Impact of Gut Microbiota on Atherosclerosis and Potential Therapeutic Strategies

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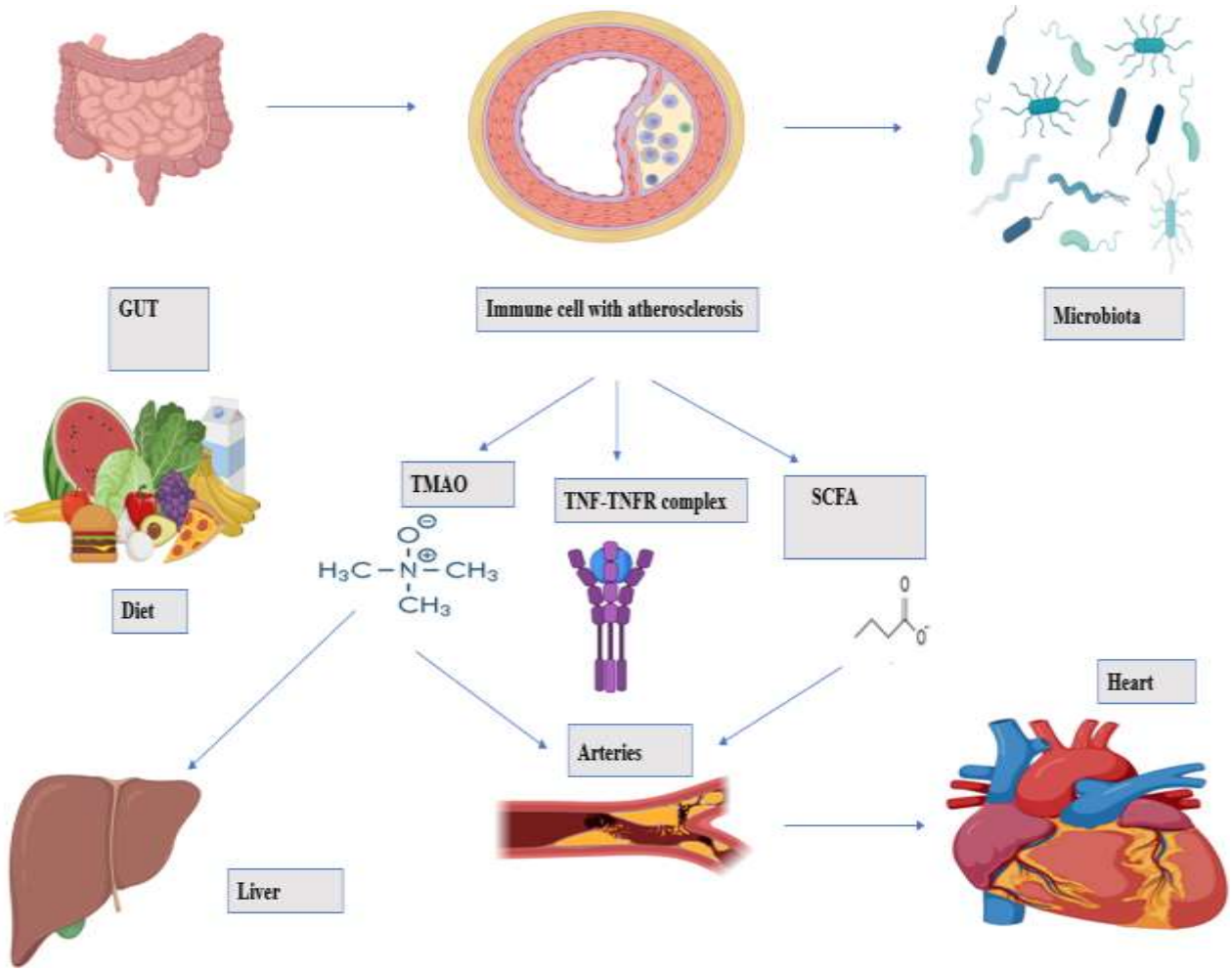
ABSTRACT:

