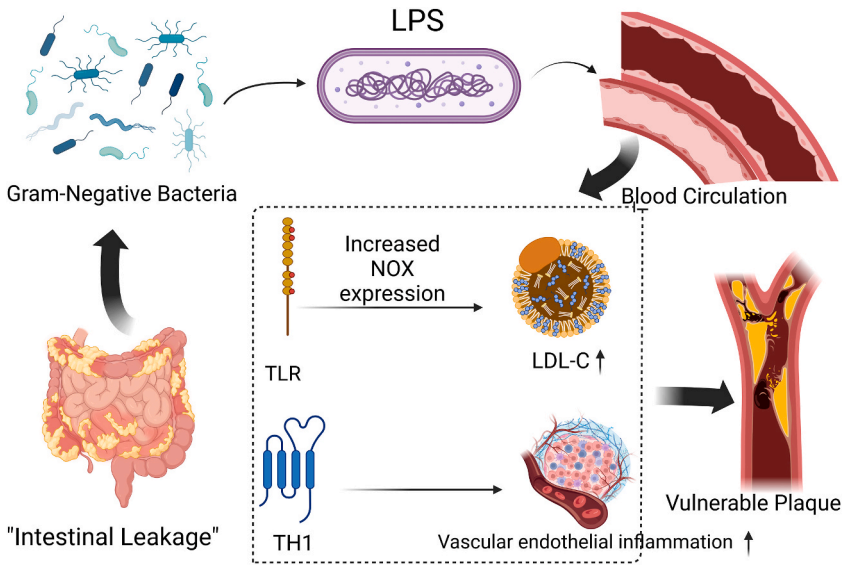

Fig. 2. LPS promotes the formation of vulnerable plaques through the molecular mechanisms stated above.
The picture was created with BioRender.com.(biorender.com)
The majority of bacteria in the human gut are Gram-negative bacillus whose cell walls contain a substance called endotoxins (LPS). When these bacteria die and lyse, there is a large amount of LPS present in the gut lumen, which is not pathogenic in healthy people with normal intestinal barriers. When the intestinal barrier is damaged, known as "intestinal leakage," entering the bloodstream activates cytokines and helper T cells that lead to chronic inflammation in the vascular endothelium, thus damaging the stability of atherosclerotic plaques and promoting the formation of vulnerable plaques. Molecular mechanisms may be involved: LPS binds to toll-like receptors to activate monocytes and promote increased of Nox2 expression; LPS promotes inflammation driven by Th1 cells and enhances systemic immune cell activity, leading to systemic and local vascular inflammation. "Inflammation" is the core of vulnerable plaque formation.

they also found that LPS, similar to TMAO, can activate monocytes through toll-like receptors, and that their intracellular signaling mechanism involves increased expression of Nox2 [96]. Nox2, It is one of the most important producers of oxygen radicals (Fig. 2). Oxygen radicals can lead to increased oxidative LDL formation downstream, and the atherosclerotic hypothesis currently recognized by major scholars is closely related to oxidative LDL, proving that LPS is a molecule that promotes atherosclerosis and may cause plaque rupture [97–100].

Yoshida et al. detected microbial species with different abundances between coronary heart disease and healthy controls by sequencing the 16SRNA gene, showing that the abundance of Bacteroides vulgatus, Bacteroides dorei, was significantly reduced, while increased concentrations of LPS, which in turn confirmed that inhibition of atherosclerotic formation is associated with decreased LPS production by gut microbes [101]. In this context, they discussed that a decrease in LPS production could lead to atherosclerosis remission, possibly by which low concentrations of LPS in plasma suppressed inflammation driven by Th1 cells and reduced systemic immune cell activity, the decrease of LPS concentration may be due to Bacteroidetes induction treatment [101].

As a result, LPS, as a pro-inflammatory substance produced by gutl bacteria, can cause chronic inflammation of the vascular endothelium by entering the bloodstream and activating cytokines and helper T cells, thereby causing impaired stability of atherosclerotic plaques and promoting the formation of vulnerable plaques.

4.3. PAG may promote plaque rupture

At the current level of research, TMAO and LPS appear to have become the mainstream in studies of gut flora and cardiovascular disease. Scientists have shed some light on the underlying mechanisms that drive the formation of vulnerable plaques. With the development of research, although the causal relationship between some products and atherosclerotic plaques has not been fully confirmed, some experimental studies have found that there may be a certain relationship between them and vulnerable plaque [22, 102–105].

