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ROLE OF PROBIOTICS IN THE PREVENTION AND MANAGEMENT OF CARDIOVASCULAR DISEASES: INSIGHTS FROM A DOXORUBICIN-INDUCED MODEL

Cardiovascular diseases (CVDs), particularly acute myocardial infarction, represent a critical global health concern driven by multifactorial risk factors, including hypercholesterolemia. While conventional lipid-lowering therapies remain effective, their side effects and limitations have prompted the exploration of alternative approaches. Probiotics, postbiotics, and functional foods have emerged as innovative strategies capable of modulating the gut microbiota to enhance lipid metabolism and mitigate oxidative stress and inflammation, offering new possibilities for CVD management. This review emphasizes the significance of doxorubicin-induced models in studying CVD mechanisms and evaluating therapeutic potentials. By leveraging insights into the gut-microbiota-heart axis, these models facilitate the development of novel interventions targeting hypercholesterolemia-induced CVDs. Cholesterol-lowering probiotic strains and functional food products stand out for their ability to provide safer complementary options to traditional therapies. Advancing research in this field requires optimizing experimental models, investigating molecular pathways, and translating findings into clinical practice through rigorous trials. The integration of these innovative solutions holds the potential to improve cardiovascular health, address unmet clinical needs, and reduce the global burden of CVDs.

Keywords: *cardiovascular diseases, probiotics, postbiotics, functional foods, gut microbiota, cholesterol metabolism, doxorubicin-induced models, therapeutic interventions*

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Cardiovascular disease (CVD) remains the leading cause of nearly one-third of deaths worldwide, despite advancements in pharmacological interventions, such as statin therapy, over the past decades. Among these diseases, acute myocardial infarction (MI) stands out as the most fatal, with approximately three million cases reported annually (Starovoitova et al., 2025; Wang et al., 2024b; WHO, 2023). According to the World Health Organization (WHO), CVDs accounted for estimated 17.9 million deaths globally in 2023, representing 32% of all fatalities (Tsao et al., 2023).

Hypercholesterolemia is a key contributor to CVD, metabolic syndrome, and type 2 diabetes. Elevated levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) significantly increase the risk of CVD events, with a 1% rise in TC correlating with a 2—3% higher risk of heart disease. Conversely, reducing LDL-C by 1% can lead to a more than 1% decrease in CVD risk (Starovoitova et al., 2025; Jianga et. al., 2020; Wargocka-Matuszewska et al, 2023; Hansen et al., 2024; Wang et al., 2024b; Upadhyay, 2023). The pathological consequences of hypercholesterolemia, including atherosclerosis, stroke, and xanthomas, are summarized in Table 1.

Cholesterol management in hypercholesterolemic patients typically involves medications (such as statins, fibrates, ezetimibe, inhibition of angiopoietin-related protein 3 (ANGPTL3) and apolipoprotein C-III (apoC-III) etc.), and lifestyle modifications (such as improved diet and physical activity) (Starovoitova et al., 2025; Morofuji et al., 2022; Duan et al., 2022; Khan et al., 2020). However, the side effects and contraindications of lipid-lowering drugs have prompted growing interest in alternative approaches, including probiotics, prebiotics, postbiotics, and functional foods (Starovoitova et al., 2024; Moludi et al., 2021; Wu & Chiou, 2021; Oniszczuk et al., 2021; Fernandez-Calderon et al., 2022; Dixon et al., 2020; Aswani et al., 2021; Neverovskyi et al., 2021; Daliri et al., 2022; Pushpass et al., 2022; Frappier et al., 2022; Romero & Duarte, 2023; Taslim et al., 2023; Yilmaz & Arslan, 2022).

Recent studies highlight the gut microbiome as a promising target for CVD prevention and treatment (Starovoitova et al., 2025; Starovoitova et al., 2024; Prete et al., 2020; Oniszczuk et al., 2021; Wang et al., 2024b; Romero & Duarte, 2023). Dysbiosis and altered microbial metabolites have been implicated in conditions such as hypertension, heart failure, and ischemic heart disease (Schupack et al.,2022; Wang et al., 2024b; Jianga et al., 2020; Yang et al., 2023; Lei et al., 2023a; Lei et al., 2023b; Ghanbari et al., 2024; Romero & Duarte, 2023; DiRienzo, 2024; Antony & de Leon, 2018; Masenga et al., 2022; Habib et al., 2019).