Cardiovascular diseases (CVDs), primarily driven by atherosclerosis, remain the leading cause of mortality globally. Emerging studies have shown a significant contribution of the gut microbiome in both onset and progression of atherosclerosis by influencing host metabolism, immune response, and inflammation. This review describes the intricate relationship between gut microbiota and atherosclerosis with a focus on microbial composition, associated metabolites and the effect of these on cardiovascular health. Certain microbials, for example, Prevotella and Collinsella, are under lab studies as the causes of the development of an atherosclerotic plaque. Various other metabolites, such as SCFAs, TMAO, and bile acids, have to play a key role in modulating disease progression. Furthermore, the interaction between the gut and oral microbiome highlights an additional pathway influencing atherosclerosis development.Given the growing understanding of microbiota-associated mechanisms in atherosclerosis, novel therapeutic strategies targeting the gut microbiome, including probiotics, prebiotics, faecal microbiota transplantation (FMT), and microbial enzyme inhibitors, are gaining attention. This review also discusses potential microbiome-based interventions for mitigating atherosclerosis risk and improving cardiovascular outcomes. While microbiota-targeted therapies hold promise, further research is needed to address challenges related to inter-individual microbial variability, long-term efficacy, and clinical applicability. Future advancements in microbiome science and precision medicine could revolutionize cardiovascular disease prevention and treatment by leveraging the gut microbiota's role in atherosclerosis.

Key word- Atherosclerosis, Gut microbiome, Microbial metabolites, Trimethylamine-N-oxide (TMAO), Probiotics, Prebiotics, Microbiota-targeted therapy.

GRAPHICAL ABSTRACT: -



1. INTRODUCTION: -

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, responsible for approximately 17.8 million of the total 54 million deaths each year. This means that nearly one-third of all deaths globally are due to heart-related conditions, such as heart attacks, strokes, and heart failure. In the atherosclerosis, recognized as the main cause of cardiovascular diseases (CVDs), is becoming more common worldwide [1].Among the primary risk factors related to the development of atherosclerosis are diabetes mellitus, obesity, smoking, hypertension, and high lipid levels (such as triglycerides and cholesterol) [2]. At present years, the problem of atherosclerosis is increasing, and the mechanism of disease development is not clear. This calls for an urgent need for deeper research into the fundamental biological mechanisms of atherosclerosis to improve prevention and treatment strategies. The technological developments have greatly helped us to better grasp the role of microbes in the human body. A probable link between microbes and atherosclerosis have been studied by using 16S rRNA sequencing and high-throughput sequencing [3]. Moreover, many studies showed that microbiota-derived metabolites are involved in the regulation of atherosclerosis progression. Among these, short-chain fatty acids (SCFAs) have been pivotal for plaque destabilization and cardiovascular disease (CVD) risk [4] [5]. Both lipopolysaccharide and trimethylamine-N-oxide have the ability to cause vascular endothelium disorders and

plaque uncertainty, which in turn makes thrombosis easier to occur; however, the fundamental mechanism behind this effect is unidentified yet [6] [7]. According of numerous investigations, there is a connection between the microbiota in the gut and atherosclerosis, which suggests that there is a connection between cardiovascular diseases and the characteristics of their plaque [8] [9]. , This review investigates the impact that gut microbiota plays in the stability of plaque as well as the potential association that exists between bacterial flora and conditions that cause atherosclerosis. The potential therapeutic approaches that target intestinal bacteria in order to prevent the progression of atherosclerosis.

