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THE ROLE OF PROBIOTICS AS ADJUVANT THERAPY IN INFLAMMATORY CARDIOVASCULAR DISEASES

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Abstrak

Penyakit kardiovaskular adalah penyebab utama kematian di seluruh dunia. Probiotik adalah mikroorganisme hidup yang dapat memberikan manfaat kesehatan bagi inang bila diberikan dalam jumlah yang memadai. Efek anti-inflamasi dari probiotik pada awalnya dipelajari pada penyakit Crohn (CD) dan kolitis ulserativa (UC). Penelitian ini bertujuan untuk memberikan bukti dan penjelasan ilmiah mengenai efek pemberian probiotik sebagai terapi adjuvan untuk penyakit inflamasi pada sistem kardiovaskular. Penelitian ini menggunakan pendekatan deskriptif dengan menggunakan metode tinjauan literatur sistematis pada PubMed, Scopus, SAGE, dan Web of Science. Sebanyak 13 artikel diinklusikan dalam penelitian ini. Probiotik yang digunakan termasuk *Bifidobacterium* dalam satu uji klinis, *Lactobacillus* dalam delapan uji klinis, *Enterococcus* dalam satu uji klinis, kombinasi *Bifidobacterium* dan *Lactobacillus* dalam satu uji klinis, dan kombinasi *Lactobacillus* dan *Propionibacterium* dalam satu uji klinis.
Kata Kunci: *Inflamasi, penyakit kardiovaskular, probiotik, terapi adjuvan.*

Abstract

Cardiovascular diseases are the leading cause of death worldwide. Probiotics are live microorganisms that can provide health benefits to the host when administered in adequate amounts. The anti-inflammatory effects of probiotics were initially studied in Crohn's disease (CD) and ulcerative colitis (UC). This research aim to provide scientific evidence and explanation on the effects of probiotic administration as adjuvant therapy for inflammatory diseases in cardiovascular health. The study employed a descriptive approach using the systematic literature review method on PubMed, Scopus, SAGE, and Web of Science. A total of 13 articles were included in this study. The probiotics used included *Bifidobacterium* in one clinical trial, *Lactobacillus* in eight clinical trials, *Enterococcus* in one clinical trial, a combination of *Bifidobacterium* and *Lactobacillus* in one clinical trial, and a combination of *Lactobacillus* and *Propionibacterium* in one clinical trial.
Keywords: Adjuvant therapy, cardiovascular diseases, inflammation, probiotics.

1. INTRODUCTION

In 2021, the World Health Organization (WHO) stated that there were over 17.9 million deaths annually due to cardiovascular diseases, with one-third occurring in developing countries. This makes cardiovascular diseases the leading cause of death worldwide (WHO, 2021). Acute myocardial infarction (AMI) is a form of coronary heart disease that occurs abruptly when the heart experiences ischemia for more than 30-45 minutes, causing irreversible cell damage leading to necrosis or death of the myocardium or heart muscle (Waly, & Listiyanto, 2014). The pathophysiology of acute myocardial

infarction involves chronic inflammation in the endothelium and disturbances in platelets resulting in thrombosis and hypertension, leading to inappropriate angiogenesis (Blann et al., 2022).

Probiotics are live microorganisms that, when administered in adequate amounts, can provide health benefits to the host (Hill et al., 2014). Probiotics commonly found in fermented products such as bread, kefir, cheese, various dairy products, and others generally fall under the category of generally recognized as safe (GRAS), indicating they are considered safe for consumption (Brandelli, 2021; Rigobelo, 2012). Probiotics can be formulated into various products, including foods, medicines, and dietary supplements (Rigobelo, 2012). Some known usage of probiotics include anti-pathogenic, anti-diabetic, anti-obesity, anti-inflammatory, anti-cancer, anti-allergy, and angiogenic activities (George Kerry et al., 2018). The anti-inflammatory effects of probiotics were initially studied in Crohn's disease (CD) and ulcerative colitis (UC) (George Kerry et al., 2018). Research indicates that an imbalance (dysbiosis) in gut microbiota plays a significant pathophysiological role in the positive regulation of inflammatory bowel disease (IBD). Supplementation of probiotics, prebiotics, and synbiotics can alter these disruptions (Cammarota et al., 2016).