Phenylacetyl glutamine (PAG) is a metabolite of phenylalanine that is produced by gut microbes. Recently, Nemet et al. found that PAG is associated with CVD because of its increased likelihood of thrombosis [102]. Multiple studies have shown that PAGln can interact with G protein-coupled receptors (GPCRs), including α and β adrenergic receptors (ADRs) [103]. Adrenergic receptors are essential in heart disease and platelet function. Liu et al. found that plasma PAG levels correlated with the severity of coronary atherosclerosis with the help of coronary CTA evaluation, and preliminarily concluded that plasma PAG levels correlated with the severity of coronary atherosclerosis in patients with suspected CAD (transcoronary CTA demonstrated an independent association between plasma PAGln levels and coronary atheroplaque load [22,104,105]. Currently, researchers do not have a thorough understanding and understanding of PAGln, so it still has great potential to be explored whether it can promote the development of atherosclerosis and plaque rupture, which is also a new direction for future research on the mechanisms of vulnerable plaque formation.

4.4. SCFAs can stabilize atherosclerotic plaques

Short-chain fatty acids (SCFAs), a carbon chain number <6, the main metabolite produced and fermented by the gut microbiota under dietary fiber and resistant starch diets. They are considered as an energy source for many gut microbes and can promote their growth. The major components of SCFAs are acetate (C2), propionate (C3) and butyrate (C4), which account for about 95 % of SCFAs.

Butyric acid was used as the primary study subject, and it was found that short-chain fatty acids can delay the progression of atherosclerosis and increase the stability, either directly or indirectly. It was found that after feeding ApoE mice a diet containing 1 % butyrate for ten weeks reduced aortic atherosclerosis by 50 %, with reduced macrophage penetration and increased collagen deposition resulting in a more stable fibrous cap of atheromatous plaque. Most of these phenomena are associated with a decrease in CD36 molecules in macrophages and endothelial cells, a decrease in pro-inflammatory cytokines, and a decrease in NFkB activation [23]. Several studies have shown that butyrate can also prevent the development of atherosclerosis by inhibiting the proliferation of vascular smooth muscle cells, and it is well known that vascular smooth muscle cell proliferation is an indispensable part of the pathogenesis of atherosclerosis [24–26]. In addition, Bartolomaeus et al. found that propionate application to ApoE mice reduced vascular inflammation and atheroplaque load, and lowered blood pressure levels [102]. A recent human and animal model study demonstrated that proprionate supplementation reduces atherosclerosis by lowering blood total cholesterol and LDL levels. In addition, SCFAs provide 2%–10 % of the total energy to the human body, which can provide "fuel" for intestinal mucosal cells, strengthen the intestinal barrier, improve "leaky gut", thereby reducing the amount caused by LPS Mediated chronic inflammation of the vascular endothelium [106].

The above studies have introduced a new approach that can inhibit the development of atherosclerosis and stabilize plaque in actual cardiovascular events by complementing SCFAs. However, with a limited number of human-level studies, more exploration of the function and mechanisms of SCFAs is still needed in the future.

4.5. Trans-ferulic acid is positively correlated with plaque stability

Trans-ferulic acid is a phenolic acid that is abundant in plant cell walls, and one of the active ingredients of traditional Chinese medicine such as ferulina, chuanqiong, angelica, and cohosh [107,108]. It is involved in the metabolism of the gut flora, and scientists have found that it is effective in deoxygenatng free radicals, inhibiting lipid peroxidation, and has anti-platelet aggregation and antithrombotic effects.

In the study of Qi Y et al., it was found that TongXinLuo (a traditional Chinese medicine) can improve the stability of atheroplaque

in model rabbits and reduce inflammation by regulating intestinal flora and intestinal metabolism, and the study confirmed that the mechanism of TongXinLuo's role may be TongXinLuo increased content of *trans*-ferulic acid, which works by inhibiting the NLRP3 pathway-mediated inflammatory pathway [109]. NLRP3 activates IL-1 β and TNF-α, activated IL-1 β can increase the expression of various pro-inflammatory factors, and excessive inflammatory response can impair plaque stability. Some clinical studies, such as CANTOS, have shown that inhibiting the expression of IL-1β is essential for reducing cardiovascular events [109]. Other scholars have proposed that IL-1β antagonists stabilize fragile plaques. Therefore, inhibition of the expression of NLRP3 inflammosome and related inflammatory factors in vascular plaques and macrophages is critical for stabilizing fragile plaques [110].