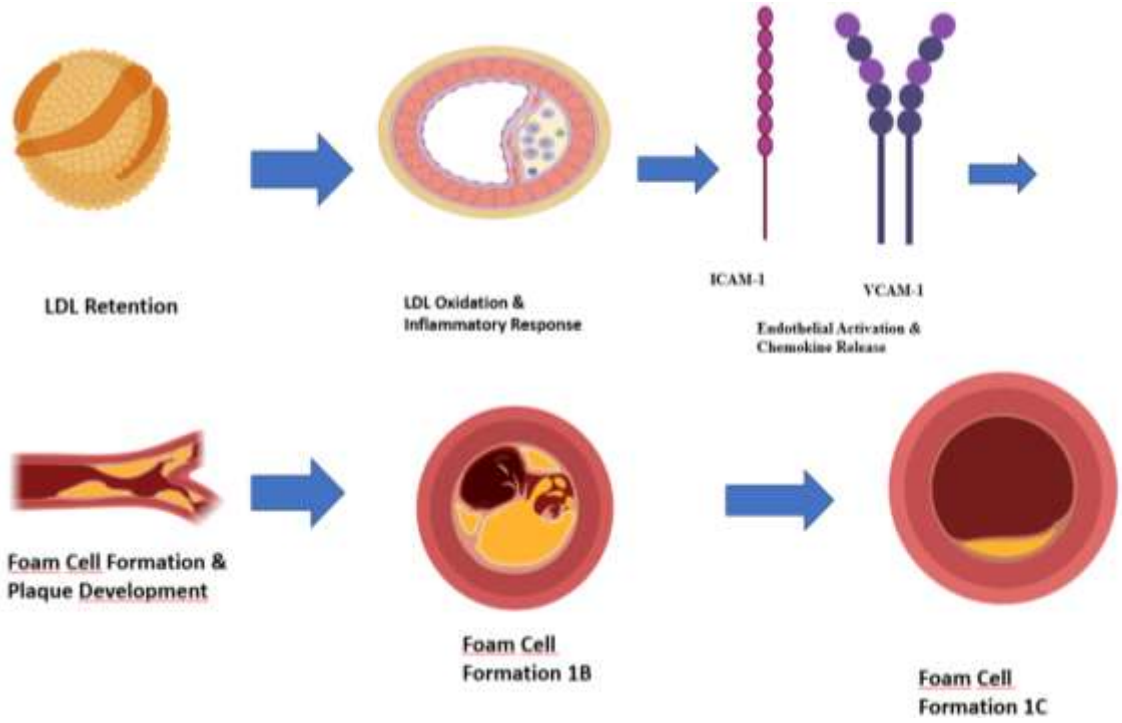
2. PATHOPHYSIOLOGY OF ATHEROSCLEROSIS: -

A diverse range of activities involves the extraction and fermentation of unexplained substances, the synthesis of certain metabolites as well as vitamins and production of short chain fatty acid. Thereby allowing the gut microbiota to be involved in many metabolic pathways and regulate the gut barrier [10] [11]. Consequently, any remarked change of GM can impose astonishing alterations to a host of various biological activities which might damage the epithelial barrier and leading to the bacterial translocation with subsequent assimilation of their by-products [12].

This leads to immune response inflammation and alterations in a variety of metabolic pathways. Atherosclerosis originates with endothelial dysfunction together with low-density lipoprotein (LDL) retention with alteration in the intima [13] [14]. Altered LDLs along with further atherogenic factors develop the activation of ECs, thereby resulting in monocyte recruitment. Altered LDLs are vigorously captured and up taken by macrophages or dendritic cells and VSMC leading to foam cell formation [15] [16].

During the span of fibrous plaque formation, atheroma plaques undergo a transition from fatty streak to intimal growth. This transition is characterised by the existence of a necrotic core that is free of cells and rich in lipids [17]. In the early stages, atherosclerosis, and LDLs develop in the subendothelial region, where they become modified. The changes to LDLs cause VSMCs to release chemotactic agents like CCL2 and CCL5, which help bring in monocytes [18]. Furthermore, oxidised and slightly changed in LDLs may recruit leukocytes, cause endothelial damage, and trigger pro-inflammatory reactions in macrophages and endothelial cells. Additionally, marginally altered LDLs may bind to TLR2 and Class 4 PRRs, triggering the NF-kB-dependent release of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α [19]. CD36-mediated oxLDL uptake activates the NLRP3 inflammasome, resulting in the robust secretion of the inflammatory cytokine IL-1β36 [20]. Cholesterol crystals activate NLRP3 inflammasome through lysosomal damage [21]. Several studies have shown that activated ECs overexpress cell adhesion molecules, such as VCAM-1, ICAM-1, PECAM-1, E-selectin, and P-selectin, on their surfaces [22]. Consequently, these activated endothelial cells serve as the local source for the introduction of leukocytes into atherosclerotic lesions [23].

Fig.1. The figure represents, pathophysiology of LDL retention, oxidation, endothelial activation, foam cell formation, and plaque development leading to atherosclerosis.



3. THE ROLE OF THE GUT MICROBIOME IN THE DEVELOPMENT AND PROGRESSION OF ATHEROSCLEROSIS: -

3.1 Gut microbiota in host:

A complex population of bacteria that can have an effect on both health and disease is known as gut microbiota. In addition to viruses, bacteria, fungi, archaea, and protozoa, it is composed of approximately 3×10^{13} bacteria, the majority of which are symbiotic gut microbes present. Fusobacteria, Actinobacteria, Proteobacteria, Bacteroidetes, Firmicutes and Verrucomicrobia are all members of the population of microorganisms that present in the gut [24]. Because of the ratio of firmicutes to bacteria, the microbiota in the gut, which is primarily composed of bacteria and firmicutes, is an important sign of health [25]. A huge amount of differentiation exists between particular organism of the gut microbiome, which is impacted by host characteristics as well as environmental factors, including lifestyle, nutrition, and diseases [26].