There is no detailed explanation yet regarding the mechanism of action of probiotics in reducing inflammation. However, some speculated mechanisms include increased production of short-chain fatty acids with anti-inflammatory properties (such as butyrate), enhancement of antimicrobial peptide synthesis affecting inflammatory resolution pathways in the mucosa, and improvements in the intestinal luminal environment, intestinal mucosal barrier, and regulation of the mucosal immune system. Probiotics can influence various cells involved in innate and acquired immunity, such as DC, monocytes, Natural Killer (NK) cells, macrophages, lymphocytes, and epithelial cells (Cristofori et al., 2021). To date, there have been no studies on adjuvant probiotic therapy for inflammatory heart disease, prompting researchers to conduct studies on this topic. The results of this research are expected to provide scientific evidence and serve as a reference for further studies on the effects of probiotic administration as adjunctive therapy for inflammatory diseases in cardiovascular health.

2. RESEARCH METHOD

The study employed a descriptive approach using the systematic literature review method or structured article review. This paper was written using the systematic literature review method to identify, assess, and summarize research findings in a structured and systematic manner.

2.1 Article Selection Method

The selection criteria, comprising inclusion and exclusion criteria for the search of literature on the benefits of adjuvant probiotic therapy on the kidneys and heart, are presented in Table 1.

Table 1. Selection criteria for searching literature on the benefits of adjuvant probiotic therapy in cardiovascular health

Criteria	Inclusion	Exclusion
Population	Adults (≥ 18 years old) with acute or chronic kidney disease	• Children (<18 tahun) • Patients with comorbidities
Intervention	Probiotic	• Prebiotic • Synbiotic • Sterile preparations
Outcome	• Pro-inflammation cytokine • Anti-inflammation cytokine • Serum lipid profile	
Study Design	• RCT • Placebo-controlled trials • In-human studies • Full-text article	• Meta-analysis • Systematic review • Pooled data analyses • Observative study • Animal or *in vitro* studies • Non-fulltext or abstract articles
Publication Time Limit	-	-
Language Limitations	English	Non-English

2.2 Article Search Methods

This study employed a literature search strategy utilizing online platforms, including searches on PubMed, Scopus, SAGE, and Web of Science. The list of database sites and keyword combinations for searching literature on the benefits of adjuvant probiotic therapy in the cardiovascular system is outlined in Table 2.

Table 2. Database sites and keyword combinations for searching literature on the benefits of adjuvant probiotic therapy in cardiovascular health

Database	Keyword Combination
Pubmed	(Ischemic Heart Disease OR Myocardial Ischemias OR Coronary Artery Diseases OR Coronary Atherosclerosis OR Hypercholesterolemia OR High Cholesterol Levels OR Elevated Cholesterol) AND (Probiotic OR Probiotic*) AND (Randomized controlled trial OR Clinical Trial)
Web of Science, SAGE, Scopus	(Ischemic Heart Disease OR Myocardial Ischemias OR Coronary Artery Diseases OR Coronary Atherosclerosis OR Hypercholesterolemia) AND (Probiotic) AND (controlled trial)

2.3 Analysis Studies

The collected research data will be extracted and summarized narratively based on groups of research outcomes. The author will summarize and compile a descriptive record of the research in a tabular format. The research description table will outline a summary of all studies, including the researchers, publication year, and a summary of research findings. The summarized results in table form will be thoroughly reviewed for research methodology, process, and findings obtained from the full-text articles. Following a detailed and comprehensive review, the author will proceed with analysis and drawing conclusions. The synthesis of research findings and discussion will be utilized to derive conclusions.

