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The two-way interaction of tea polyphenols with gut microbiota and their effect on atherosclerosis

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ABSTRACT

Atherosclerosis is the main cause of most cardiovascular diseases. Given the increasing morbidity and mortality in these diseases in recent years, it is important to investigate novel treatments and preventive strategies for atherosclerosis. Tea polyphenols (TPs), natural substances derived from tea, have a variety of functions such as anti-inflammation and antioxidants. Numerous studies have closely linked TPs and gut microbiota to the development of atherosclerosis. By retrieving EBSCO, PubMed, Wiley InterScience, and Google Scholar databases, our review selects relevant literature from 1998 to 2023 to summarize the mutual interaction between TPs and gut microbiota and their protective effect on atherosclerosis. Specifically, TPs influence the diversity and abundance of gut microbiota, which may relieve atherosclerosis by promoting the colonization of beneficial microbiota and inhibiting the colonization of harmful microbiota. Simultaneously, the involvement of gut microbiota in TPs metabolism not only increases the bioavailability of TPs but also generates active metabolites, like gallic acid and protocatechuic acid, which have been found to alleviate atherosclerosis. Furthermore, the review outlines recent advances and challenges in the utilization of gut microbes and TPs for the prevention and treatment of atherosclerosis. In general, the review reflects the great potential of the interaction between TPs and gut microbes in the prevention and treatment of atherosclerosis.

1. Introduction

Atherosclerosis is a progressive chronic disease characterized by plaques in the inner layer of the artery wall, mainly caused by abnormal lipid metabolism and inflammatory responses[1]. Many pathways contribute to the progression of atherosclerosis, including platelet activation, foam cell formation, cytokine and chemokine release, oxidation of low-density lipoprotein cholesterol (LDL-C) and triacylglycerol, macrophage polarization, oxidative stress, and inflammatory responses[2]. Platelet activation accelerates thrombosis and the formation of arterial plaques, while the accumulation of foam cells aggravates plaque formation and instability[3]. Concurrently, the release of cytokines and chemokines orchestrates the inflammatory response, thereby promoting endothelial cell damage and leukocyte infiltration, subsequently accelerating plaque advancement[4]. Oxidative stress and the oxidation of LDL-C and triacylglycerols further endorse plaque progression, rendering plaques more susceptible to rupture[5]. Additionally, macrophage polarization significantly influences plaque stability, with M1-type macrophages exhibiting pro-inflammatory properties and

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M2-type macrophages exhibiting anti-inflammatory properties[6]. Lipoxygenase oxidation intensifies atherosclerosis by generating proinflammatory metabolites[7]. The conversion of trimethylamine (TMA) into trimethylamine N-oxide (TAMO) in the liver amplifies the accumulation of LDL-C in the vascular wall, expediting atherosclerosis and worsening plaque formation and instability through heightened inflammation and oxidative stress, hence escalating the risk of cardiovascular disease[8]. These pathways interact to promote the formation and instability of plaques. Eventually, the plaques lead to the narrowing and blockage of blood vessels in several organs, with the most common being coronary heart disease[9]. Additionally, the rupture or blockage of plaques can result in serious complications such as stroke and heart attack[10].

As the standard of living rises, atherosclerosis is becoming a global disease[11]. In addition to lifestyle modifications, current treatments for atherosclerosis include medications and surgery. However, medications have side effects. For example, aspirin may cause gastrointestinal bleeding and the stenting procedure has a certain probability of triggering bleeding and infection[12-13]. Consequently, research into new atherosclerosis prevention and treatment strategies is warranted. Notably, many studies have shown a two-way interaction between tea polyphenols (TPs) and the gut microbiota, which may alleviate atherosclerosis[12-15].

As a compound rich in antioxidants and potential health benefits, TPs naturally exist in various teas, such as green tea and black tea, which are known as the healthiest and most popular functional drinks in the world. The highest consumption of tea in the world is black tea, followed by green tea, oolong tea, etc.[16-17]. However, the content of TPs in green tea is higher, because black tea is fully fermented, while green tea is not fermented[16]. TPs is a general term for more than 30 polyphenols in tea[17]. In recent years, TPs have garnered considerable attention due to their beneficial effects on human health. Numerous studies have shown that TPs play an important role in atherosclerosis at the molecular level[15]. Through several processes, such as lowering oxidative stress, blocking the synthesis of inflammatory mediators, and controlling blood cholesterol levels, TPs can directly reduce atherosclerosis. Importantly, TPs also indirectly promote cardiovascular health by influencing gut microflora and enhancing the production of beneficial metabolites[18].

