Quality in Sport. 2026;51:68248. eISSN 2450-3118.

https://doi.org/10.12775/QS.2026.51.68248

Quality in Sport. eISSN 2450-3118

Journal Home Page
https://apcz.umk.pl/QS/index

KOMARCZEWSKA, Anna Maria, MATUSIAK, Filip, BRZOZA, Klaudia, KOCIŃSKI, Michał, IGLEWSKI, Patryk and PIETRASZ, Michał. Psilocybin-Induced Neuroplasticity and Sustained Antidepressant Effects. Quality in Sport. 2026;51:68248. eISSN 2450-3118. https://doi.org/10.12775/QS.2026.51.68248

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 14.01.2026. Revised: 31.01.2026. Accepted: 31.01.2026. Published: 05.02.2026.

The link between Gut Microbiota and Coronary Artery Disease (CAD) - A Review of literature

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Abstract

Background: Coronary artery disease (CAD) is the leading cause of mortality worldwide. Although established risk factors such as hypertension or dyslipidaemia are well recognized, they do not fully account for the residual cardiovascular risk. Growing evidence suggest that the gut microbiota may play a significant role in development and progression of CAD through inflammatory, metabolic and immune-mediated mechanisms.

Aim: This review aims to summarize current evidence on the association between the gut microbiome, its metabolites and CAD, and to discuss potential therapeutic strategies targeting the gut microbiota in CAD prevention and management.

Materials and methods: The search was conducted using databases such as PubMed or Google Scholar. Following keywords were used: coronary artery disease, cardiovascular disease, gut microbiota, gut microbiome, dysbiosis, SCFAs, TMAO.

Results: Patients with CAD exhibit gut microbiome dysbiosis, characterized by decrease of SCFA-producing bacteria and increase of microorganisms capable of TMAO synthesis.

Decreased SCFAs production leads mainly to disrupted intestinal barrier integrity, resulting in leakage of pro-inflammatory LPS. On the other hand, TMAO has been strongly associated with CAD risk factors such as atherosclerosis. Emerging microbiota-targeted interventions like probiotics, prebiotics, symbiotics or fecal microbiota transplant have demonstrated promising results in the management of CAD.

Conclusions: Gut microbiota represents an important and modifiable factor in the pathophysiology of CAD. At present, the dietary modifications offer the most accessible and effective strategy of microbiota modification and further research is needed to define the role of microbiome-related therapies.

Keywords: coronary artery disease, cardiovascular disease, gut microbiota, gut microbiome, dysbiosis, SCFAs, TMAO

1. Introduction.

Coronary artery disease (CAD), considered as the most prevalent form of the cardiovascular disease, is the foremost single cause of mortality and loss of Disability Adjusted Life Years (DALYs) globally [1]. It is characterized by the build-up of atheromatous plaque in the arteries of the heart and reduction of blood flow to the cardiac muscle, which can lead to stable/unstable angina, myocardial infraction and myocardial ischemia [2]. Overall, CAD is responsible for almost one third of deaths in individuals older than 35 years of age [3]. Risk factors include among others hypertension, elevated total cholesterol and low-density lipoproteins (LDL), diabetes mellitus or obesity [4]. Despite the noticeable downward trend in deaths from CAD, especially in the developed countries, it remains one of the main epidemiological concerns. Lately, more scientists are proposing wider approach to the prevention and treatment of CAD, some of them focusing on the role of gut microbiota. Gut microbiota refers to the entire population of mutualistic bacteria, archaea, viruses and protozoans that colonize the intestinal

tract, mainly the large intestine, and help in the synthesis of vital components such as vitamin K, metabolism of certain compounds like bile and sterols, and fermentation of dietary products. Composition of the gut microbiota varies depending on environmental and lifestyle factors [5] [6]. An increasing number of studies reveal importance of gut microbiota in CAD development, both through changes in its composition and their specific metabolites.