Studies conducted in recent years have demonstrated that the microbiota in the gut plays an important role in a range of physiological processes, such as metabolism, inflammation, and immunity [27]. Clostridium difficile and vancomycin-resistant Enterococcus are two examples of pathogenic symbiotic species that can flourish in the gut when the microbiota in the gut is not operating properly. In order to regulate barrier function, maintain mucosal homeostasis, prevent infection, manage bacterial overgrowth, and regulate metabolism, the microbiota of the gut interacts with the epithelial cells of the gut [28]. Through the regulation of bacterial overgrowth, this relationship contributes to the preservation of intestinal homeostasis and the prevention of infection.

3.2 Microbiota's Role in Atherosclerosis:

There is a condition known as atherosclerosis, which is characterized by the degeneration of vascular cells and the accumulation of low-density lipoprotein particles in plaque [29]. The complications of ruptured atherosclerotic plaque, ranging from myocardial infarction to ischemic stroke, are serious cardiovascular diseases leading to considerable morbidity and mortality rates. Atherosclerotic lesions in the gut of the specific characteristic have shown the presence of microbes such as Staphylococcus, Proteus vulgaris, Klebsiella pneumoniae, and Streptococcus. Such findings suggest that the gut microbiome may plays an important role in the initiation and progression of atherosclerosis for the individual [30] [31].

However, the frequency of some butyrate-producing bacteria is decrease in patients with atherosclerosis, while the prevalence of opportunistic infections is higher in affected individuals [32]. Although the frequency of gut microbes varies from population to population, it is possible that they play a role in atherosclerosis. A type of gut bacterium known as prevotella was discovered to be more prevalent in middle-aged males in eastern Poland, which suggests that it may have a role in the progression of atherosclerosis [33] [34]. Many factors, such as nutrition, lifestyle, and geographic location, can have an effect on the quantity of prevotella, which is an essential component of both health and disease [35]. There are more than 50 different species of Prevotella, and each of these species has a large amount of genetic variability among its strains [36]. Several findings have indicated that elevated levels of Prevotella have been linked with increased risk for local and systemic diseases such as rheumatoid arthritis and low-grade systemic inflammation [37]. However, a study performed in eastern Poland suggested that a species of microorganism known as Prevotella might be the cause of atherosclerosis, yet low prevalence among Chinese populations might be due to factors such as diet and pathogenicity of various strains of Prevotella calls for additional research to be conducted [38]. Uncertainty persists over the bacterial species that predominate in the genesis and maintenance of atherosclerosis.

Nielsen et al. found that particulars with symptomatic atherosclerosis had a greater prevalence of Collinsella, whereas shotgun sequencing showed that healthy controls had a higher prevalence of Eubacterium and Roseburia [39]. Alteration in the composition of the microbiome in patients are associated with an increase in the quantity of inflammatory genes. Gut bacteria including Bacteroides, Clostridium, and Lactobacillus are able to predict coronary artery disease. In comparison to the control group, patients with atherosclerosis had higher ratios of Lactobacilli and Firmicutes/Bacteroidetes in their stool, but the abundance of Bacteroidetes was decreased [40]. According to the findings of the study, additional research is required to validate these findings and establish whether or not changes in the microbiota are the cause of the condition or only reflect the severity of the condition.

A significant surge was observed in the number of genera of Enterobacteriaceae and Streptococcus in the stool*s* of atherosclerosis patients, while there was a drop in the number of beneficial microbes, such as Faecalibacterium prausnitzii, in the stools of healthy individuals, according to a study that compared the gut microbiome of 218 atherosclerosis patients that 187 healthy individuals. According to the findings of the study, the abundances of Streptococcus and Enterobacteriaceae had a positive correlation with blood pressure and cardiac indicators. This led to the construction of a statistical model developed for predicting risk for