This article **aims** to provide a comprehensive analysis of the potential applications of probiotics, postbiotics, and functional foods for both the prevention and treatment of cardiovascular diseases. In our previous studies, we have evaluated various experimental models of cardiovascular diseases to assess the therapeutic effects of probiotic microorganisms with proven cholesterol-lowering activity *in vivo*. Among these models, the doxorubicin-induced model is particularly advantageous, as doxorubicin exhibits both acute and chronic cardiotoxicity and has been widely used to induce heart failure in various animal species (Starovoitova et al., 2025; Starovoitova et al., 2024). Building on this foundation, the present study focuses on analyzing the therapeutic effects of probiotic strains with pronounced hypocholesterolemic activity in *in vivo* models of cardiovascular diseases.

Probiotics' and postbiotics' mechanisms in CVD prevention. Probiotics offer significant protective benefits against CVDs through several mechanisms, including enhancing the epithelial barrier function, competing with pathogens for nutrients and adhesion sites, modulating immune responses, and reducing oxidative stress

(Sánchez et al., 2017). These effects are mediated by the restoration of gut microbiota balance and the promotion of anti-inflammatory pathways. Probiotics also contribute to lowering cholesterol levels, managing blood pressure, and mitigating key factors like oxidative stress and inflammation, which are involved in atherosclerosis — a primary risk factor for coronary heart disease and stroke (Oniszczuk et al., 2021; Yang et al., 2023; Vasquez et al., 2019; Brandsma et al., 2019; Scarlatescu et al., 2024; Gebrayel et al., 2022). Key mechanisms include:

▪ *cholesterol metabolism*: probiotics deconjugate bile acids, reduce their resorption, incorporate cholesterol into their cell membranes, and convert cholesterol to coprostanol for excretion;

▪ *short-chain fatty acid (SCFA) synthesis*: SCFAs modulate physiological activities such as immune regulation, cellular differentiation, and lipid dynamics. The SCFAs, namely acetate, propionate, and butyrate, are integral to the metabolism of glucose, cholesterol, and lipids. Research has demonstrated that butyrate suppresses the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, the key enzyme controlling endogenous cholesterol biosynthesis, and mitigates the conversion of primary bile acids to secondary bile acids due to colonic acidification. HMG CoA reductase is downregulated by cholesterol originating from the degradation of internalized LDL-C, and its inhibition stimulates the expression of hepatic LDL receptors, thereby promoting the catabolism of LDL-C;

▪ *reduction of trimethylamine N-oxide* (TMAO): this compound is linked to atherosclerosis;

▪ *downregulation of the Niemann-Pick C1-like 1 (NPC1L1) gene*, which is associated with cholesterol absorption in the intestines. Probiotic strains *Lactobacillus rhamnosus* BFE5264 and *Lactobacillus plantarum* NR74 have been shown to influence cholesterol absorption through the downregulation of NPC1L1 expression (Bhat et al., 2019). This downregulation may contribute to reducing cholesterol uptake in the intestines and its reuptake in the liver;

▪ *bile acid metabolism*: probiotics, particularly lactobacilli, enhance bile salt hydrolase (BSH)

Table 1. **Common diseases associated with high cholesterol levels**

Disease	Causes	Pathophysiological effects
Atherosclerosis	Buildup of fats, cholesterol, and other substances on and within artery walls	Causes arteries to narrow, blocking blood flow. Plaque may also rupture, leading to blood clots.
Stroke	Blocks blood supply to part of the brain or occurs when a blood vessel in the brain bursts.	Parts of the brain become damaged or die, leading to paralysis or numbness in the face, arm, or leg.
Cardiovascular disease	Disease of the heart or blood vessels	Coronary heart disease, heart attacks, blood clots (thrombosis), and the buildup of fatty deposits inside arteries.
Xanthomas (associated with familial hypercholesterolemia)	An autosomal dominant genetic disorder characterized by disturbances in lipoprotein metabolism	Persistent hypercholesterolemia
Tangier disease (familial HDL deficiency)	Inherited disorder characterized by significantly low levels of HDL cholesterol	Significantly reduced levels of high-density lipoprotein (HDL) cholesterol in the blood