In Qi Y's study, model rabbits with unstable plaques were significantly reduced in the expression of caspase-1, IL-1 β, and IL-18 after TongXinLuo intervention, and TongXinLuo significantly altered the structure and function of the intestinal flora of these model rabbits, reversed the intestinal flora imbalance, increased the content of *trans*-ferulic acid, and exerted its anti-inflammatory effect by inhibiting the expression of NLRP3 inflammatory pathway members, thereby acting as a plaque stabilizing effect [109].

We need to be aware that many gut flora metabolites, including TMAO and PAG, are metabolized by the kidneys. Elevated levels of these metabolites are more pronounced in patients with impaired kidney function, who may be at higher risk for ASCVD [111]. Therefore, for patients with chronic kidney disease (CKD), it is beneficial to reduce the occurrence of ASCVD by delaying the decline of glomerular filtration rate (eGFR) and protecting renal function.

5. 4. reduce atherosclerosis and reduce the formation of vulnerable plaques by intestinal flora regulation

While the composition of the gut microbiome varies from individual to individual, scientists agree that a healthy gut microbiome generally shares two characteristics, diversity and balance of species. The dominance of gut microbiome diversity can be explained by the diversity of forest species. When forests are suffering from fires, forests with more species have a greater potential to return to their original state. The same is true for species balance, where forest systems tend to be disrupted if there are too many species or too few others, and striking a balance between species prevents one species from dominating.

As living standards has improved, many factors, such as overuse of antibiotics, diets lacking dietary fiber, sedentary lifestyles, and high levels of stress at school and work, have affected the diversity and balance of gut flora. As mentioned above, unhealthy intestinal flora can destroy the intestinal barrier, increase "leaky gut", lead to pro-inflammatory substances into the bloodstream, and promote the occurrence of cardiovascular adverse events. Gut microbial metabolites have also been associated with atherosclerosis and plaque rupture events. It is therefore not uncommon to hope that by regulating the gut microbiome, atherosclerosis may be delayed the formation of vulnerable plaques reduced.

5.1. Dietary structure adjustment

Diet has a large impact on the composition and abundance of the gut microbes. Jonsson et al.experimentally found that conventional ApoE mice were fed on a diet with low cholinergic levels compared to sterile ApoE mice fed by conventional feeding, Western diet (by adding choline supplementation). The lower atherosclerotic lesion size and plasma cholesterol levels in mice demonstrated that the composition of diet determines the composition of the gut microbiota [11]. A shift from a high-cholesterol, high-sugar diet to a low-cholesterol, fiber-rich diet can rapidly alter the gut microbiome, and the change can occur even within a day. A low-cholesterol, fiber-rich diet not only reduces TMAO and LDL-C levels from the intake route, but also reduces atherosclerosis and stabilizes plaque by regulating the composition of the gut flora, increasing the amount of SCFAs, and inhibiting inflammatory cell activity. At the same time, a high intake of plant-based, minimally processed foods and a small intake of animal-proven, highly processed foods, namely the Mediterranean diet, can also reduce cardiovascular mortality [112,113]. Scientists speculate that a high-intensity Mediterranean diet may reduce atheroplaque vulnerability through mechanisms that are anti-inflammatory, regulating changes in the microbiota and interactions between gene expression [114]. Therefore, by adjusting the dietary structure and gradually changing to a Mediterranean diet, atheroplaque can be stabilized at the root and benefit patients with coronary heart disease.

5.2. Endurance exercises

Several studies have shown that endurance exercise (i.e., aerobic exercise) can regulate the gut microbiota and play a physiological role in regulating the intestinal microbiota under hyperlipidemia and high cholesterol diets [115,116]. Endurance exercise can reduce the relative abundance of Vibrio desulfurizae, Parabacteroides, Bacteroides, Lactococcus, Peptococcaceae, Tyzerella, and Lachnospiraceae significatly in ApoE mice compared to those without endurance exercise, this result is consistent with the pathogenesis of atherosclerosis inhibition by exercise [117]. As a result, endurance exercise can effectively prevent intestinal dysbacteriosis due to hyperlipidemia, maintain the stability of the intestinal flora, delay the onset of atherosclerosis, and prevent plaque rupture. Moreover, endurance exercise can also increase the concentration of SCFAs in the feces of ApoE mice, suggesting that endurance exercise can significantly increase the level of intestinal microbial metabolites [117]. Supplementation with SCFAs has been shown to prevent the development of atherosclerosis and stabilize plaque in the event of an actual cardiovascular accident [118].