The human gut microbiota is an extremely diverse and complex ecosystem containing nearly 1 000 species, divided into four main phyla, including Actinobacteria (3%), Proteobacteria (8%), Bacteroidetes (23%), and Firmicutes (64%)[19]. The genomic enrichment of the gut microbiota contributes to their remarkable functional diversity[19-20]. Many gut microbiotas are endowed with enzymes that endow them with strong metabolic capabilities[20]. The metabolites of the gut microbiota participate in the regulation of many physiological processes; for example, short-chain fatty acids (SCFAs) are involved in maintaining the integrity of the blood-brain barrier[21]. Hence, sustaining the homeostasis of the gut microbiota ecosystem is necessary for several physiological processes in the host, including food catabolism, vitamin synthesis, and regulation of the immune system[22]. Conversely, the imbalance of gut microbiota homeostasis may trigger metabolic, inflammatory, and immune dysregulation in the host, which can lead to diseases such as inflammatory bowel disease and atherosclerosis[23]. Therefore, it has been a hot topic to investigate the mechanisms of gut microbiota in the development of various diseases and its application in disease treatment in the research field[24]. In particular, the latest research has focused on the mechanisms by which the gut microbiota alleviates atherosclerosis through its participation in the metabolism of TPs. The research showed that the metabolism of TPs by gut microbiota could improve the bioavailability of TPs. Furthermore, the active metabolites of TPs derived from gut microbiota, such as protocatechuic acid (PCA) could alleviate atherosclerosis[12-14].

In general, studies have demonstrated that the two-way interaction between gut microbiota and TPs may alleviate atherosclerosis. Here, we summarize the synergistic effects of TPs and gut microbiota on atherosclerosis. Moreover, we emphasize recent advances and challenges in the applications of TPs and gut microbiota as strategies for the prevention and treatment of atherosclerosis, shedding light on further research.

2. Metabolic fate of TPs by the gut microbiota and role of active metabolites in atherosclerosis

Although TPs are proven to be highly beneficial in alleviating atherosclerosis, their low absorption *in vivo* restricts bioavailability due to their strong gut first-pass effect and rapid metabolism[26-27]. Studies demonstrated that 90%−95% of undigested and unabsorbed TPs enter the large intestine and are converted to active small-molecule chemicals by gut microbiota, implying the vital role of the gut microbiota in determining the intestinal fate of TPs[25]. In this section, we outline the metabolic fate of TPs by gut microbiota in detail (Table 1), and highlight the potential effects of gut microbiota-derived metabolites of TPs on atherosclerosis.

2.1 TPs

TPs mainly consist of catechins, flavonoids, phenolic acids, and anthocyanins. Catechins make up about 60%−80% of TPs and have a basic chemical structure of C6-C3-C6, with a backbone structure of 2-phenyl benzopyran[26]. According to different types of carbon rings, they are broadly classified into ester-type catechins and non-ester-type catechins. The former mainly includes epicatechin gallate (ECG) and epigallocatechin-3-gallate (EGCG), and the latter boasts epicatechin (EC) and epigallocatechin (EGC). Catechins, especially EGCG, are the main components responsible for the health benefits of TPs[27].

2.2 The gut microbiota metabolizes TPs

The degradation pathways of catechins by gut microbiota were investigated in detail and roughly divided into 3 processes. First, the gallate moiety of some ester-type catechins can be hydrolyzed and removed by gut microbiota. For example, EGCG is metabolized to EGC, whereas ECG is metabolized to EC[35-36]. Multiple gut microbiotas, such as *Enterobacter aerogenes*, *Raoultella planticola*, *Klebsiella pneumoniae* subsp. *pneumonia*, and *Bifidobacterium longum* subsp. were found to be able to hydrolyze (−)-EGCG into (−)-EGC[34]. Bifidobacteria was revealed to play a crucial role in the biotransformation of (−)-ECG in human fecal suspensions *in vitro*[37]. In addition, theaflavins (TF) are catechins that undergo oxidative polymerization during the processing of fermented tea varieties, especially black tea. Studies have verified

Table 1
Metabolites of TPs from gut microbiota.

TPs/Material		Metabolites	Conversion rate, detected concentration of metabolites	Study model and intake routine of TPs	Responsible gut microbiotas	Reference
Catechins	(−)-EGCG	(−)-EGC; GA	Unknown conversion rate of EGCG degradation, more than 90% EGC degradation	Mice, 1 mL 10 mg/mL EGCG solution fermentated by bacteria of feces (*in vitro*), 200 mg/mL EGC solution injection (*in vivo*)	*E. aerogenes*; *R. planticola*; *K. pneumoniae* susp. *pneumoniae*; *B. longum* subsp. *infantis*	[27-28, 30-34,40]
	(−)-ECG	(−)-EC	(−)-EC	Human, 100 mg/mL ECG solution incubated with human intestinal bacteria (*in vitro*)	*Bifidobacterium* strain	[37]
	TFDG	TF; GA; pyrogallol	Unknown conversion rate of TFDG degradation	Mice and human, mice by gavage of 200 mg/kg TFDG (*in vivo*); human by 10 mg/mL TFDG fermentated by human bacteria of feces (*in vitro*)	*L. plantarum* 299v; *B. subtilis*	[33]
	(−)-EC	5-(3′,4′-Dihydroxyphenyl)-*γ*-valerolactone	45.0%−49.2% 3,4-diHPV accounted of total metabolites	Human, 100 μmol/L EC fermentated by human bacteria of feces (*in vitro*)	Gut microbiota	[39]
	(−)-EGC	1-(3,4,5-Trihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol; 5-(3,4,5-trihydroxyphenyl)-*γ*-valerolactone	0.6 mmol/L metabolite 1, after 22 h by *A. equolifaciens*; 0.6 mmol/L metabolite 1, after 50 h by *Eggerthella lenta*; 100% degradation rate of metabolite 1, after 24 h by *Flavonifractor plautii*	Human, broth containing 0.45 mmol/L EC fermentated by human bacteria of feces (*in vitro*)	*A. equolifaciens*; *E. lenta*; *Eggerthella* sp.; *F. plautii*	[40]
	(−)-EC	3-(3′,4′-Dihydroxyphenyl)propionic acid; PCA	91% EC recovery rate after 2 h	Human, broth containing 0.45 mmol/L EC fermentated by human bacteria of feces (*in vitro*)	Gut microbiota	[43]
	(−)-EC	5-(3,4-Dihydroxyphenyl)-*γ*-valerolactone; 4-hydroxy-5-(3,4-dihydroxyphenyl)valeric acid	60% EC recovery rate after 8 h	Human, broth containing 100 μmol/L EC fermentated by human bacteria of feces (*in vitro*)	*E. lenta* rk3; *F. plautii* ak2 (formerly *Clostridium orbiscindens*); *F. plautii* DSM 6740	[86]

