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BACTEROIDES UNIFORMIS–DERIVED METABOLITES, CHOLESTEROL HOMEOSTASIS AND ATHEROSCLEROSIS: MOLECULAR MECHANISMS, CURRENT EVIDENCE AND THERAPEUTIC POTENTIAL

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ABSTRACT Cardiovascular disease (CVD) represents a major public health challenge in South India and globally, with atherosclerosis and elevated low-density lipoprotein cholesterol (LDL-C) being important modifiable risk factors. Although cardiovascular disease affects individuals across different age groups, its burden increases with advancing age, and adults aged 40 years and above represent an important population for cardiovascular risk assessment and prevention in South India. Increasing evidence indicates that the gut microbiota contributes to host lipid metabolism, inflammation, and cardiovascular health through the gut–liver and gut–vascular axes. Among intestinal microorganisms investigated for their metabolic benefits, Bacteroides uniformis has emerged as a promising candidate. Experimental studies have reported beneficial effects of selected B. uniformis strains on metabolic dysfunction and serum lipid profiles. Recent mechanistic evidence has further linked B. uniformis to hepatic LDL-C clearance and the regulation of cholesterol synthesis through a microbial metabolite, pentadecanoic acid (C15:0). In experimental models, B. uniformis or C15:0 supplementation has been associated with reduced plasma lipid concentrations and atherosclerotic plaque burden. This review examines current knowledge concerning B. uniformis, cholesterol homeostasis, microbial metabolites, bile-acid metabolism, and atherosclerosis, with particular consideration of its potential relevance to cardiovascular risk reduction in South Indian populations. However, the anti-atherosclerotic evidence remains predominantly preclinical, and its clinical efficacy and safety in humans require confirmation through well-designed clinical trials.

KEYWORDS : Bacteroides Uniformis; Gut Microbiota; LDL Cholesterol; Pentadecanoic Acid; HMG-CoA Reductase; LDL Receptor; Atherosclerosis; Cardiovascular Disease; Gut–Liver Axis; Microbiome.

1. INTRODUCTION

Atherosclerotic cardiovascular disease is strongly associated with disturbances in lipid metabolism, particularly elevated circulating low-density lipoprotein cholesterol (LDL-C). LDL particles can enter the arterial intima, undergo modification and contribute to macrophage foam-cell formation, vascular inflammation and progressive plaque development [1,2]. The gut microbiome is increasingly recognized as a regulator of host metabolism through microbial metabolites, bile-acid transformation, immune signalling and gut–liver communication [3,4].

Bacteroides uniformis is an anaerobic intestinal bacterium belonging to the phylum Bacteroidota. Experimental studies have reported beneficial metabolic effects of selected *B. uniformis* strains, including improvements in metabolic dysfunction and lipid-related parameters in high-fat-diet animal models [5]. More recent mechanistic research has strengthened interest in this organism by connecting *B. uniformis* and its metabolites with hepatic cholesterol handling and atherosclerotic plaque development [6].

A scientifically important distinction is that current evidence does not demonstrate that *B. uniformis* literally "breaks down bad cholesterol" inside blood vessels. Rather, experimental evidence suggests that it may influence hepatic cholesterol synthesis and increase the clearance of circulating LDL-C through a microbial metabolite, pentadecanoic acid (C15:0) [6]. These findings are currently based primarily on experimental and mechanistic evidence and require further clinical validation in humans.

2. Bacteroides Uniformis and Metabolic Health

Earlier animal research demonstrated that B. uniformis CECT 7771 could counteract metabolic abnormalities associated with a high-fat diet. Administration of this strain reduced body-weight gain, hepatic steatosis and hepatic lipid accumulation and improved serum cholesterol and triglyceride concentrations. These observations suggested that B. uniformis can influence systemic metabolism beyond the intestinal lumen [7].

More recent studies have reported effects of B. uniformis on bile-acid metabolism and the gut–liver axis, providing an additional route through which this species may affect host lipid and glucose homeostasis[8].

3. Gut Microbiota and Atherosclerosis

The gut microbiome has been associated with coronary artery disease, vascular stiffness and atherosclerosis. Metagenomic studies have identified differences in bacterial composition and microbial metabolic pathways between individuals with and without cardiovascular disease. However, association alone does not establish causation [9].

Experimental evidence involving B. uniformis is therefore particularly relevant because animal studies allow researchers to manipulate the organism and examine downstream changes in circulating lipids and arterial plaque. Such studies support the possibility that selected B. uniformis strains or their metabolites can influence cardiovascular risk through host metabolic pathways [10].

4. Proposed Mechanism of Cholesterol Reduction

B. uniformis → microbial metabolite production → hepatic signaling → increased LDL-receptor-mediated LDL uptake and/or reduced endogenous cholesterol synthesis → lower circulating LDL-C → reduced cholesterol deposition and atherosclerotic plaque formation [9,11].

Recent mechanistic evidence has identified pentadecanoic acid (C15:0) as an important bioactive metabolite associated with B. uniformis-mediated anti-atherosclerotic effects. The reported mechanism involves inhibition of hepatic HMG-CoA reductase, a central enzyme in endogenous cholesterol biosynthesis, together with enhanced hepatic LDL-C clearance [9,11].

This mechanism is conceptually important because it connects a gut microbial organism with a classical host cholesterol pathway that is also targeted pharmacologically by statins [11].

5. Role of Pentadecanoic Acid

Pentadecanoic acid (C15:0) is an odd-chain saturated fatty acid. Recent experimental work has identified it as a bioactive metabolite associated with B. uniformis and reported reductions in atherosclerotic plaque burden following supplementation in mouse models [9,12].

