Role of Gut Microbiota Modulation through Probiotics in Managing Cardiovascular Risk: An Indian Regional Perspective

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Abstract
Cardiovascular diseases are responsible for 28% of all deaths in India, making it one of the leading causes of mortality. The gut microbiota has a profound impact on heart health through mechanisms such as lipid metabolism, inflammation, and metabolite production, including trimethylamine N-oxide (TMAO). In this review, we consider the potential of probiotic exposure as an opportunity to manipulate the gut microbiota and reduce cardiovascular risk factors that are specific or unique to the Indian population. We focus on special consideration for Indian-specific dietary patterns and genetic predisposition to CVDs and other environmental factors that set them apart from other populations. Here, we review the current understanding of the gut-heart axis, clinical trials of probiotic supplementation aimed at reducing CVD risk, and the use of traditional Indian fermented foods as a probiotic source. It is essential to conduct more population-specific research as the Indian population has more variations in their makeup of microbiomes and cardiovascular risk profiles.

Keywords: Gut microbiota; probiotics; cardiovascular disease; TMAO; fermented foods

1. Introduction

1.1 Cardiovascular Disease Burden in India

There is a huge burden of CVD in India such that between 1990 and 2016, the mortality increased by 34% (Prabhakaran et al., 2018). Indians have unique CVD risk profiles with earlier prevalence of disease, as well as higher prevalence of MetS and genetic susceptibilities compared to the Western populations (Gupta et al., 2020). Conventional risk factors like hypertension, diabetes, dyslipidemia and obesity are exacerbated by rapid urbanization, dietary shifts and sedentary activities.

1.2 The Gut Microbiota-Cardiovascular Axis

The human gastrointestinal tract is home to ~100 trillion microorganisms known as the gut microbiota, which are essential for host metabolism, immune responses and disease development (Sender et al., 2016). Recent studies have revealed the gut microbiome as a critical regulator of cardiovascular health by multiple interrelated mechanisms. These include the synthesis of metabolites such as short-chain fatty acids (SCFAs), trimethylamine N-oxide (TMAO), and secondary bile acids, and also modulation of immune responses that regulate systemic inflammation and innate immunity, as well as metabolic pathways controlling lipid and glucose metabolism. Furthermore, the gut microbiota is involved in blood pressure management by producing vasoactive metabolites and affecting vascular function by inducing endotoxemia due to lipopolysaccharide translocation.

1.3 Probiotics as Therapeutic Interventions

A probiotic is defined as live microorganism(s) which, when administered in adequate amounts, confer a health benefit on the host (Hill et al., 2014). The most frequently investigated probiotic strains belong to the *Lactobacillus*, *Bifidobacterium*, *Streptococcus* and *Saccharomyce*s genera. Due to their effects on modulation of both gut microbiota composition and function, probiotics are a potential non-pharmacological approach for cardiovascular risk management.

2. Mechanisms Linking Gut Microbiota to Cardiovascular Health

2.1 Trimethylamine N-Oxide (TMAO) Pathway

Among the best studied mechanisms that have been proposed to connect gut microbiota with CVD is TMAO pathway. Nutritional precursors, including choline and phosphatidylcholine, found in high amounts in red meat, eggs, and fish (but also present in other animal-derived foods such as milk), are metabolized by gut microbiota to produce trimethylamine (TMA), which is then oxidized to TMAO via the liver (Wang et al., 2011). Higher plasma levels of TMAO have been linked to higher risk for major adverse cardiovascular events, atherosclerosis, and thrombosis. The Indian diet, especially in vegetarians has lesser content of choline and L-carnitine than Western diets leading to a different TMAO production profile (Jayanama et al., 2021). However, regional differences in fish intake and the rising popularity of Western dietary habits could affect TMAO concentrations among certain Indian communities.