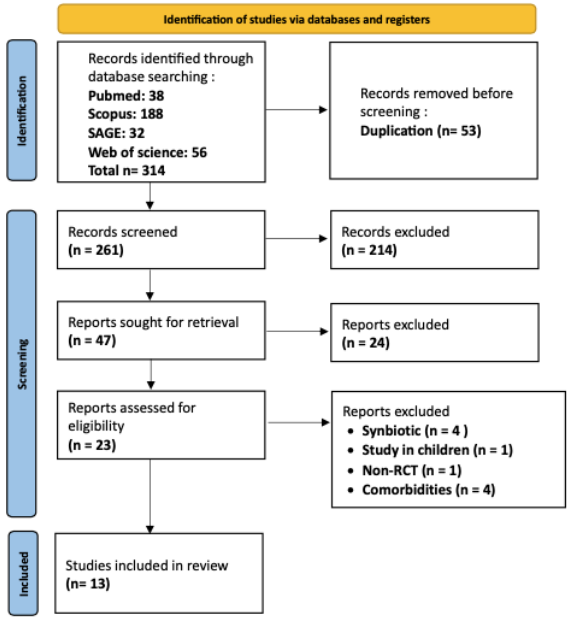

Figure 1. PRISMA Flow Diagram reviewing the effects of probiotics as adjuvant therapy in inflammatory heart disease

3. RESULTS AND DISCUSSION

Out of the 38 clinical trials identified, 23 full-text articles were considered after implementing exclusion criteria. A total of 13 articles were included in this study. The PRISMA diagram can be seen in Figure 1.

Based on the systematic review, various studies utilized single-strain probiotics, while others employed multi-strain probiotics. Detailed data regarding the studies included in the research can be found in Table 3. The probiotics used included *Bifidobacterium* in one clinical trial,

Lactobacillus in eight clinical trials, *Enterococcus* in one clinical trial, a combination of *Bifidobacterium* and *Lactobacillus* in one clinical trial, and a combination of *Lactobacillus* and *Propionibacterium* in one clinical trial.

In a clinical trial involving healthy subjects who received probiotic supplements for 12 weeks, 33 patients were tested with Bifidobacterium longum BB536 and red yeast rice (RYR). There was a decrease in LDL-c levels observed. Furthermore, the plasma lathosterol circulation, which is a marker for cholesterol synthesis, significantly reduced ($p = 0.0206$). The study found that B. longum BB536 and red yeast rice influenced lathosterol biosynthesis (Ruscica et al., 2019).

Ten clinical trials were conducted on participants with hypercholesterolemia, showing quite varied results. Significant reductions in total cholesterol were observed in the clinical trials by (Guerrero-bonmatty et al., 2021), (Costabile et al., 2017), (Fuentes et al., 2013), (Hlivak et al., 2005), (Ataie-Jafari et al., 2009), and (Chiu et al., 2021). A significant decrease in LDL was reported in the clinical trials by (Guerrero-bonmatty et al., 2021), (Costabile et al., 2017), (Fuentes et al., 2013), and (Chiu et al., 2021). Two different results were found by (St-Onge et al., 2002) and (Hatakka et al., 2008), where no changes were observed in total cholesterol, HDL cholesterol, LDL cholesterol, or triglycerides after supplementation. However, both clinical trials had a shorter supplementation duration compared to other studies, which was 4 weeks.

The study conducted by (Costabile et al., 2017) aimed to assess the effect of probiotics on proinflammatory cytokine levels. However, no significant changes were observed in IL-6, TNF-α, CRP, and IL-10 after 12 weeks of Lactobacillus plantarum supplementation. The clinical trial by Cavallini et al. found no changes in CRP levels. A study conducted on patients with a history of myocardial infarction by Moludi et al. showed a significant decrease in LPS and TNF-α levels between the probiotic group and the placebo group after administering *L. rhamnosus GG* (LGG) supplementation at 1.6×10^9 CFU/day for 12 weeks. The intake of *Lactobacillus rhamnosus GG* (LGG) showed beneficial effects in reducing metabolic endotoxemia and inflammation. Another study with 44 participants diagnosed with myocardial infarction and undergoing PCI found an increase in total antioxidant capacity, a decrease in MDA, and hs-CRP in the probiotic group (Moludi et al., 2022).