atherosclerosis from 47 Chinese gut microbiota [41]. According to the findings of the study, Vampirovibrio, Ruminococcus, and Eisenbergiella are associated with mild coronary artery stenosis, stable angina pectoris, and acute myocardial infarction. The gut microbiome-derived prediction model was found to be more accurate than clinical markers for dealing with these disorders. Creatine kinase levels were found to have a positive link with the presence of Sporobacter and Eisenbergiella in patients who had suffered an acute myocardial infarction, whereas haemoglobin levels exhibited a negative correlation with these two bacteria [42]. A study found that the presence of proinflammatory microorganisms in a mouse strain that was sensitive to the disease increased the progression of atherosclerosis by boosting the production of certain inflammatory factor [43]. These specific strains of bacteria were then introduced into a mouse model of atherosclerosis, resulting in a decrease in the levels of lipopolysaccharide and endotoxin and the formation of tight junctions in the intestinal epithelium. Inflammation and atheromatosis were successfully prevented. The degree of short-chain fatty acids (SCFA) decline was noted, without any correlation to trimethylamine N-oxide (TMAO) [44].

3.3 The Interaction Between the Gut and Oral Microbiome in Atherosclerosis:

Oral bacteria such Porphyromonas gingivalis and Treponema denticola abound in atherosclerotic plaques, which might help to explain cardiovascular disease. Along with the gut's microbiome, the mouth cavity might potentially be important in the onset of cardiovascular disease [45]. Poor dental hygiene has been connected to acute myocardial infarction, and studies have shown that periodontal disease is associated with cardiovascular problems [46] [47]. In a mouse model, it was demonstrated that the injection of bacteria in the mouth cavity, whether through oral or intravenous means, can exacerbate atherosclerosis [48] [49] [50]. Research has demonstrated that microbial species can be transferred from the mouth cavity to the gut and that microbiota of both oral and gut cavities may react to each other. Due to a relationship established between oral health and endothelial dysfunction and other atherosclerotic disorders, the gut indeed may act as a recipient of pathogens transiting through the blood and originating from the oral cavity. Studies have shown oral bacteria to be associated with cardiovascular disease and the ability to determine formation and stability of atherosclerotic plaques in the circulation [51] [52]. There is currently a lack of clarity on the role that microbial species plays in cardiovascular disease; therefore, the focus of future research should be on gaining a knowledge of how the microbiome promotes the development of atherosclerosis.

4. METABOLITES PRODUCED BY GUT MICROBIOTA: THEIR ROLE AND IMPACT

4.1 Short-Chain Fatty Acids: Metabolic Products of Gut Microbiota:

Microbes in our gut have the ability to ferment dietary fiber and convert it into SCFAs are important to human health for the expression of nourishing functions; however, the human gut is incapable of breaking down the complex carbohydrates in dietary fiber [53]. They contain from one to six carbon atoms in their structure. Examples of SCFAs that are propyl, and acetic acids are due to their high abundance in the gut [54]. In patients with atherosclerosis, the pathogenic microbes were found to be higher, while butyrate-producing bacteria were found decreased [55]. Pro-inflammatory gut microorganisms started to occupy chronic atherosclerosis tissues, beginning with a temporary reduction of the SCFA bacteria species in the faeces and in caecal SCFA levels.

Certainly, butyrate supplementation in Apolipoprotein E-deficient mice led to the effective suppression of atherosclerosis formation provided with a high-fat diet had been shown to promote cholesterol efflux through macrophages, inhibit atherosclerosis and hepatic steatosis, and modulate the microbiota in the intestinal tract, according to the findings of the experimental study [56].

The administration of Roseburia intestinalis, a colonizing butyrate-producing bacterium, was found to lower inflammatory markers and improve atherosclerosis in mice that consumed dietary plant polysaccharides, based on the findings of the study. According to the research findings of the study, modifications in food and interactions between microbiota could potentially have an effect on cardiovascular disease, and therapies that involve increased butyrate-producing bacteria could potentially prevent atherosclerosis. Haghikia et al.'s research on ApoE −/− mice, the injection of propionate was found to minimize the arteriosclerotic phenotype and hypercholesterolemia that were generated by a high-fat diet. This reduction was observed regardless of the gut flora [57]. Based on the conclusions of the study, propionate was discovered to have the ability to block the expression of Npc111, increase the levels of intestinal regulatory T cells and interleukin-10, and decrease serum cholesterol levels. As per the findings of Bartolomaeus et al., it also offered protection against heart hypertrophy, fibrosis, vascular dysfunction, and hypertension [58].