2.2 Short-Chain Fatty Acids (SCFAs)

The gut microflora ferment dietary fiber to short-chain fatty acids (SCFAs), mainly acetate, propionate, and butyrate, all with powerful cardioprotective effects by different ways. SCFAs control blood pressure studied by stimulating G protein-coupled receptors (GPR41 and GPR43), which leads to the reduction of vascular tone and blood pressure (Pluznick, 2017). They are also anti-inflammatory as butyrate is an inhibitor of histone deacetylases, resulting in the suppression of pro-inflammatory cytokine synthesis. Moreover, propionate is involved in lipid metabolism via hepatic cholesterol synthesis inhibition and butyrate has beneficial effects on gut barrier integrity through being the major energy substrate of colonocytes as well as for its role in the preservation of intestinal barrier function. The typical Indian diet, which is also known to be rich in cereals and legumes, vegetables as well-provides high amount of dietary fiber facilitating the production of SCFA (Ghosh et al., 2020). In addition, regional differences in fiber consumption among Indian population may impact CVD outcomes via differing amounts of SCFA generated.

2.3 Inflammation and Immune Modulation

Dysbiosis, or a dysregulation in the structure of gut microbiota, leads to systemic inflammation and is an initiator for atherosclerosis. Hyperpermeability of intestines can facilitate the translocation of bacterial lipopolysaccharides (LPS) produced by gut microbiota across the intestinal barrier to enter systemic circulation, thereby activating an inflammatory response via TLR4-mediated mechanism in microglia (Pastori et al., 2017). This condition called metabolic endotoxemia causes endothelial dysfunction, foam cell formation and plaque instability that are at the core of cardiovascular disease initiation and evolution. The underlying mechanisms may involve improving intestinal barrier integrity, competing with pathogens, generating bioactive anti-inflammatory metabolites as well as regulating differentiation and cytokine expression of immune cells.

2.4 Bile Acid Metabolism

Gut bacteria controlled the metabolism of bile acids by deconjugating and then dehydroxylating primary BA to produce secondary BA. It is known that these metabolites activate farnesoid X receptor (FXR) and G-protein-coupled bile acid receptor 1 (TGR5) related with lipid metabolism, gluconeogenesis. Dysregulation of bile acid metabolism has been linked to metabolic syndrome and cardiovascular diseases.

2.5 Blood Pressure Regulation

The gut microbiome is involved in the regulation of blood pressure homeostasis through a variety of mechanisms. One mediator in this context is formation of short chain fatty acids (SCFAs) that activate olfactory receptor 78 (Olfr78) in renal afferent arterioles leading to regulation of vascular tone, and blood pressure. The gut microbiome also produces vasoactive substances, including nitric oxide and hydrogen sulfide, both of which are critical mediators of vascular tone. Microbial metabolites can also influence the activity of the renin-angiotensin system, a key regulator of blood pressure, and sodium handling/fluid balance in the body (Marques et al., 2017). Together, these mechanisms underscore the complex interaction of the gut microbiota in the preservation of cardiovascular homeostasis.

3. Probiotic Interventions for Cardiovascular Risk Reduction

Lipid Profile: Several meta-analyses have well-documented the lipid reducing potential of probiotics. Guo et al. (2011) showed in 13 RCTs that probiotics significantly decreased the levels of neither TC (-0.20 mmol/L) nor LDL-C (-0.15 mmol/L), such effects had multiple pathophysiological pathways and mechanisms. Bile salt hydrolase (BSH) activity is also expressed by probiotics, with consequent deconjugation of the BA and increased faecal elimination, promoting hepatic cholesterol as source for bile acid formation. They can also incorporate cholesterol directly into their cell membranes and produce short chain fatty acids (SCFAs) like propionate which inhibits the HMG-CoA reductase -the rate limiting enzyme in cholesterol biosynthesis. Cholesterol coprecipitation with deconjugated bile acids adds to this effect. General, *Lactobacillus plantarum*, *Lacterius reuteri* and *acidophilus* are particularly effective in reducing the cholesterol (Khalesi et al., 2014).

Blood Pressure Regulation: Khalesi et al. (2014) reported that the reduction in both SBP and DBP was statistically significant by 3.56 and 2.38 mmHg, respectively. Such effects were strong-er in those having higher basal blood pressure levels (bSBP >130 mmHg), interventions longer than 8 weeks and multi-strain formulations with high doses (CFU/day $\geq 10^{11}$). Hypotensive mechanisms suggested include the production of angiotensin-converting enzyme (ACE)-inhibitory peptides, enhancement of endothelial function as a result of diminished oxidative stress and also SCFA-induced blood pressure modulation.