that *Lactobacillus plantarum* 299v and *Bacillus subtilis* can metabolize theaflavin-3,3′-gallate (TFDG) extensively to TF, gallic acid (GA), and pyrogallol[33]. Second, the C ring of the catechin moiety undergoes cleavage and then produces diphenyl propyl 2 alcohol intermediates, which convert to corresponding phenyl valeric acids (PVAs) and phenyl-*γ*-valerolactones (PVLs) by a-ring fission under specific microbiota. Numerous studies have proved that the C-ring of ECs is cleaved by the gut microbiota and finally transformed into 5-(3′,4′-dihydroxy phenyl)-*γ*-valerolactone with strong antioxidant activity[38-40]. However, EGC is converted to intermediate 1-(3,4,5-trihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl) propan-2-ol by *Adlercreutzia equolifaciens* through C-ring cleavage, which is finally transformed to 5-(3′,4′,5′-trihydroxyphenyl)-*γ*-valerolactone[38,41]. Intriguingly, one of the major PVL-M4 in EGCG can be dehydroxylated at the C-5′ position and converted to the metabolite PVL-M6 of the ECG, demonstrating a correlation between the *in vivo* conversion of ECG and EGCG[42]. Third, the gut microbiota decomposes the PVLs/PVAs into smaller phenolic acids by the constant depletion of carbon atoms through *β*- or *α*-oxidation[43]. Studies have shown that the gut microbiota metabolizes 5-(3′,4′-dihydroxyphenyl)valeric acid to the intermediate product 3-(3′,4′-Dihydroxyphenyl) propionic acid by *β*-oxidation. Then the intermediate continues to be converted to PCA or 2-(3′,4′-dihydroxyphenyl)acetic acid through *β*-oxidation or *α*-oxidation[44]. Ultimately, these microbial metabolites enter the enterohepatic circulation and systemic circulation to perform a wide range of physiological functions in various target organs.

2.3 TP-derived active metabolites by the gut microbiota in atherosclerosis

In recent years, gut microbiota-derived active metabolites of TPs, especially GA, PCA, benzoic acid derivatives, and PVLs, have attracted extensive attention in the early pathological process of atherosclerosis. The mechanism by which these active metabolites alleviate atherosclerosis is shown in Fig. 1. Firstly, GA is the main metabolite of (−)-EGCG, TFDG, and DP metabolized by the gut microbiota[12-13]. The latest study showed that GA improved atherosclerosis and vascular senescence in $ApoE^{-/-}$ mice, which corresponded to indices of lower inflammation, such as interleukin-3 (IL-3), IL-10, IL-12, and tumor necrosis factor-alpha (TNF-α)[45]. Moreover, tea extract was shown to significantly reduce atherosclerotic lesions in the aortic sinus and aorta of $ApoE^{-/-}$ mice, which may be attributed to the inhibition of the oxidation of leukocyte-type 12-lipoxygenase and LDL in macrophages by ethyl gallate, a formal condensation of GA with ethanol[46]. Secondly, PCA, a typical metabolite of cyanidin in anthocyanins, also has promising atheroprotective effects at physiological concentrations[47]. On the one hand, PCA hinders the progression of atherosclerosis by inhibiting M1 and promoting M2 macrophage polarization[48]. On the other hand, it can promote Mer tyrosine kinase (MERTk) up-regulation and inhibit mitogen-activated kinase 3/1 (MAPK3/1) in macrophages, leading to the normalization of arterial inflammation and therefore alleviating atherosclerosis. Furthermore, PCA plays an anti-atherosclerotic role by regulating the miRNA-10b-ABCA1/ABCG1 cascade to accelerate cholesterol