5.3. Targeted metabolite inhibitors

In recent research work, a small molecule inhibitor targeting the gut microbiota, a choline structural analogue: 1,3 dimethylbutanol (DMB), has been developed. DMB is an inhibitor of microbial choline lyase. A series of studies have shown that DMB can reduce TMAO

production in vivo without affecting microorganisms [119]. DMB reduces the formation of atherosclerotic plaques by inhibiting dietary-dependent choline conversion to TMA, reducing the formation of macrophages and foam cells. At the same time, according to some scientists, DMB can also prevent hypertension in offspring in adulthood, restoring RAS balance and AHR signaling antagonism. Hypertension is an extremely important traditional risk factor for coronary heart disease. The arteries are hit by high-pressure blood flow for a long time, causing damage to the vascular endothelium, and reducing the occurrence of hypertension can delay the progression of atherosclerosis to some extent [120].

The result is a cutC gene inhibitor 10,000 times stronger than DMB - fluoromethylcholine (FMC), which can target aggregation in the gut microbiota. Reducing systemic exposure in the host, FMC can act as a stabilizing atheroplaque by targeting the production of TMAO produced by cholinergic nutritional precursors that have adverse effects on the heart without affecting other precursors of gut microbial metabolism [67].

Although these inhibitors have not been tested in clinical studies, given their targeting, the authors believe they have theoretical benefits, which of course need to be validated in follow-up clinical studies based at the human level.

5.4. Fecal transplantation

In recent years, some scientists have discovered that fecal transplantation (FMT) can be a potential treatment for some non-digestive diseases, such as coronary heart disease, diabetes, metabolic syndrome, etc. In a study of FMT in obese patients, it was found that obese patients infused with donor gut microbes could enhance sensitivity to insulin, a traditional risk factor for atherosclerosis [121,122]. In some mouse model experiments, FMT has achieved some benefits in coronary heart disease, such as increasing the production of SCFAs and reducing heart inflammation [123,124]. However, there have also been clinical trials that have shown that while FMT can effectively alter the composition of the gut microbiome, it has not been shown to have an actual effect on cardiovascular disease, such as FMT does not lowering TMAO levels. Moreover, the safety of FMT is unclear. First, it destroys the recipient's existing gut flora, whether the bacteria are beneficial or harmful. In addition, FMT may transfer endotoxins or infectious agents to the recipient's circulatory system, resulting in infection. Therefore, the use of fecal transplantation for cardiovascular treatment requires more laboratory experiments and clinical experiments to explore the efficacy of its application and possible adverse events [125,126].

5.5. Supplement probiotics/prebiotics

Obviously, the intestinal flora is also "good and bad", the human intestine has no lack of bifidobacteria, Przewalskii bacteria, Rocheskiia and other beneficial bacteria, increasing such probiotics can obviously bring benefits to cardiovascular diseases, such as by reducing the number of Firmicuti or increasing the number of Bacteroides, reducing the F/B ratio may reduce the risk of coronary heart disease, increase Przewalskii Bacterium, Roche bacteria can increase the content of butyrate (one of SCFAs) to enhance the intestinal mucosa screen, increase bifidobacteria can enhance intestinal immunity, etc [18]. There is no shortage of such probiotic supplements on the market, and it is believed that when the relationship between gut flora and atherosclerosis becomes clearer in the future, the use of certain probiotic supplements will benefit atherosclerosis patients.

Prebiotics are defined as food ingredients that promote the metabolism and proliferation of beneficial bacteria in the body and improve the health of the body [127]. The gut microbiota is dynamically changing and responds to human diet and lifestyle, and without adjusting the composition and abundance of the gut microbiota, the metabolism of the gut microbiota can be improved by supplementing the components of prebiotics [128]. It can also avoid some of the side effects that directly affect the composition of the body's gut microbiome, such as diarrhea associated with gut bacteria [128].

Therefore, it is feasible to modulate the human gut microbiome by supplementing it with probiotics/prebiotics to delay atherosclerosis and prevent coronary heart disease, which may become a new direction in the primary prevention of coronary heart disease.

5.6. Genetic engineering

The enzymes mentioned above that promote TMAO production in the gut microbiome are encoded by the cutC gene, and researchers have genetically engineered MecutC mutants to confirm the function of the gut microbiome cutC gene cluster [67]. TMAO has the potential to promote thrombosis and plaque rupture in the body, blocking or reducing the formation of TMAO may reduce adverse cardiovascular events [64,74]. Clinicians may be able to stabilize vulnerable plaques from a genetic engineering perspective, a new therapeutic direction in the cardiovascular field. Of course, many of the problems faced by genetic engineering, including safety issues, ethical issues, and socia issues, need to be addressed urgently, but this does not prevent genetic engineering from providing new ideas for the prevention and treatment of adverse cardiovascular events in humans.