4.2 Trimethylamine N-oxide:

TMAO is predominantly formed in the liver of the host through the metabolic processes of bacteria that activate by the consumption of choline and phosphatidylcholine [59]. In order to produce A precursor to Tri-Methyl Amine-Oxide (TMA) is trimethylamine, this requires contributions from the gut microbiota. They convert choline, betaine, and carnitines into trimethylamine due to the synthesis of TMA lyase by some of the microbes. This TMA is eventually oxidized in the liver by the flavin-containing monooxygenase (FMO) to generate TMAO [60]. Increased TMAO levels are thus considered an independent risk factor for cardiovascular diseases: heart failure, myocardial infarction, and peripheral artery disease [61] [62]. The plasma levels of intestinal microbiota metabolites, TMAO, and p-cresyl sulphate were found to correlate significantly with the phenotypic traits of the disease in the data collected from more than 3000 patients with atherosclerosis [63].

The bacterial enzyme choline TMA-lyase is responsible for the conversion of choline into trimethylamine (TMA), which is then converted into trimethylamine-N-oxide (TMAO) in the liver by flavin-containing monooxygenase 3 (FMO3). This information was discovered through research conducted on the microbiota of the gut ecosystem. Jiang et.al has confirmed that the choline–TMA–TMAO pathway is responsible for the production of TMAO thanks to the identification of gut bacteria that encode FMOs [64].According to the findings of the study, the presence of Lachnoclostridium saccharolyticum and choline in ApoE −/− mice has the potential to elevate serum TMAO levels and exacerbate atherosclerosis. L. saccharolyticum has the ability to convert choline into TMA, which in turn promotes the beginning and progression of atherosclerosis. A link has been established between L-carnitine, which is a precursor of TMA, and an increased risk of atherosclerosis through the gut microbiota [65]. To improve the development of targeted dietary intervention strategies for the purpose of reducing the formation of TMA from l-carnitine, the purpose of this study is increased [66] [67].

4.3 Bile acids:

Bile acids represent an important signalling molecule that influences metabolic processes such as lipid metabolism, glucose metabolism, energy metabolism, inflammation, and the immune response, as mediated via bile acid receptor (FXR) and G-protein-coupled receptor 5 (TGR5) [68]. FXR proteins, mostly expressed in the liver and intestines, modulate lipid metabolism through triacylglycerol transport, synthesis, and degradation [69]. FXR is activated by bile acids and inhibits development of atherosclerosis. Mice with double-knockout for FXR and ApoE displayed exacerbation of atherosclerosis when they were fed a high-fat, high-cholesterol diet [70]. The receptor FXR possesses the capacity to restore abnormal lipid metabolism so as to hinder the onset of atherosclerosis. Another way in which bile acids inhibit atherosclerosis is through TGR5 activation. Bile acids conjugated to either taurine or glycine may reduce nuclear factor kappa-B levels through TGR5 activation, leading to decreased levels of proinflammatory cytokines, which further inhibit inflammation at the atherosclerotic plaques and developing atherosclerosis [71]. Researchers have found that a lack of FXR and TGR5 can make the development of atherosclerosis worse. This finding suggests that activating these genes could be an important strategy for both the prevention and treatment of atherosclerosis [72]. ApoE −/− mice that were fed a diet high in cholesterol exhibited elevated levels of serum FGF19/FGF15, which were regulated by FXR in the intestines. Furthermore, these levels were positively correlated with circulating ceramide levels, thereby inhibiting the FXR/SMPD3 axis in the intestines [73]. In this study, taking GW4869, also known as glycoursodeoxycholic acid, as a supplement resulted in a reduction in the levels of serum ceramide and an improvement in the severity of atherosclerosis.

Table 1.-Role of Bile Acid Receptors (FXR & TGR5) in Atherosclerosis.