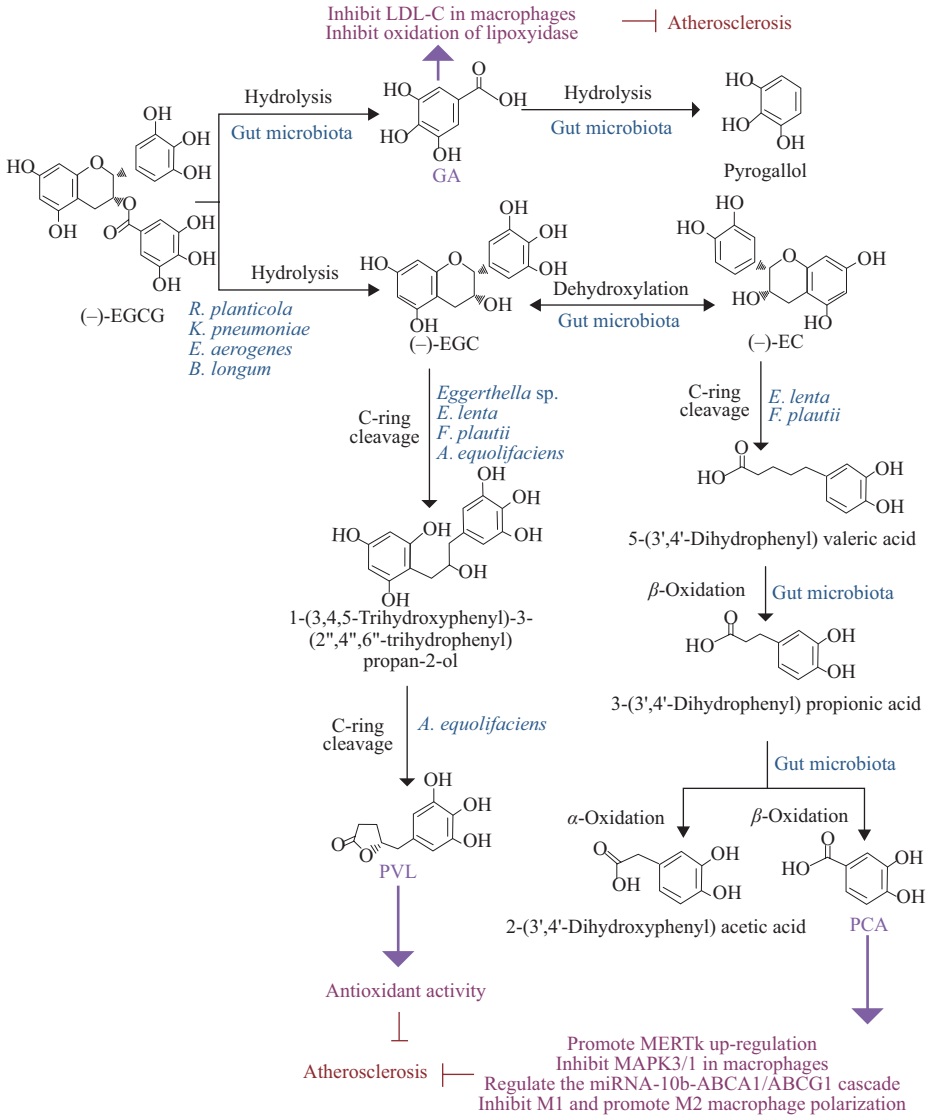

Fig. 1 Mechanism underlying the gut microbiota-derived active metabolites of TPs in alleviating atherosclerosis.

efflux in macrophages[49]. Thirdly, benzoic acids are closely related to atherosclerotic issues, with typical examples including 3-monohydroxybenzoic acid, 3,5-dihydroxybenzoic acid (α-melphanic acid), 2,3-dihydroxybenzoic acid (pyrophosphate), 2,5-dihydroxybenzoic acid (gentiolic acid) and PCA[48]. The first 2 compounds may trigger hydroxycarboxylic acid receptors, reduce lipolysis in adipocytes, and improve blood lipids[50]. The latter 3 chemicals are capable of activating the nuclear factor erythroid 2-related factor (NRF2) signaling pathway and increasing the production of antioxidant enzymes, hence reducing systemic inflammation that may contribute to atherosclerosis. Fourthly, 5-(3,4-dihydroxyphenyl)-γ-valerolactone, a type of PVL, is the main metabolite of (−)-EC, (−)-ECG, and proanthocyanidins, which has strong antioxidant activity. Studies confirmed that it can prevent Tamm-Horsfall protein-1 (THP-1) monocyte-endothelial cell adhesion by down-regulating the expression of vascular cell adhesion molecule-1 and monocyte chemoattractant protein-1[51].

Gut microbiota-derived active metabolites of TPs hold diverse biological activities, including primary, secondary, and tertiary metabolites. They participate in the progression of atherosclerosis not only directly by modulating blood lipids and macrophages but also indirectly by influencing vascular endothelial cells[15]. Current studies have demonstrated that some TPs metabolites of the intestinal microbiota play crucial roles in alleviating atherosclerosis; however, most substrates, such as pyrogallol, PVAs, 3,4-dihydroxyphenylacetic acid (DOPAC), cinnamic acid, vanillic acid, and syringic acid, are still not well studied. Consequently, more studies are required to understand how various microbiota metabolize TPs and how active metabolites influence atherosclerosis and cardiovascular health.