Table 1: Mechanisms of Gut Microbiota-Probiotic Action in Cardiovascular Health

Mechanism	CV Impact	Probiotic Action	Key Strains
TMAO Pathway	↑ Atherosclerosis, thrombosis	Reduce TMA/TMAO production	*L. plantarum*, *L. reuteri*
SCFA Production	↓ BP, inflammation, cholesterol	Enhance fiber fermentation	*Bifidobacterium* spp., *L. plantarum*

Bile Acid Metabolism	↓ Cholesterol, improves lipid profile	Deconjugate bile acids; ↑ fecal excretion	*L. acidophilus*, *L. reuteri*
Inflammation	↑ Endothelial dysfunction	↓ LPS translocation; ↓ TNF-α, IL-6	*L. rhamnosus*, *B. longum*
Lipid Metabolism	↓ TC, LDL-C, TG	Assimilate cholesterol; inhibit HMG-CoA	*L. plantarum*, *B. longum*
Blood Pressure	Hypertension control	Produce ACE-inhibitory peptides	*L. helveticus*, *S. thermophilus*

Abbreviations: CV = Cardiovascular; TMAO = Trimethylamine N-Oxide; TMA = Trimethylamine; SCFA = Short-Chain Fatty Acids; LPS = Lipopolysaccharide; ACE = Angiotensin-Converting Enzyme; ↑ = Increased; ↓ = Decreased

4. Indian Regional Perspective: Unique Considerations

4.1 Distinct Microbiome Profile and Dietary Influences in India

The Indian gut microbiome is characterised by distinctive compositional features correlating with diet, genetics and environment. Dhakan et al. (2019) found that *Prevotella* abundance was higher and *Bacteroides* lower in Indian populations than Western populations due to carbohydrate and fiber-rich diets. Regional variations are stark: North Indians display a higher Firmicutes:Bacteroidetes ratio, associated with wheat-rich diets; South Indians show increased presence of *Prevotella* due to rice-based and vegetarian diets; tribes have unique microbial signatures and high diversity. Differences in some of these baselines may in turn affect pro biotic colonization efficacy, metabolic and cardiovascular responses, which emphasize the necessity for region specific probiotic investigation.

India's millennia-old culture of enjoying fermented food also adds to its distinctive microbial environment. Probiotic yoghurts (dahi) containing *Lactobacillus* and *Streptococcus* species, chaas (buttermilk), idli and dosa fermented *with L. fermentum* and *Leuconostoc mesenteroides* respectively, kanji from black carrots, dhokla, some pickles are made from lactic acid fermentation rich in *Lactobacilli* have been widely accepted as one of the potential source of probiotic bacteria. These are the accepted and affordable probiotic sources in local cuisines. Yet, common hurdles to be overcome include: the standardization of microbial content, maintaining viability during storage and demonstrating their clinical efficacy in controlled studies.

4.2 Genetic Predispositions

The gut flora has been described to be in association with unique genetic variants linked to cardiovascular risk of Indian populations. There is a greater prevalence of the metabolic syndrome, also referred to as the Asian Indian Phenotype, which exhibits an abnormal accumulation of abdominal fat even at lower body mass index (BMI). Furthermore, cytokine gene polymorphisms also have a role in determining increased systemic inflammation with higher prevalence of pro-inflammatory TNF-α and IL-6 alleles. Genetic variation in lipid metabolism genes like APOE, CETP, and LDLR also modulates plasma lipids as well as responses to dietary fats. Furthermore, FMO3 gene variants have also been shown to be related with the transformation of trimethylamine (TMA) into trimethylamine N-oxide (TMAO), a metabolite associated with cardiovascular disease. Together, these genetic factors might modify host–microbiome interactions and modify response to probiotic interventions, thus underscores the significance of personalized as well as population-specific strategies employing probiotics for promoting cardiovascular health in Indians.

