



# Research Progress of Intestinal Microecological Regulation in the Management and Therapy of Coronary Heart Disease

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**Abstract:** In the contemporary period, the involvement of intestinal microecology in the management and therapy of coronary heart disease (CHD) has attracted significant attention. Research has demonstrated that intestinal microecology significantly influences the occurrence and development of CHD through microbial-derived metabolites (e.g. trimethylamine N-oxide, short-chain fatty acids), immune regulation, inflammatory response, and other mechanisms. In this comprehensive review, we discuss the evolution of research on intestinal microecology as a modulator of CHD, aimed at the mechanism of gut bacterial ecosystem dysbiosis among patients with CHD, as well as intestinal microecology-based CHD curative interventions, comprising probiotics, prebiotics, dietary interventions along with faecal bacterial transplantation, to offer novel insights and potential targets for the management and therapy of CHD. However, there are some limitations, including individual variability, unclear mechanisms, and limited clinical translation. Future studies should focus on mechanistic exploration and personalized interventions.

**Keywords:** intestinal microecology; coronary heart disease; dysbiosis

## 1. Introduction

Coronary heart disease (CHD) is a complex, multifactorial condition with traditional risk factors like hypertension, dyslipidemia, diabetes, and smoking [1]. Recent evidence highlights the gut microecology, the "second genome," as a key player in CHD onset and progression, with trillions of microorganisms (bacteria, fungi, viruses, protozoa) influencing host metabolism, immunity, and inflammation [2]. Gut microbiota dysbiosis promotes CHD by producing trimethylamine N-oxide (TMAO) from dietary choline and L-carnitine, an independent CHD risk factor linked to atherosclerosis [3]. Additionally, gut flora regulate short-chain fatty acid (SCFA) production, modulating immune and inflammatory responses that affect CHD progression [4]. Gut microecology-based strategies show promise for CHD prevention and treatment [5], but challenges like individual microbial variations, limited mechanistic studies, and clinical translation hurdles remain. Summarizing these advances deepens CHD pathogenesis understanding and guides future research and applications.

## 2. Association of intestinal microecology with CHD

### 2.1 Composition and function of intestinal microecology

The gut microecology, a complex ecosystem of microorganisms like bacteria, fungi, viruses, and protozoa, is dominated by bacteria (up to  $10^{14}$ , over 10 times human cells) [6]. Bacteroidetes and Firmicutes make up over 90% of colonic microbiota, with minor amounts of Actinobacteria, Proteobacteria, and Verrucomicrobia [7,8]. Gut flora support health via metabolic, immunomodulatory, and barrier functions. They ferment dietary fiber into short-chain fatty acids (SCFAs) like butyrate, which provide energy, reduce inflammation, and regulate intestinal epithelial cell growth via G protein-coupled receptors and histone deacetylase inhibition, maintaining barrier integrity [9,10]. Immunologically, gut microbiota modulate T and B lymphocytes and macrophages, promoting immune balance. Certain *Mycobacterium anthropophilum* strains induce regulatory T cells, reducing autoimmune risks [11]. They also reinforce the intestinal barrier with physical defenses and antimicrobial peptides, preventing pathogen invasion [12].

### 2.2 Gut Microbiota Dysbiosis in the Context of Coronary Heart Disease Pathogenesis

A growing number of studies in recent years have illustrated that gut microbiota dysbiosis exerts a significant influence on the progression of CHD. The gut microbiota in CHD patients demonstrates a pronounced decrease in diversity, and the ratio of Bacteroidetes to Firmicutes is significantly altered. The intestinal tract exhibited a significant reduction in Bacteroidetes abundance by about 30%, alongside a substantial rise in Firmicutes by 20%-40%, leading to a significant increase in F/B ratio. This dysbiosis may lead to metabolic disorders and increased inflammatory responses [13]. In addition, gut microbiota dysbiosis influences the course of CHD through its metabolites and inflammatory factors. Trimethylamine

oxide (TMAO) is a metabolite produced by gut flora metabolizing choline and levocarnitine, and its elevated levels are strongly associated with atherosclerosis and thrombosis.

### **3. Mechanisms of intestinal microecology regulating CHD**

#### **3.1 Role of metabolites**

Gut microbiota influence CHD development through metabolites like trimethylamine oxide (TMAO) and short-chain fatty acids (SCFAs). TMAO, produced from dietary choline and L-carnitine by gut microbiota, promotes atherosclerosis by enhancing macrophage cholesterol uptake and foam cell formation, and increases thrombosis risk by activating platelets [14]. Conversely, SCFAs (butyrate, propionate, acetate) from dietary fiber fermentation have anti-inflammatory and immunomodulatory effects, protecting against CHD. Butyrate suppresses the NF- $\kappa$ B pathway, reducing pro-inflammatory cytokines and attenuating atherosclerotic inflammation [15]. SCFAs also maintain immune balance by activating G protein-coupled receptors (GPCRs) [16].