3. Modification of gut microbiota by TPs and role of TP-modified gut microbiota in atherosclerosis

Many studies have linked TPs with gut microbiota in the past decade, revealing the synergy between TPs and gut microbiota[52]. In addition to the metabolic effects of the gut microbiota on TPs, TPs may be involved in regulating the abundance of the gut microbiota

and play an important role in alleviating atherosclerosis[53]. In this section, we summarize how TPs regulate the abundance of gut microbiota, thereby alleviating atherosclerosis.

3.1 TPs regulate the abundance of gut microbiota

TPs have been reported to possess the capability to regulate the abundance of gut microbiota. As for the mechanism involved, it is hypothesized that TPs resulted in an improvement of the intestinal redox state, which is vital for maintaining the homeostasis of the gut microbiota[54].

Based on their effects on atherosclerosis, gut microbiotas can be categorized as beneficial, harmful, or neutral[55]. Research has shown that TPs may exert alleviating effects on atherosclerosis by promoting the colonization of beneficial microbiota[53]. For instance, in an *in vitro* experiment, 0.1 mmol/L of EGCG (extracted from green tea) was added to a human fecal suspension from healthy donors for incubation. Microbiome analysis showed that, compared to the blank samples, the abundance of beneficial microbiota, including Christensenellaceae, *Bacteroides vulgatus* and *Bifidobacterium*, significantly increased in the samples treated with EGCG for 72 h[56]. Moreover, it was reported that 28 days of TPs (extracted from green tea) supplementation at a dosage of 90 mg/kg promoted the relative abundance of atherosclerosis-relieving gut microbiota, *Blautia* and *Roseburia*, in the Kunming mouse model[57].

In addition to increasing the abundance of beneficial gut microbiota, TPs may also decrease the abundance of pro-atherogenic gut microbiota. As the most abundant substance in TPs, EGCG extracted from green tea was found to reduce the abundance of Desulfovibrionaceae in C57BL/6J mice, which is considered one of the pro-atherogenic gut microbiota[58-60]. Notably, the modulatory effects of TPs on the gut microbiota may be gender-dependent[61]. It is hypothesized that this difference may be attributable to the different compositions of the gut microbiota in males and females at baseline[61]. In conclusion, more research is needed regarding the regulatory effects of TPs on the gut microbiota

3.2 TPs modulated gut microbiota and microbiota-derived metabolites in atherosclerosis

A growing number of studies indicate that TPs may relieve atherosclerosis by modulating the abundance of the gut microbiota[53]. Mechanistically, it was suggested that TP-modulated gut microbiota can suppress the synthesis of atherogenic substances like TMAO and lipopolysaccharide (LPS) while concurrently enhancing the production of atherosclerosis-relieving substances such as bile acids and SCFAs[62-63]. Additionally, TPs may also relieve the progression of atherosclerosis by decreasing the Firmicutes/Bacteroidetes (F/B) ratio. This section summarizes the TP-regulated gut microbiota and microbiota-derived metabolites in atherosclerosis (Table 2).

TP-modulated gut microbiota may relieve atherosclerosis by suppressing the synthesis of TMAO. It was discovered that TPs facilitated the colonization of *Akkermansia muciniphila* and Bifidobacteria, which are able to lower the level of TMAO[17,56,64-65]. An epidemiological study has revealed that elevated serum TMAO levels are positively linked to increased carotid intima-media thickness, which is widely considered an indicator of cardiovascular events[66]. Gut microbiotas can metabolize TMA from ingested food to TMAO, which promotes atherosclerosis by activating platelets and promoting foam cell formation[67]. The process by which TMAO promotes foam cell formation involves multiple mechanisms, for instance, upregulation of macrophage scavenger receptors

Table 2
TP-modulated gut microbiota and their roles in atherosclerosis.

Altered gut microbiotas	Change of abundance	Main functions	Study model and intervation duration	Source of TPs, dose and intake routes of TPs	Reference
A. muciniphila	Increase	Produce SCFAs; decrease TMAO	C57BL/6J mice, 8 weeks	Green tea, 0.32%, high-fat diet	[58]
Bifidobacteria	Increase	Decrease TMAO	Human faecal suspension, 72 h	Green tea, 0.1 mmol/L, human fecal suspension	[56]
			C57BL/6 *ApoE*$^{-/-}$ mice, 16 weeks	Green tea, 0.4, 0.8, and 0.6 g/L, drinking water	[17]
B. vulgatus	Increase	Decrease LPS	Human faecal suspension, 72 h	Green tea, 0.1 mmol/L, human fecal suspension	[56]
Parabacteroides	Increase	Produce bile acids; and precursor of SCFAs	Sprague-Dawley mice, 12 weeks	Green tea, 400 mg/kg, high-fat diet	[73]
Desulfovibrionaceae	Decrease	Decrease bile acids synthesis	C57BL/6J mice, 8 weeks	Green tea, 0.32%, high-fat diet	[58]
Bacillus	Decrease	Decrease bile acids synthesis	C57BL/6J mice, 8 weeks	Pu-erh tea, 1.5 mg/mL, chow diet and high-fat diet	[63]
Lactococcus	Decrease	Decrease bile acids synthesis	C57BL/6J mice, 8 weeks	Pu-erh tea, 1.5 mg/mL, chow diet and high-fat diet	[63]
Streptococcus	Decrease	Decrease bile acids synthesis	C57BL/6J mice, 8 weeks	Pu-erh tea, 1.5 mg/mL, chow diet and high-fat diet	[63]
Christensenellaceae	Increase	Produce SCFAs	Human faecal suspension, 72 h	Green tea, 0.1 mmol/L, human fecal suspension	[56]
Blautia	Increase	Produce SCFAs	Kunming mice, 28 days	Green tea, 360 mg/kg, gavage	[57]
Roseburia	Increase	Produce SCFAs	Kunming mice, 28 days	Green tea, 360 mg/kg, gavage	[57]
Ruminiclostridium	Increase	Produce SCFAs	C57BL/6J mice, 28 weeks	Green, oolong, and black tea, 1%, high-fat-diet	[77]
Acetatifactor	Increase	Produce SCFAs	C57BL/6J mice, 28 weeks	Green, oolong, and black tea, 1%, high-fat-diet	[77]
Prevotellaceae	Increase	Produce SCFAs	C57BL/6J mice, 28 weeks	Black tea and green tea, 0.25%, low-fat/high-sucrose diet	[62]
Pseudobutyrivibrio	Increase	Produce SCFAs	C57BL/6J mice, 28 weeks	Black tea and green tea, 0.25%, low-fat/high-sucrose diet	[62]
F/B ratio	Decrease	Increase carotid intima-media thickness	C57BL/6J mice, 8 weeks	Green tea, 0.02% and 0.005%, high-fat diet	[80]
			Human colonic model, short-term	Green tea, 0.67 mg/mL, gifu anaerobic medium	[81]