Table 3. Descriptive table of the effects of probiotics on inflammatory diseases in cardiovascular health

Author	Study design	Population	Control & Intervention Arms	Outcomes	Adverse Effects
(Ruscica et al., 2019)	Randomized, double-blind, placebo-controlled, parallel-group trial (RCT) in Italy	33 participants, aged 18-70 years, healthy subjects, low risk of cardiovascular disease	33 participants were randomly divided into a control group (n=17) and an experimental group (n=16). Probiotics were administered in the form of Lactoflorene Colesterolo supplements (Bifidobacterium longum BB536, with RYR extract, niacin, and coenzyme Q10) at a dosage of 1 sachet per day for 12 weeks	Significant differences were observed ($p < 0.005$) ➔ TC decreased, LDL-C decreased, non-HDL-C decreased, and apoB decreased. However, TG, HDL-C, apoAI, Lp(a), PCSK9 did not change.	No side effects were observed
(Moludi et al., 2022)	Double-blind, four-arm parallel randomized controlled trial in Iran	96 participants, aged 18-85 years, with an average age of 51.25 years, diagnosed with coronary artery disease (CAD)	The 96 participants were randomly divided into 4 groups: control (n=24), probiotic group (n=24), inulin group (n=24), and probiotic-inulin group (n=24). Probiotic L. rhamnosus GG (LGG) at a dosage of 1.6 × 109 CFU/d was administered for 12 weeks	Significant differences observed between the probiotic group and the placebo ➔ LPS decreased, TNF-α decreased	No side effects were observed
(Guerrero-bonmatty et al., 2021)	Randomized, double-blind, placebo-controlled, parallel-group trial (RCT) in Spain	39 participants, aged 18-79 years, with total cholesterol levels >=200 mg/dL, not consuming statins	39 participants were randomly divided into a control group (n=18) and an experimental group (n=21). Probiotics: 109 CFU of L. plantarum strains CECT7527 (KABP011™), CECT7528 (KABP012™), and CECT7529 (KABP013™) in a 1:1:1 ratio with RYR extract. Analysis at baseline, 6 weeks, and 12 weeks	Significant differences observed ➔ TC decreased ($p=0.023$), LDL decreased ($p=0.011$)	No side effects were observed

(Costabile et al., 2017)	parallel, double blind, placebo controlled, randomized design in UK	46 participants with normal to mild hypercholesterolemia; Aged = 30–65 years; Average BMI = 26.43 kg/m2	46 participants were randomly divided into a control group (n=23) and an experimental group (n=23). Probiotics: Lactobacillus plantarum ECGC 13110402 4 × 109 CFU/day for 12 weeks	Significant decrease in TC, LDL-C, TAG. However, there were no significant changes in IL-6, TNF-α, CRP, and IL-10 after 12 weeks	No side effects were observed
(Cavallini et al., 2016)	Randomized placebo-controlled double-blind trial	49 male participants with mild hypercholesterolemia; Aged = 45–48 years	49 participants were randomly divided into 3 groups: control (n=15), fermented soy-probiotic group (n=17), fermented soy-probiotic+isoflavone group (n=17). Probiotics: Isoflavone-supplemented soy product fermented with Enterococcus faecium CRL 183 and Lactobacillus helveticus 416 11 × 109 CFU/day (or) Probiotics with ~100 mg of total isoflavones for 42 days	In the fermented soy-probiotic group, HDL levels were maintained. There were no changes in CRP levels	No side effects were observed
(Jones et al., 2013)	Double-blind, placebo-controlled, randomized, parallel-arm, multicenter in Czech Republic	139 participants with hypercholesterolemia	Subjects with healthy hypercholesterolemia (LDL-c > 3.4 mmol/L; TG < 4.0 mmol/L; BMI range = 22–32 kg/m2); Probiotic group, n = 66 (38 females, 28 males), placebo group, n = 61 (34 females, 27 males) Probiotic: L. reuteri NCIMB 30242 2 × 109 CFU twice/day	Increased circulation of 25-hydroxyvitamin D in the probiotic group	No side effects were observed
(Fuentes et al., 2013)	Controlled, randomised, double-blind trial in Spain	60 participants, aged 18-65 years, with hypercholesterolemia	The 60 participants were randomly assigned into a control group (n=30) and an experimental group (n=30). One capsule per day containing 1.2 × 109 CFU of Lactobacillus	Reduced levels of TC, LDL-c, and LDL-c oxidation in the probiotic group. Decreased risk of CVD	No side effects were observed