#### **3.2 Immune and Inflammatory Regulation**

The gut microbiota exerts regulatory control over the functionality of diverse immune cell populations, encompassing T lymphocytes, macrophages, and dendritic cells, thereby playing a pivotal role in immune system modulation. They can also modulate the systemic inflammatory cascade by regulating T cell differentiation and function through metabolites and antigen presentation [17-19].

#### **3.3 Intestinal barrier function**

Gut microbiota dysbiosis impairs intestinal barrier function, allowing lipopolysaccharide (LPS) to enter the bloodstream, triggering systemic inflammation. LPS, a potent pro-inflammatory agent, worsens atherosclerosis by activating the Toll-like receptor 4 (TLR4) pathway, increasing pro-inflammatory cytokine production and amplifying vascular inflammation [20]. Elevated plasma LPS levels correlate with atherosclerosis severity. Maintaining intestinal barrier integrity is a vital therapeutic strategy for CHD prevention and management, as it reduces systemic inflammation and metabolic dysregulation, key drivers of CHD pathogenesis.

### **4. CHD prevention and control strategies based on intestinal microecological regulation**

#### **4.1 Probiotics and prebiotics**

Probiotics like *Lactobacillus* and *Bifidobacterium* aid CHD prevention by modulating gut microbiota. *Lactobacillus* reduces TMAO levels, lowering atherosclerosis risk [21], while *Bifidobacterium bifidum* produces SCFAs with anti-inflammatory effects [22]. A 12-week RCT (n=120) showed *Lactobacillus plantarum* DSM 9843 reduced TMAO by 38% (p<0.01) and improved endothelial function (FMD +2.1%, p=0.02) [23]. Prebiotics, such as inulin, promote beneficial bacteria. A 6-month trial (n=150) with 15g inulin increased butyrate-producing bacteria by 40% (p<0.001) and reduced serum LPS by 29% (p=0.003), lowering CHD risk via enhanced butyric acid, reduced cholesterol, and improved insulin sensitivity [24,25,26,27].

#### **4.2 Dietary interventions**

Diet significantly influences gut microecology, with the Mediterranean and high-fiber diets protecting against coronary heart disease (CHD). The Mediterranean diet, rich in fruits, vegetables, whole grains, nuts, olive oil, and fish, enhances Bacteroidetes and Firmicutes while reducing pro-inflammatory bacteria, fostering a gut microbiome that supports cardiovascular health. Extra Virgin Olive Oil, a key component, contains hydroxytyrosol, a polyphenol with antioxidant, anti-inflammatory, and anti-atherosclerotic properties. High-fiber diets promote short-chain fatty acid (SCFA) production, like butyrate and propionate, which offer anti-inflammatory and immunomodulatory benefits against CHD. They also lower plasma cholesterol and improve insulin sensitivity, further reducing CHD risk.

#### **4.3 Faecal Bacterial Transplantation**

Faecal Microbiota Transplantation (FMT) restores gut microbiota balance by transferring fecal microorganisms from healthy donors to patients. In CHD treatment, FMT enhances beneficial bacteria, reduces pro-inflammatory bacteria, and lowers systemic inflammation and atherosclerosis risk. Animal studies show FMT from healthy mice to atherosclerosis models significantly reduces plaque formation. However, FMT's therapeutic potential requires further investigation through

rigorous clinical trials to confirm safety and efficacy, alongside mechanistic studies to clarify biological pathways. Potential risks include infections, immune reactions, and metabolic disorders. Long-term effects and individual variability need validation in large-scale studies. Optimizing FMT techniques and protocols is crucial for improving its safety and efficacy in CHD treatment.

#### 4.4 Other strategies

CHD prevention and treatment strategies targeting gut microecology, beyond probiotics, prebiotics, diet, and FMT, include drugs inhibiting TMAO production and personalized interventions. TMAO, a pro-atherosclerotic metabolite from gut microbiota processing choline and levocarnitine, is a key CHD target. 3,3-dimethyl-1-butanol (DMB) lowers TMAO levels by suppressing microbial enzyme activity, reducing atherosclerosis risk. Other drugs, such as choline and levocarnitine analogs, are in development as future CHD treatments. Personalized interventions, using high-throughput sequencing to tailor probiotics, prebiotics, and diets to individual gut microbiota profiles, enhance CHD prevention and treatment efficacy. AI and big data-driven predictive models of gut microecology and CHD risk can further support precise interventions.

### 5. Conclusion

Despite the potential of gut microecology in CHD prevention and management, challenges include interindividual microbiota variability, unclear mechanisms linking microbiota to host immune and metabolic systems, and difficulties translating animal model findings to human trials, necessitating robust experimental designs and longitudinal studies. Future research should focus on novel drugs targeting TMAO (e.g., DMB) and SCFA pathways (e.g., butyrate analogs), personalized interventions using high-throughput sequencing, AI, and big data, and large-scale, multicenter RCTs to validate the safety and efficacy of these strategies for CHD treatment.

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