and restriction of macrophage reverse cholesterol transport[68]. Interestingly, there is a crosstalk between TMAO and bile acid synthesis. It was found that increased TMAO levels indirectly inhibit hepatic bile acid synthesis through activation of the nuclear receptor farnesoid X receptor (FXR), ultimately resulting in an enhancement in the total aortic plaque area[8].

In addition, TP-modulated gut microbiota may exert protective effects against atherosclerosis *via* diminishing LPS production. It has been observed that TP intervention promotes the abundance of *B. vulgatus*, which could reduce LPS levels[69]. As an immunogenic component of the outer membrane of the Gram-negative microbiota, LPS has been reported to be higher in the serum of atherosclerotic patients compared with healthy individuals[70]. Mechanistically, LPS can be recognized by Toll-like receptor-4 (TLR-4), which contributes to atherosclerosis-associated inflammation by promoting macrophages and monocytes to produce cytokines and chemokines[71].

Moreover, TP-modulated gut microbiota may alleviate atherosclerosis by promoting the production of secondary bile acid, which is considered one of the relieving factors of atherosclerosis. Primary bile acids are synthesized from cholesterol in the liver and then converted into secondary bile acids in the ileum by the gut microbiota. The secondary bile acids exert atherosclerosis-relieving effects by reducing the production of triacylglycerol and the proportion of LDL-C[72]. TPs supplementation in Sprague-Dawley mice was found to increase the proportion of *Parabacteroides*[73]. Available evidence suggests that *Parabacteroides* play a dominant role in alleviating hyperlipidemia by producing secondary bile acids[74]. In addition to promoting the abundance of bile acid-producing microbiota, TPs also decrease the abundance of microbiota that can reduce bile acid levels. In the C57BL/6J mouse model, EGCG was found to reduce the abundance of Desulfovibrionaceae, which inhibits the conversion of cholesterol into bile acids by impacting the expression of the key enzyme cholesterol 7 alpha-hydroxylas (CYP7A1) for bile acid synthesis[58-60]. Furthermore, theabrownins, water-soluble polyphenol polymers formed during the fermentation of Pu-erh tea, were observed to mitigate hypercholesterolemia by reducing the colonies of *Bacillus*, *Lactococcus*, and *Streptococcus* at the genus level, which are associated with bile salt hydrolase activity[63,75]. This microbial modification leads to elevated ileal conjugated bile acid levels, which in turn inhibit the intestinal farnesoid FXR-fibroblast growth factor 5 (FGF5) signaling pathway. As a result, hepatic production of bile acids increases, accompanied by a decrease in hepatic cholesterol levels and lipogenesis[63]. Additionally, a higher prevalence of *Streptococcus* species in the gut has been associated with an increased risk of atherosclerotic plaques in the small coronary arteries[76].

Many experiments have observed that TPs may alleviate atherosclerosis by up-regulating the abundances of SCFA-producers, including *A. muciniphila*, Christensenellaceae, *Roseburia*, *Blautia*, *Parabacteroides*, Prevotellaceae, *Pseudotinaviruses*, *Ruminiclostridium* and *Acetatifactor*[56-58,62,77]. SCFAs are saturated aliphatic organic acids produced by the gut microbiota, mainly including acetate, propionate, and butyrate[78]. Considered a potential therapeutic target for atherosclerosis, SCFAs decrease the production of pro-inflammatory cytokines like IL-1 and IL-8 by inhibiting the nuclear factor-κB (NF-κB) pathway. Furthermore, SCFAs yield anti-atherosclerotic effects by reducing oxidative stress. For example, butyrate was reported to relieve oxidative stress in vascular smooth muscle cells by upregulating glutathione-S-transferase (GST) levels[79].