2. Gut microbiota and cardiovascular health.

Gut microbiota can affect CAD development both directly and indirectly. The short-chain fatty acids (SCFAs) are products of fermentation of indigestible dietary fibers and oligosaccharides by anaerobic microorganisms in the colon [7]. The most abundant SCFAs are acetate, propionate and butyrate. They play an integral part in maintaining intestinal barrier integrity by regulating the expression of tight junction proteins. SCFAs exert anti-inflammatory properties by binding to G-protein couple receptors GPR41, GPR43 and GPR109A via induction of the Foxp3 promoter-controlled Treg cells [8]. Various experiments conducted on mice revelated that SCFAs contribute to improvements of lipid and glucose metabolism, as well as to the reduction of atherosclerotic plaque [9] [10]. Furthermore, some studies showed that reduced abundance of SCFAs-producing bacteria is associated with hypertension, indicating the key role of SCFAs in maintaining proper blood pressure [7]. Moreover, gut microbiota can affect the regulation of cholesterol in the liver and influence the systemic cholesterol levels by its involvement in altering the bile acids [8]. Primary bile acids are synthetized directly from cholesterol within the liver and released from the gallbladder into the intestine, where they are conversed into secondary bile acids by the intestinal microbiota. Secondary bile acids act as an agonist of the bile acid receptors such as the farnesoid X receptor (FXR). Activation of the FXR is associated with a decrease in the development of the atherosclerosis in mice models [6]. LPS, also known as endotoxin, is a major component of Gram-negative bacteria outer membrane. Upon the bacteriophage-induced membrane disruption, LPS is released, causing systemic inflammation. However, healthy individuals have an intestinal blood barrier that prevents LPS from entering the bloodstream. Loss of SCFAs producing bacteria, mainly ones producing butyrate, as observed in CAD patients, may result in dysfunctional gut mucosal barrier, facilitating passive leakage of LPS. LPS binds to receptors of innate immune system like Toll-like receptors, thereby triggering inflammation [11]. Additionally, LPS activate JNK1 in macrophages, resulting in upregulation of CD14 and SR-AI expression, leading to increase of oxidized LDL uptake and foam cell production, suggesting its proatherogenic properties [11] [12]. Previous studies also have linked circulating LPS levels to insulin resistance and

abdominal obesity [11]. The most compelling evidence of a link between the gut microbiome and CAD is related to the trimethylamine-N-oxide (TMAO), which is considered a strong predictor of CAD. Dietary choline, phosphatidylcholine, lecithin and L-carnitine, predominantly abundant in animal-based diet, are metabolized into trimethylamine (TMA) though of action of gut microbial enzymes. Then, TMA is absorbed by the intestinal epithelium and transported via the portal circulation to the liver, where flavin-containing monooxygenase 3 (FMO3) within hepatocytes catalyses the oxidation of TMA to TMAO [7] [8].Various studies have proved the strong correlation between TMAO and the coronary atherosclerosis and other well-known CAD risk factors like the metabolic syndrome [13] or non-fatty liver disease [14]. It metabolic effects include reduction of the reverse cholesterol transport from peripheral tissues to the liver, inhibition of the bile acid synthesis, increasing of serum lipid concentration and fat mass and promotion of foam cell formation [5]. TMAO is associated with C-reactive protein (CRP) and endothelial dysfunction, resulting in elevated LPS serum levels and inflammation [15]. Additionally, TMAO may have a prothrombotic effect. Zhu et al. (2016) revealed that TMAO promotes platelet responsiveness by enhancing the stimulus-dependent release of Ca^{2+} from intracellular Ca^{2+} stores [5] [16].

3. Gut bacterial dysbiosis in CAD.

According to recent research abnormal microbiota predisposes to the development of CAD and gut bacterial composition differs in CAD patients compared with the healthy ones [5]. In healthy adults' gut microbiota mostly consists of Bacterioidetes and Firmicutes. Bacterioidetes play an essential role in maintaining a healthy gut ecosystem. They are involved in the degradation of non-digestible dietary carbohydrates and host - derived carbohydrates from gastrointestinal tract secretions producing butyrate and acetate [8]. Cui et al. [2017] reported decreased levels of Bacterioidetes in patients with CAD [17]. Jie et al. [2017], followed by Zu at al. [2018] additionally reported decreased abundance of other known butyrate producers such as *Roseburia, Faecalbacterium* and *Eubacterium*. On the other hand, they revelated increased amount of, *Escherichia - Shigella*, *Enterococcus* and *Streptococcus* species that may accelerate inflammation and development of atherosclerotic plaque [18][19][20]. Toya et al. [2020] showed depletion of *Lachnospiracenae,* also responsible for butyrate production and reduction of cholesterol to coprostanol, which lowers blood cholesterol levels [20] [21].