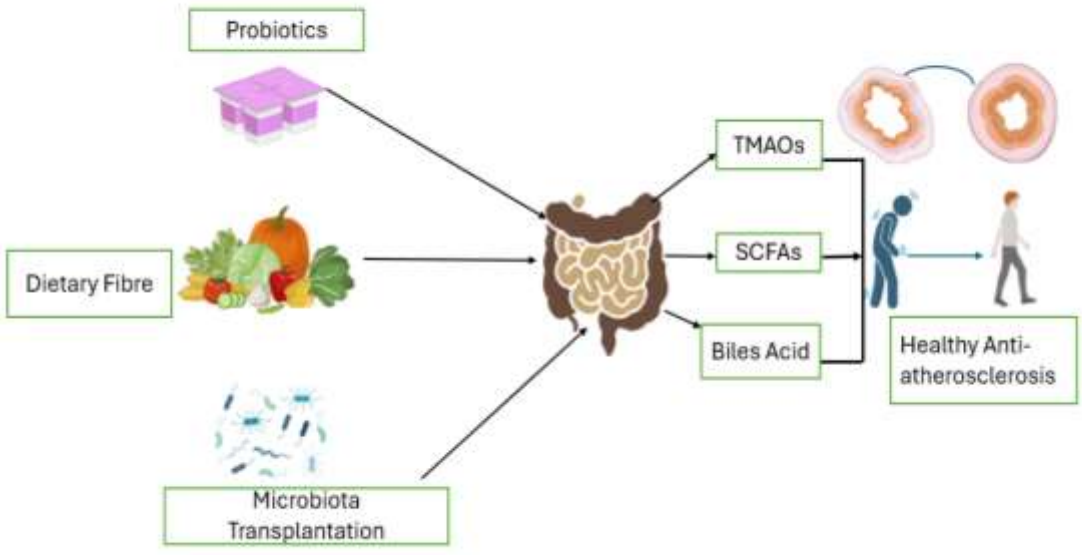
Receptor	**Mechanism in atherosclerosis**	**Reference**
FXR	FXR regulates lipid transport, synthesis, and breakdown, reducing atherosclerosis risk.	[74]
TGR5	TGR5 activation decreases NF-κB levels, reducing proinflammatory cytokines and inhibiting plaque inflammation.	[75]
FXR	FXR regulates FGF19/FGF15, which correlates with ceramide levels, impacting atherosclerosis.	[76]

GW4869	GW4869 (glycoursodeoxycholic acid) reduces serum ceramide and improves atherosclerosis severity.	
FXR & TGR5	Lack of FXR and TGR5 worsens atherosclerosis, suggesting their activation as a therapeutic target.	[77]

5. GUT MICROBIOTA-TARGETED THERAPEUTIC APPROACHES FOR ATHEROSCLEROSIS

Gut microbiota, which is known to play an important role in their progression of atherosclerosis, has been identified as a potential target for the treatment of atherosclerosis [78] [79]. A wide variety of techniques, including faecal transplants, prebiotics, probiotics, and natural components, are commonly used to ensure regulate of the microbiota found in the gut.

Fig.2-Therapeutic strategies like probiotics, prebiotics, and fecal microbiota transplantation (FMT) aim to reshape gut microbiota structure and composition. These approaches regulate microbiota-derived metabolites, promoting anti-atherosclerosis effects and improving cardiovascular health.



Probiotics are a broad category of bacteria. These bacteria have a number of beneficial results on host's metabolism [80] [81] [82].The most commonly used probiotics are Lactobacillus, Bifidobacterium, and Streptococcus [83]. According to the findings of a clinical trial that was randomised and double-blind, the probiotic known as CECT 7527, 7528 and 7529, which is derived from Lactobacillus plantarum, demonstrated

capacity to less levels of circulating cholesterol and block the production of atherosclerotic plaque in individuals who had hypercholesterolaemia.

Additionally, participants who took Lactobacillus reuteri NCIMB 30242 have been shown to consideradly lower levels of LDL cholesterol and total cholesterol [84]. Various strains of Lactobacillus, including Lactobacillus fermentum CECT5716 (LC40), Lactobacillus coryniformis CECT5711 (K8), and Lactobacillus gasseri CECT5714 (LC9), were studied for their ability to regulate blood pressure in spontaneously hypertensive rats. Findings indicated that long-term administration of these bacteria led to decreased systolic blood pressure [85]. In a study that was carried out not more than a few months ago, the probiotic L. plantarum ECGC13110402 was shown able to be tolerated and has the potential to be utilised as an alternative or supplement in order to reduce the risk of cardiovascular disease [86]. According to the newly findings capacity of prebiotics to alter gut microbiota composition enhance host metabolism. Researchers using insulin-type fructans (ITFs) found that giving these to ApoE-/- mice improved the function of their endothelial cells. Furthermore, researchers linked this addition to increased butyrate synthesis and observed atheroprotective effects [87] [88]. Investigations revealed that long-chain insulin could prevent atherosclerotic plaque formation in ApoE-/- mice, potentially due to alterations in lipid metabolism [89]. A clinical trial indicated that β-glucan consumption influenced the gut microbiota composition, leading to reduced cardiovascular disease risk factors. Additionally, the intake of mannan oligosaccharides (MOS) improved atherosclerotic plaque appearance in high-cholesterol-fed mice. Both types of prebiotics demonstrated efficacy in lowering plasma cholesterol levels while enhancing gut microbiota profiles [90]. Herbal products such as berberine—a compound extensively researched—have been found to exert medicinal effects on cardiovascular disease by modifying the gut microbiota. Berberine's ability to help Akkermansia grow in ApoE-/- mice has been linked to its ability to lower the risk of atherosclerosis [91]. Resveratrol, for example, might help protect against heart disease risk factors like high cholesterol and TMAO by changing the microbiota and gene expression in the gut, which keeps the gut barrier strong [92]. It was discovered that resveratrol may decrease TMAO-induced atherosclerosis by lowering the rate of TMAO synthesis that is mediated by the gut flora and by increasing the amount of BA metabolism [93]. A promising procedure for delivering good microbes from fit person inside gastrointestinal tract of patients who have malfunctioning intestines is called faecal microbiota transplantation, or FMT for short [94].