4.3 Environmental and Socioeconomic Factors

India's wide range of ecologies and social profiles pose challenges and possibilities for gut health and probiotic interventions. Dichotomized access to clean water and sanitation may influence establishment of the gut microbiome, while antibiotic use is extensive in both medical and agricultural arenas, leading to dysbiosis. The urban-rural dichotomy explains additional different microbiota and CVD risk profiles which could be utilized in future context-dependent interventions. Moreover, cost-effective probiotic interventions that can be universally applicable across all economic strata need to focus on affordability and accessibility.

4.4 Disease-Specific Considerations

Disease related factors also modulate the possible effects of probiotics in Indian populations. Cardiovascular diseases usually appear in a particular manner, with an early coronary artery disease (CAD) 10–15 years before that observed among the Western populations. The South Asian phenotype is typified by elevated triglycerides, low HDL-C, and high prevalence of small dense LDL particles, and the South Asian population has a very high prevalence of diabetic dyslipidemia because of the steep rise in type 2 diabetes. Despite some declines, RHD is still occurring in pockets of the world. These observations indicate that the probiotic interventions would require customization in order to target metabolic and cardiovascular phenotypes predominant in Indian subjects, influenced by both genetic predispositions and environmental factors.

5. Clinical Evidence from Indian Studies

5.1 Cholesterol Reduction Studies

Evidence on probiotic interventions is limited but growing among Indian populations. A randomized controlled trial included 125 hypercholesterolemic Indian patients conducted by Kumar et al. who received *Lactobacillus plantarum* supplementation for 12 weeks. Results showed significant reductions in TC (8.2%), LDL-C (9.4%), and TC/HDL-C ratio compared to placebo. Rajkumar et al. (2014) evaluated indigenous *Lactobacillus* strains isolated from traditional Indian fermented foods, demonstrating cholesterol-lowering efficacy in vitro and in animal models. However, human clinical trials remain limited.

5.2 Diabetes Management

India having an enormous diabetes prevalence, many studies have been conducted on probiotic supplementation and glycaemic control. Mohan et al. In this vein, Vijay-Kumar et al (2015) has observed for 12 weeks that multi-strain probiotics therapy in Indian type 2 diabetic patients caused a reduction of fasting serum glucose and HbA1c levels as well as improvement of inflammatory markers.

5.3 Hypertension Studies

Studies to investigate the role of probiotic on BP in Indian subjects are scarce. Preliminary studies have demonstrated the beneficial effects of fermented dairy products on BP among prehypertensive subjects however, larger trial evidence is still needed (Yadav et al., 2018).

5.4 Traditional Fermented Food Studies

Various reports on the probiotic profile and possible health benefits of traditional Indian fermented products are documented. It is believed that idli, dosa batter contained *lactobacillus fermentum*, *L.plantarum* and *Leuconostoc mesenteroides* studies have shown the antioxidant and anti-inflammation property (Antony & Chandra, 1998). The indigenous Indian yogurt 'dahi' shows strain-specific cholesterol reducing ability emphasizing on its use in lipid management (Sharma et al., 2012). Furthermore, vegetable fermentations like the traditional pickles are sources of some Lactobacillus population which may exert potential cardiovascular effects. However, the number of clinical trials investigating directly fermented foods in relation to CVD outcomes is still limited and highlighting some rigorous (for populations studied) population-specific studies that require to be performed for evidence based benefit assessment.

Conclusion

The gut microbiota represents a modifiable factor in cardiovascular health, and the probiotics have promising therapeutic potentials. Worldwide evidence supports benefits such as favourable changes in lipid profile, blood pressure reduction, improved glycaemic control and anti-inflammatory effects; however, the Indian population has unique variables that need to be considered including a different microbiome and dietary habits/genetics/phenotypes of disease. Cultural acceptability of traditional fermented foods as sources of probiotics is high but clinical validation is lacking. Future studies should examine locally specified strains, rigorous trials with cardiovascular endpoints, and a personalized approach including microbiome profiling and genetic genotyping to drive targeted, Culturally relevant interventions.

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