5.7. Antibiotics

While antibiotics can be effective in destroying bacteria in the gut, this effect is not targeted, killing or inhibiting the bacteria associated with atherosclerosis development and also destroying the protective gut bacteria. And systemic side effects caused by antibiotics, including gastrointestinal reactions, drug-resistant bacterial infections, and superinfections, cannot be ignored. Several studies havetargeted plaque clearance and have also intervened with antibiotic therapy as a secondary preventive measure, but the results have not reduced the incidence of cardiovascular events. As a result, there is currently no strong evidence that antibiotics can be

used to prevent cardiovascular events. Perhaps it can be considered after more clinical trials and weighing the pros and cons [129,130].

5.8. Some other preventive measures (Pu'erh tea and glycouric oxocholic acid)

In addition to the interventions that the above scientists have studied more, Xiao et al. found that ApoE mice that consumed Pu'erh tea could alleviate the progression of chronic inflammation by reducing NF-κB activation and promoting apoptosis of macrophages, thereby reducing the formation of early fat streaks and the volume of late fibroadipose plaques [131]. Huang et al. have noted that Pu-erh tea alters the gut microbiota in mice and humans, primarily inhibiting microorganisms associated with biliary salt hydrolase (BSH) activity [132]. Intracellular BSH microorganisms may be a novel therapeutic direction for anti-hypercholesterolemia and anti-hyperlipidemia. Because the most researched substances of Pu'erh tea are tea polyphenols, the author guesses that Pu'erh tea may play a lipid-lowering role through tea polyphenols, which may mean that not only Pu'erh tea, but also green tea or black tea on the market may play a role in regulating intestinal flora and hyperlipidemia [133].

In addition, Huang et al. have demonstrated that Glycoureoxycholic Acid (GUDCA) can reduce the area of atheroca plaque and improve plaque stability [132]. Hill C et al. found that mice fed with GUDCA could partially recover from dysbiotic gut microbiota, suggesting that GUDCA may work by regulating the intestinal flora, which could be a potential way to prevent atherosclerosis and complications [134].

6. Conclusion

This paper summarizes recent advances in gut microorganisms, metabolites, and atherosclerosis, and analyzes the mechanisms by which TMAO exacerbates the vulnerability of arterial plaque, which can promote plaque rupture by promoting thrombosis and activating inflammatory responses. In addition, the potential mechanisms of LPS and PAG that may contribute to plaque rupture are discussed. However, not all metabolites of gut microorganisms are detrimental to the heart, and some, such as SCFAs and *trans*-ferulic acid, can delay atherosclerosis and stabilize plaque. While current levels of research do not suggest that specific bacteria promote the formation of vulnerable plaques, there is no doubt that the dysregulation of the gut flora is closely related to the vulnerability of plaques. In the process of summarizing the relationship between intestinal microbe, metabolites and arterial plaque vulnerability, many interventions with the treatment direction of regulating intestinal flora will naturally emerge, including dietary adjustment, endurance exercise, targeted metabolite inhibitors, fecal transplantation, genetic engineering, and prebiotic supplementation/Probiotics, etc., the latest research also shows that Pu'erh tea and glycouric oxygen cholic acid can play a role in regulating the intestinal flora. In the past ten years, many researchers have made unremitting efforts to expose the relationship between gut microbiome and cardiovascular disease, which is of great significance for the prevention and treatment of coronary heart disease, and also provides a basis for future research on the treatment of delayed atherosclerosis and stable vulnerable plaques.

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Data availability statement

No data was used for the research described in the article.

Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because [This paper is a review].
Informed consent was not required for this study because [This paper is a review].

CRediT authorship contribution statement

Shujiao Zheng: Writing – original draft, Conceptualization. **Zuheng Liu:** Writing – review & editing, Resources. **Haiyue Liu:** Supervision. **Jie Ying Lim:** Writing – review & editing. **Dolly Wong Hui Li:** Writing – review & editing. **Shaofeng Zhang:** Resources. **Fang Luo:** Supervision. **Xiujing Wang:** Validation. **Changqing Sun:** Supervision. **Rong Tang:** Validation. **Wuyang Zheng:** Supervision. **Qiang Xie:** Writing – review & editing, Funding acquisition.

Declaration of competing interest

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