			plantarum (CECT 7527, CECT 7528, and CECT 7529) for 12 weeks		
(Hlivak et al., 2005)	Controlled, randomised, double-blind trial, Country not reported	43 participants with hypercholesterolemia	The 43 participants were randomized into two groups. Probiotic group, n = 20 (17 females, 3 males; Mean age = 75.35 ± 1.49 years; Mean BMI = 29.40 ± 0.86 kg/m2); Placebo group, n = 18 (14 females, 4 males; Mean age = 78.05 ± 1.68 years; Mean BMI = 29.08 ± 1.14 kg/m2) Probiotic: Enterococcus faecium M-74 and selenium (Se) → two × 109 CFU/day; 50 µg of Se for 60 weeks	Reduced serum cholesterol levels in the probiotic group. HDL and TG showed no changes.	No side effects were observed
(Ataie-Jafari et al., 2009)	Randomized and crossover trial in Iran	14 participants with serum total cholesterol levels of 5.17-7.76 mmol/l, aged 40-64 years, with an average age of 50.5 years	They were randomly allocated into 2 groups to receive 300g of regular yogurt or probiotic yogurt (fermented with a starter comprising *Lactobacillus acidophilus* and *Bifidobacterium lactis* in addition to bacteria found in regular yogurt) for 6 weeks, followed by a 4-week washout period → crossover	Significantly reduced TC levels in the probiotic yogurt group. Levels of LDL-C, HDL-C, LDL-C/HDL-C, and TAG showed no significant differences	No side effects were observed
(Chiu et al., 2021)	Double-blind, placebo-controlled, randomized clinical trial in Taiwan	40 participants with mild hypercholesterolemia, aged 18-60 years, with an average age of 42.5 years	The 40 participants were randomly divided into 2 groups, namely the control (n=20) and the probiotic group (n=20). Using a probiotic mixture in milk form (PMF) (bacterial strains) including L. acidophilus (La5), L. casei (TMC), and B. lactis (Bb12) at a concentration of 2 ×	Significantly increased ($p < 0.05$) stool weight, bowel movements (reduction in defecation time) by enhancing gut microbiota (increase in beneficial bacterial species like *Lactobacillus, Bifidobacterium*	No side effects were observed

			106 CFU/g for 10 weeks	spp.), and LDL oxidation time. Total cholesterol (TC; 8.1%) and LDL-C (10.4%) levels significantly decreased	
(Moludi et al., 2019)	Randomized, double-blind, and placebo-controlled clinical trial in Iran	44 participants diagnosed with myocardial infarction and underwent PCI	Out of the 44 participants, 42 were randomly divided into 2 groups, namely the control (n=22) and the probiotic group (n=22). Probiotic intervention: capsules containing 1.6 × 10 colony-forming units of Lactobacillus rhamnosus (active intervention group) or capsules containing maltodextrin (placebo control group) for 12 weeks	There were significant differences observed in the increase in total antioxidant capacity, decrease in MDA, and hs-CRP levels in the probiotic group	One side effect occurred in the placebo group → experiencing symptoms of heart failure with reduced cardiac output
(St-Onge et al., 2002)	Randomized crossover trial, Country not reported	Thirteen male participants, aged 27 to 61 years (47 ± 9 years), with a BMI ranging from 26 to 38 kg/m2 (30.2 ± 4.4 kg/m2), and an average serum cholesterol of 6.54 ± 0.78 mmol/L were involved in the study	These 13 participants were divided into two groups: the first group consumed kefir supplements, while the second group consumed milk for 4 weeks. After a washout period of 4 weeks, they switched	Neither the kefir supplements nor the milk showed any reduction in total cholesterol, HDL cholesterol, LDL cholesterol, or triglyceride concentrations	At the onset of kefir supplementation, two subjects reported cramps and constipation. With milk consumption, one subject experienced bloating and increased bowel movements, while two subjects reported increased frequency of bowel movements or cramps
(Hatakka et al., 2008)	Double-blind, randomised, placebo-controlled, two-period crossover	38 participants with mild to moderate hypercholesterolemia, aged 24 to 55 years, with an average age of 42 years, were involved in the study	These 38 participants were divided into two groups. They were given treatment and a placebo for 4 weeks, after which the groups were	No changes in total cholesterol, HDL cholesterol, LDL cholesterol, or	No side effects were observed