4. Potential therapeutic interventions targeting the gut microbiota.

Given the previous findings, numerous potential therapeutic options targeting gut microbiota in CAD patients were proposed. The most prevalent ones are those focused on the probiotics.

Probiotics are defined as „live microorganisms, that, when administered in adequate amounts, confer a health benefit to the host" [22]. The *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, *Lactococcus* and *Streptococcus* are predominately used as probiotics [23]. Published research shows that anti-inflammatory, antithrombotic, antioxidant and endothelium-protective effects of probiotics could provide significant cardiovascular benefits [24]. Other potential mechanisms include the strengthening of gut epithelial tight junctions to reduce LPS leakage, supressing TMAO formation, as well as inducing of the bile acid deconjugation, thus increasing bile acid excretion and cholesterol utilization [24] [25] [26]. The most well studied in this regard are *Lactobacilli.* Oral administration of *Lactobacillus rhamnosus* GR-1 in rats with induced acute myocardial infraction ameliorated cardiac remodelling and pump failure [27]. Moreover, a randomized, double-blind trial of 44 CAD patients revealed that 12-week supplementation with *Lactobacillus rhamnosus*, together with caloric restriction, provided anti-inflammatory effects and notable weight loss, compared to caloric restriction alone [25] [28]. Another randomized trial of 77 dyslipidemic patients concluded that administration of *Lactobacillus plantarum* with simvastatin 20 mg resulted in better improvement of the lipid profile and reduction of calculated cardiovascular risk than while taking simvastatin 20 mg alone [25] [29]. On the other hand, double-blind, randomized, placebo-controlled trial examining efficacy of the probiotic strain *Bifidobacterium lactis* Probio-M8 in CAD therapy showed that CAD patients taking it in addition to conventional treatment reported improvement in anxiety, anginal and depressive symptoms compared to the control group. Additionally, after 6 months of treatment with this strain, their interleukin-6 and LDL levels were remarkably decreased, compared to placebo, along with TMAO and proatherogenic amino-acids (l-leucine, l-valine) [25] [30]. Combinations of various probiotics are also tested - in experimental study involving male Wistar rats fed with high fat diet, administering *Lactobacillus rhamnosus* FM9 and *Limosilactobacillus fermentum* Y57 increased high-density lipoprotein cholesterol levels with similar efficacy as a lipid-lowering agent [25] [31]. In human clinical study, young and middle-aged women with arterial hypertension were treated for 8 weeks with the combination of *Lactobacillus paracasei* LPC-37, *Lactobacillus rhamnosus HN001*, *Lactobacillus acidophilus* NCFM, and *Bifidobacterium lactis* HN019 - researchers observed reduced fasting glucose, improved lipid profile and autonomic modulation, as well as the trend towards a significant blood-pressure lowering effect [25] [32].

Prebiotics are defined as indigestible food components, such as inulin, fructooligosaccharides or beta glucan, that promote the growth and/or the activity of specific microorganisms within the gut microbiota [26]. They favour growth and function of beneficial bacteria, such as those

of *Lactobacillus* or *Bifidobacterium*, and may antagonize growth of or colonization by pathogenic species. The beneficial ones are known for production of SCFAs, which could lead to enhancement of gut epithelial tight junctions. Prebiotics may be also helpful in treatment of CAD risk disorders like the metabolic syndrome - evidence in animal and human studies suggest that prebiotics intake results in reduction of ghrelin, increase of glucagon-like peptide-1 (GLP-1) and weight loss [25].