Besides the above effects, TPs may also attenuate atherosclerosis by affecting the F/B ratio. It was reported that TPs interventions decreased the F/B ratio in both the C57BL/6J mouse model and the human colon model[80-81]. A higher F/B ratio has always been considered an indicator of obesity. Notably, researchers have discovered that a higher F/B ratio is associated with an increase in carotid intima-media thickness, which is a marker of subclinical atherosclerosis[82]. Here, we summarized the TP-regulated gut microbiota in atherosclerosis *via* the microbiota-derived metabolites (Fig. 2).

4. Perspectives and obstacles of TPs and gut microbiota in the prevention and treatment of atherosclerosis

4.1 Perspectives of TPs and gut microbiota in the prevention and treatment of atherosclerosis

Recently, the two-way interaction between gut microbiota and specific TPs, as well as its role in relieving atherosclerosis, has attracted extensive attention and research. For example, an *in vitro* study verifies the bidirectional interaction between catechins and gut microbiota, as well as its role in atherosclerosis. The genera *Adlercreutzia*, *Eggerthella*, and *Lactiplantibacillus plantarum* may promote the C-ring cleavage of catechins[83]. Attractively, *L. plantarum* also converts catechins into GAs which are important in alleviating atherosclerosis. In return, these derivatives of catechins enhance the antioxidant activity of gut bacteria in the culture medium, thereby affecting bacterial growth. This was demonstrated by the fact that green TPs and their derivative compounds inhibit the phylum Actinobacteria, Bacteroides, and Firmicutes, except the genus *Lactobacillus*[84].

4.2 The obstacles of TPs and gut microbiota in the prevention and treatment of atherosclerosis

The two-way interaction between TPs and gut microbiota is an extremely complex network, and there are still many unknown contents to be explored. In particular, more studies are needed on the mechanism of the bidirectional regulatory relationship between TPs and gut microbiota, as well as its role in atherosclerosis. The specific role of derivatives produced by gut microbiota metabolizing TPs in atherosclerosis still needs to be explored in depth. Examining how the metabolites affect atherosclerosis by interacting with host receptors and modulating signaling pathways will help us understand the impact of gut microbiota on cardiovascular health more comprehensively.

5. Conclusion

TPs are a class of polyphenolic compounds extracted from tea that have remarkable antioxidant, anti-aging, and lipid-lowering properties[84]. Numerous studies have demonstrated that there is an interaction between TPs and gut microbiota, which is vital to the formation and progression of atherosclerosis (Fig. 3). Specifically, TPs could modify the abundance of gut microbiota, while gut microbiota in turn could metabolize TPs and produce metabolites with higher absorption rates and activity[85]. Thus, the findings have