study with 4-week treatment periods in Finland	switched. The treatment involved probiotics: Lactobacillus rhamnosus strain LC705 and Propionibacterium freudenreichii ssp shermanii strain JS in capsules (2 x 1010 colony forming units of each strain daily), or two placebo capsules	triglyceride levels were observed during the consumption of probiotics compared to the placebo

In cardiovascular diseases, the intestines are a primary part of the body experiencing ischemia, where microvilli and colon villi become vulnerable to cellular hypoxia and anaerobic metabolism. All these factors eventually lead to an unstable gut microbiota composition (dysbiosis), mostly characterized by a decrease in Bifidobacteria and Bacteroides (Gram-positive bacteria) and an increase in Proteobacteria and Firmicutes (Gram-negative bacteria) (Alhajri et al., 2021).

Current research acknowledges the relationship between gut microbiota and the pathophysiology of heart and blood vessel diseases. Numerous studies have established that microbial metabolites, as well as components present in bacterial structures, can move from the gut to the general circulation, thus interacting and metabolically altering related tissue functions. Gut microbiota produce TMAO, SCFAs, and bile acids that have several metabolic effects in humans (Alhajri et al., 2021).

TMAO is a bacterial metabolite considered responsible for heart disease. TMAO can accumulate in the kidneys and heart, contributing to several biotic mechanisms, such as stimulating platelet accumulation, increasing foam cell synthesis, and activating inflammatory responses. Animal products like milk, red meat, and eggs, containing high levels of trimethylamine (TMA) groups, such as L-carnitine and choline, are digested to produce TMAO (Guo et al., 2020). Studies have shown that increased TMAO can inhibit cholesterol transport and increase cholesterol accumulation in macrophages, thereby accelerating atherogenesis. Therefore, TMAO is pro-atherogenic, pro-thrombotic, and contributes to ischemic heart disease, being associated with a poor prognosis in heart failure patients (Alhajri et al., 2021).

Fermented dietary fiber produces short-chain fatty acids (SCFAs). The most common SCFAs include propionate (C3), acetate (C2), and butyrate (C4), encompassing 95% of the total SCFAs in the body. The concentration of these SCFAs in the gut ranges from 10 mM to 100 mM and functions within the digestive tract to activate ileum movement, mucus synthesis, and epithelial protection. Although most SCFAs are metabolized in the large intestine, a small portion is absorbed into the general circulation. Several experiments have revealed that SCFAs reaching the general circulation modulate cardiovascular functions (Chen et al., 2020).

Probiotics, such as Lactobacillus, Bifidobacterium, Lactococcus, and Streptococcus, can stimulate the growth and activity of specific gut microbiota, regulating

immune responses and limiting inflammation levels, thus benefiting the host (Alhajri et al., 2021). Probiotics work differently by directly or indirectly regulating the host. Firstly, they enhance the barrier function of the digestive tract through gap-junction proteins from intestinal epithelium and mucus secreted by goblet cells. Secondly, some probiotics can produce 'bacteriocins', SCFAs, and other antimicrobial factors that inhibit pathogen growth. Thirdly, probiotics regulate the phenotype and activity of T cells, natural killer cells, and macrophages, reducing the release of proinflammatory factors by regulating the NF-κB pathway (Wang et al., 2020).

4. CONCLUSIONS

Microbial dysbiosis plays a significant role in the pathogenesis of various diseases. The gut microbiome and its metabolic products contribute to the pathophysiology and development of inflammatory diseases in the cardiovascular system. From the literature review findings, probiotics have the potential to serve as an adjuvant therapy in inflammatory cardiovascular diseases by repairing gastrointestinal cells, promoting SCFA formation, and modulating the body's immune system.

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