The proposed mechanism involves inhibition of HMG-CoA reductase and consequent changes in hepatic cholesterol homeostasis. Reduced intracellular cholesterol synthesis can activate the regulatory response controlling LDL receptor expression, thereby promoting hepatic uptake of circulating LDL particles. This provides a plausible biochemical explanation for the observed reduction in plasma LDL-C [9,12].

Nevertheless, the concentration of C15:0 required for therapeutic effects, its pharmacokinetics in humans, and the extent to which

intestinal B. uniformis contributes to circulating C15:0 in humans require further investigation [12].

6. Bile-Acid Metabolism and the Gut–Liver Axis

Cholesterol homeostasis is closely linked to bile-acid metabolism. The liver converts cholesterol into bile acids, which are secreted into the intestine and subsequently transformed by microorganisms. Gut bacteria can therefore influence enterohepatic circulation and host lipid metabolism [7,12].

B. uniformis has been shown experimentally to modify bile-acid profiles. These findings suggest that its metabolic effects may involve more than one pathway, including microbial fatty acids, bile-acid transformation and gut–liver signaling. This multi-pathway activity is relevant when considering microbiome-based approaches to cardiometabolic disease [7,9,12].

7. Evidence from Human Studies

Human evidence concerning B. uniformis and cardiovascular health remains limited and should be interpreted cautiously. Observational microbiome studies have reported associations between B. uniformis and metabolic or vascular phenotypes, but findings are not uniformly consistent [9,14].

Differences among studies may arise from strain-level variation, diet, medication use, host genetics, age, metabolic status and interactions with the wider microbial community. Therefore, abundance of B. uniformis alone should not be interpreted as proof of cardiovascular benefit. The key translational question is whether specific strains and their metabolic products can reproducibly improve clinically meaningful cardiovascular endpoints in humans [14,15].

8. Potential as a Next-Generation Probiotic

Bacteroides species are increasingly being investigated as next-generation probiotics because they possess metabolic functions that differ from those of conventional probiotic organisms. Potential strategies include administration of defined B. uniformis strains, delivery of microbial metabolites, prebiotic stimulation of endogenous populations and combined synbiotic approaches 14,15].

For cardiovascular applications, strain identification and quality control will be essential. The desired strain should demonstrate reproducible metabolite production, metabolic efficacy and an acceptable safety profile. Because Bacteroides are anaerobic organisms, formulation, stability and delivery also present practical challenges [15,16].

9. Limitations and Research Gaps

Several limitations must be addressed before B. uniformis can be considered a cardiovascular therapeutic. First, there is insufficient evidence from randomized controlled human trials demonstrating reduction of cardiovascular events. Second, strain-specific differences may substantially influence metabolic activity. Third, the optimal dose, formulation and treatment duration are unknown. Fourth, long-term safety and effects on the wider microbiome require assessment. Fifth, it remains necessary to establish whether human intestinal B. uniformis populations generate sufficient concentrations of relevant metabolites to produce clinically meaningful effects [10, 12-15].

Future investigations should integrate metagenomics, metabolomics, lipidomics and cardiovascular phenotyping rather than relying on bacterial abundance alone [10].

10. Future Perspectives

Future research should move systematically from mechanistic animal studies to well-designed human trials. Initial studies could evaluate safety and pharmacokinetics in healthy volunteers, followed by trials in individuals with dyslipidemia and subclinical atherosclerosis [14-16].

Important endpoints should include LDL-C, ApoB, non-HDL-C, triglycerides, total cholesterol, inflammatory biomarkers, circulating microbial metabolites, bile-acid profiles and validated measures of vascular structure or function. A particularly valuable research question is whether baseline B. uniformis abundance or strain composition predicts response to dietary, probiotic or metabolite-based interventions. The combination of microbiome profiling with metabolite measurements may help identify individuals most likely to benefit from targeted microbiome therapy [10,12,16].

11. CONCLUSION

Bacteroides uniformis has emerged as a promising organism in the study of microbiome-mediated regulation of cardiometabolic health. Earlier experimental studies demonstrated beneficial effects of selected strains on metabolic dysfunction, while recent mechanistic evidence has linked B. uniformis and pentadecanoic acid with hepatic cholesterol metabolism and reduced atherosclerotic plaque in experimental models.

The emerging B. uniformis–metabolite–HMG-CoA reductase/LDL-receptor pathway provides a biologically plausible connection between the intestinal microbiome and circulating LDL-C. However, it is important not to overstate the evidence: current anti-atherosclerotic findings are primarily preclinical, and B. uniformis should not presently be described as a proven treatment for human heart disease. Human clinical trials are required to determine efficacy, safety, strain specificity and therapeutic feasibility.

Overall, B. uniformis-derived metabolites represent a promising area for future research into microbiome-based approaches to cholesterol management and atherosclerotic cardiovascular disease.

Table 1. Summary of Proposed Evidence and Mechanisms

Evidence area	Proposed effect	Current evidence
B. uniformis CECT 7771	Improved metabolic and serum lipid parameters	Preclinical
Pentadecanoic acid (C15:0)	Reduced cholesterol synthesis; promoted LDL clearance	Mechanistic/ preclinical
Bile-acid metabolism	Modulation of gut–liver signaling	Preclinical
Atherosclerotic plaque	Reduced plaque burden in experimental models	Preclinical
Human cardiovascular benefit	Potential LDL-C/vascular improvement	Not yet established

Table 2. Proposed Research Framework

Stage	Population/model	Key outcomes
Preclinical	Atherosclerosis mouse models	LDL-C, plaque burden, HMGCR, LDLR
Translational	Healthy volunteers	Safety, microbiome, C15:0 pharmacokinetics
Clinical	Dyslipidemia/ subclinical ASCVD	LDL-C, ApoB, inflammatory markers, vascular endpoints
Long-term	Established ASCVD	Major adverse cardiovascular events and safety

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