Ingestible combinations of probiotics and prebiotics are called symbiotics, which show the potential in managing CAD and CAD related disorders. A meta-analysis of controlled randomized trials revealed that symbiotic supplementation provides positive effects in patients with metabolic syndrome, resulting in lowered serum insulin levels, triglycerides, total cholesterol, LDL or waist circumference [25] [33]. As expected, each study used different set of compounds. The most effective mixture of symbiotics for reduction of cardiovascular risk is still unknown.

Antibiotics have been tested in the context of CAD; however, this approach has failed to show any benefit. In addition, the 10-years of follow up data from the CLARICOR trial revealed the increased prevalence of death in patients with stable CAD treated with clarithromycin [34]. This revelation has led to the FDA alert in 2018. Another study reported increased risk of cardiovascular events in elderly women with increased cumulative exposure to antibiotics in adulthood, which may occur, among others, from pro-inflammatory activities mediated by translocation of commensal gut microbes [11].

Fecal microbiota transplant (FMT), an established treatment for recurrent *Clostridioides difficile* infection, has proven to be successful in patients with cardiometabolic disorders. FMT from lean donors was previously shown to normalise insulin sensitivity in obese patients with the metabolic syndrome, although results of the studies varied widely and effects were temporary. FMT from vegan donor changed gut microbiota compositions of the with metabolic syndrome towards the donor profile, but without altering TMAO production capacity. However, FTM is not without the risk - the main concern is the possibility of transferring of pathogenic microorganisms or endotoxins. Two cases of bacteriemia induced by drug-resistant *Escherichia coli* transmitted via FTM were documented and one of them resulted in death. The role of FTM in CAD management needs further evaluation and it is critical to standardize and optimize the procedures of FTM before its widespread clinical application [11][7].

Despite all promising therapeutic interventions listed above, proper dietary intervention still come forward as the most cost-effective and straightforward approach in treatment and prevention of CAD [35]. It is widely known that dietary patterns can shape the composition of

gut microbiota. High-fatty, rich in meat diet is the source of L-carnitine and choline, from which TMAO is metabolised. Elevated TMAO levels were observed in individuals consuming high-fatty diet compared to ones consuming the low-fatty one [5] [36]. On the other hand, the high-fiber diet promotes the growth of microorganisms capable of degrading complex carbohydrates and producing SCFAs [35]. Dietary fiber is one of the compounds of the Mediterranean diet, which is considered as optimal dietary prevention of cardiovascular events [37]. Moreover, the Mediterranean diet is also rich in fish, flaxseed oil and polyphenols, which play role in reducing TMAO levels, promoting proliferation of SCFA-producing bacteria and inhibiting those producing LPS [5] [38].

5. Conclusions.

An increasing body of evidence indicates that the gut microbiota plays an important and complex role in development and progression of CAD. Gut microbiota composition and its metabolites like SCFAs and TMAO significantly influence lipid and glucose metabolism, inflammatory pathways, endothelial function and thrombogenic processes that collectively contribute to atherogenesis and plaque instability. Dysbiosis, characterized by reduced abundance of beneficial SCFA-producing bacteria and increased prevalence of pro-inflammatory microbial taxa, appears to be a consistent feature in patients with CAD. The growing understanding of gut-heart axis interactions has stimulated interest in microbiota - targeted therapeutic strategies, that, along with proper dietary interventions, represent a promising complementary approach in CAD prevention and therapy. However, current clinical evidence remains heterogeneous and insufficient, thus highlighting need of further research to clarify casual relationships, identify optimal microbial targets and determined personalized microbiota-based interventions.

Authors' contribution

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All authors have read and agreed with the published version of the manuscript.

Funding statement

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Acknowledgement

Not applicable.

Conflict of Interest

The authors declare no conflict of interest.

Declaration of the use of generative AI and AI-assisted technologies in the writing process.

In preparing this work, the authors used Google Gemini for the purpose of improving language and readability. After using this tool, the authors reviewed and edited the content as necessary and accept full responsibility for the substantive content of the publication.

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