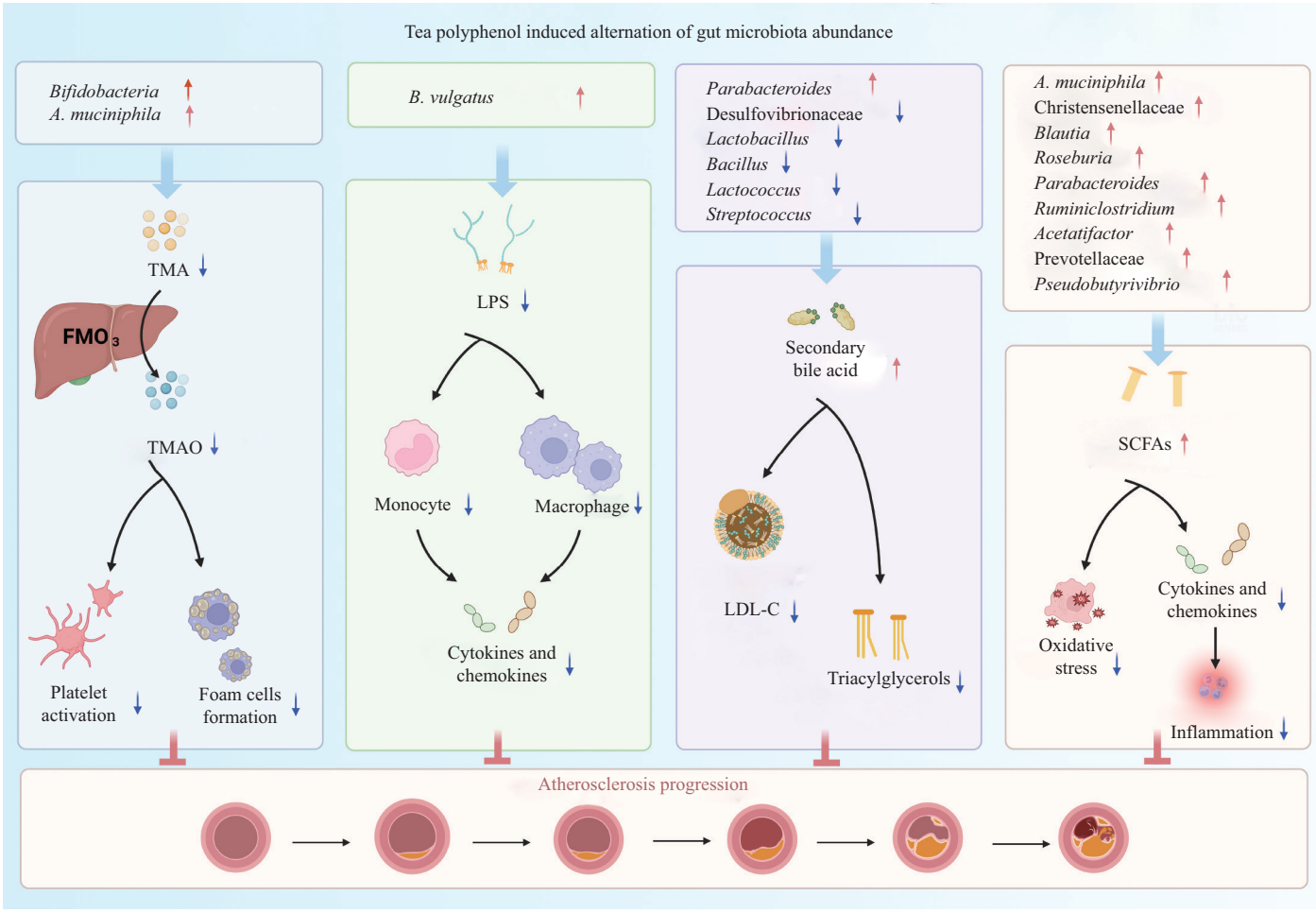

Fig. 2 Mechanism underlying the TP-modulated gut microbiota in alleviating atherosclerosis.

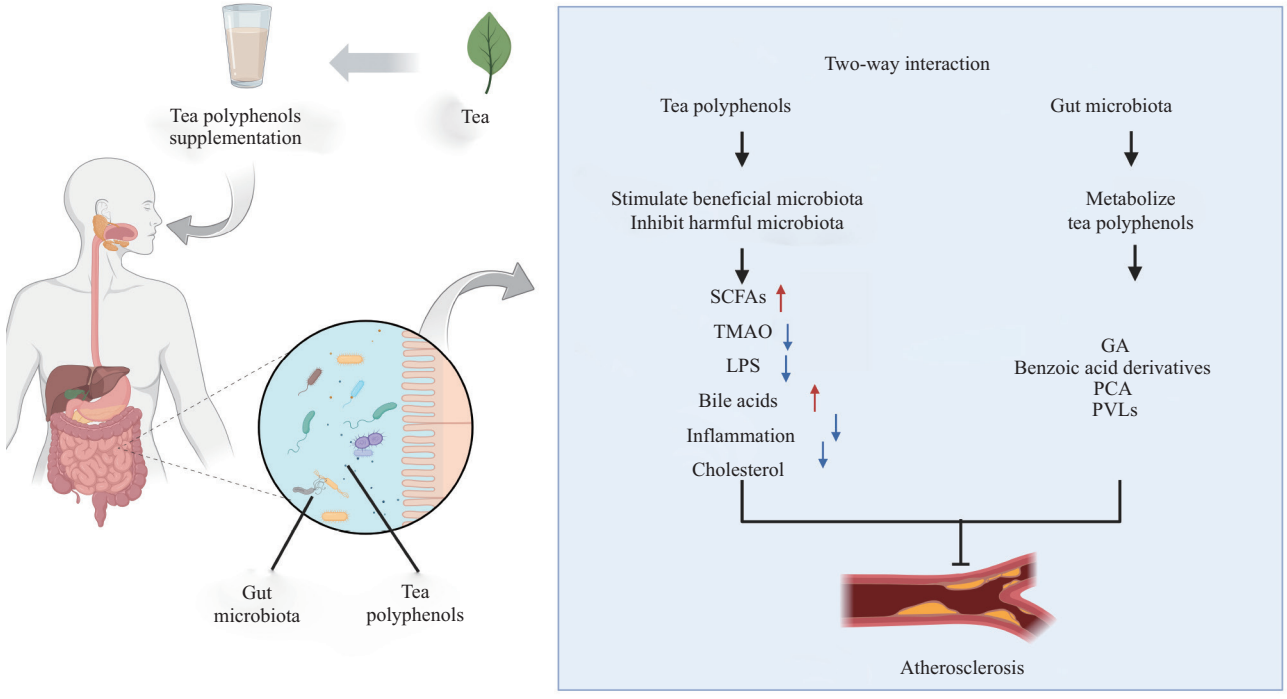

Fig. 3 Two-way interaction between TPs and gut microbiota in relieving the development of atherosclerosis.

suggested that both TPs and the gut microbiota have potential roles in preventing and treating atherosclerosis. Future studies should focus on the following directions: first, the role of some TPs metabolites in the gut microbiota, such as DOPAC, in atherosclerosis still needs to be investigated. Secondly, most of the current studies on the two-way interaction between TPs and gut microbiota are conducted in animal models or *in vitro*, and further clinical studies are still needed. Finally, regarding the applications of TPs and gut microbiota in the prevention and treatment of atherosclerosis, future studies need to address the safe dose of TPs .

Conflicts of interest

The authors declare no conflict of interest.

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