According to the findings of a study, the transfer of microbiota from lean donors to male receivers with metabolic syndrome resulted in an improvement in insulin sensitivity. This finding suggests that FMT may be a feasible technique for the treatment of cardiovascular disease [95]. The utilization of FMT in clinical settings is limited since there is a possibility that it could transmit endotoxins or infectious illnesses to the individuals who receive it [96].

Despite the fact that there have been conflicting findings documented in cutting-edge and therapeutic research, the gut microbiota-targeted therapy for cardiovascular disease (CVD) shows promise. A study that analysed the impact of probiotic interference on plasma TMAO levels in individuals with chronic kidney disease (CKD) found that after 3 months of treatment, there was no significant advancement [97]. Similar to the previous

example, FMT from vegans led to a minor change in the layer of the gut microbiota, but there was no advancement in the formation of TMAO or in the damage of the blood vessels [98].

6. CONCLUSION AND FUTURE PERSPECTIVE

The intricate relationship between the gut microbiome and atherosclerosis has opened new avenues for understanding cardiovascular disease pathogenesis. Despite significant advancements in microbiome research, several challenges and opportunities remain in translating these findings into clinical applications.One of the primary areas for future research is the precise characterization of microbial species involved in atherosclerosis. While numerous studies have identified correlations between gut microbiota composition and disease progression, establishing causality remains a challenge. Advanced techniques such as metagenomics, metabolomics, and single-cell sequencing should be employed to identify specific bacterial strains that contribute to atherogenesis and those that confer protective effects.

Additionally, the role of microbial metabolites such as short-chain fatty acids (SCFAs), trimethylamine-N-oxide (TMAO), and bile acids warrants further investigation. Understanding the complex metabolic pathways by which gut microbiota influence lipid metabolism, inflammation, and vascular health could lead to novel therapeutic targets. Developing microbial-based biomarkers for early detection of atherosclerosis may enhance risk assessment and personalized treatment strategies. Future therapeutic strategies should focus on microbiota-targeted interventions, including probiotics, prebiotics, and postbiotics, to modulate gut microbial composition favourably. Faecal microbiota transplantation (FMT) has shown promise in various gastrointestinal disorders, but its application in cardiovascular disease remains underexplored. Rigorous clinical trials are needed to evaluate the safety, efficacy, and long-term impact of such interventions. Dietary modifications tailored to an individual's gut microbiome profile could serve as a preventive approach to atherosclerosis. Personalized nutrition and microbiome-based precision medicine hold immense potential in reducing cardiovascular disease burden. Moreover, exploring the gut-heart axis and its interactions with other physiological systems, such as the immune and endocrine systems, will further deepen our understanding of microbiome-host interactions in atherosclerosis.Ultimately, bridging the gap between microbiome research and clinical practice requires multidisciplinary collaboration between microbiologists, cardiologists, bioinformaticians, and nutritionists. The integration of artificial intelligence (AI) and machine learning in microbiome research could facilitate predictive modelling and enhance the development of targeted microbiome therapies.

In conclusion, while substantial progress has been made in elucidating the role of gut microbiota in atherosclerosis, further research is needed to translate these findings into effective preventive and therapeutic strategies. By leveraging technological advancements and interdisciplinary collaborations, the future holds promising prospects for harnessing the gut microbiome in combating cardiovascular diseases.

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