activity, promoting bile acid biotransformation and improving lipid metabolism (Chen et al., 2023; Robles-Vera et al., 2020a; Robles-Vera et al. 2020b; Starovoitova et al., 2024; Prete et al., 2020; Hassan et al., 2019; Redinbo, 2020; Prete et al., 2020; Bhat et al., 2019; Daliri et al., 2022; Alaqil et al., 2020; Jia et al., 2023; Asan-Ozusaglam & Gunyakti, 2019; Park et al., 2018; Bendali et al., 2017; Singhal et al., 2019; Zhang et al., 2017; Saikia et al., 2018; Bidura et al., 2019; Majeed et al., 2019; Huang et al., 2021; Haldar & Gandhi, 2019; Tom et al., 2021; Pimenta et al., 2018; Palaniyandi et al., 2020; Yusuf et al., 2020; Fernandez-Calderon et al., 2022; Dixon et al., 2020; Aswani et al., 2021; Neverovskyi et al., 2021; Pushpass et al., 2022; Frappier et al., 2022; Romero & Duarte, 2023; Taslim et al., 2023; Din, 2019; Qiu, 2018; O'Morain & Ramji, 2020; Jiang et al., 2020; Hassan, 2020).

Recent evidence highlights the potential of probiotics, synbiotics, and postbiotics, including functional food, in managing dyslipidemia — a key risk factor for CVDs. Despite their promise, randomized controlled trials (RCTs) evaluating their effects on lipid profiles, including triglycerides, LDL-C, total cholesterol, and HDL-C levels, have shown moderate-to-high heterogeneity (Ghorbani et al., 2023). These variations are influenced by factors such as participant health conditions, dosage, and intervention duration:

- *dosage*: lower probiotic doses ($<1\times10^{10}$ CFU/day) demonstrated superior efficacy in reducing the total cholesterol and LDL-C levels compared to higher doses. This finding challenges the assumption that higher doses yield better outcomes, suggesting that lower doses may better support commensal microbial growth and activity (Liang et al., 2021; Companys et al., 2020; Mo et al., 2019).
- *duration*: supplementation lasting ≥12 weeks showed more pronounced improvements in the serum triglyceride levels than shorter interventions, emphasizing the importance of sustained use for optimal benefits (Ghorbani et al., 2023; Liang et al., 2021; Companys et al., 2020; Mo et al., 2019).
- *clinical relevance*: probiotics, synbiotics, postbiotics, and functional supplements effectively lower triglycerides and the LDL-C levels beyond minimum clinically important difference (MCID) thresholds, underscoring their therapeutic potential, particularly in individuals with hypercholesterolemia or hypertriglyceridemia. However, their impact on HDL-C and total cholesterol levels was less pronounced, except in specific high-risk populations (Yan et al., 2019; Liu et al., 2019; Jiang et al., 2020; Wang et al., 2020; Dixon et al., 2020).

The mechanisms underlying these benefits are multifaceted. Probiotics modulate lipid metabolism by influencing bile acid production, reducing intestinal cholesterol absorption, and enhancing fecal excretion. SCFAs, produced during dietary fiber fermentation, reduce inflammation, improve lipid profiles, and mitigate atherogenesis. SCFAs also activate pathways such as peroxisome proliferator-activated receptor alpha (PPARα) and bile acid receptor FXR, enhancing triglyceride metabolism and remodeling HDL particles.

Additionally, probiotics exhibit anti-inflammatory properties by inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling, reducing pro-inflammatory cytokines, and strengthening the gut barrier integrity. These actions further support their cardioprotective role by addressing the inflammatory components of CVD pathology (Ghorbani et al., 2023; Yan et al., 2019; Hadi et al., 2021).

Moreover, specific bacterial strains, particularly from the *Lactobacillus* and *Bifidobacterium* genera, have shown significant promise. Multi-strain probiotics demonstrated greater effectiveness than single-strain formulations, highlighting the potential of combined strategies for comprehensive lipid management (Ghorbani et al., 2023; Lakshmanan et al., 2021).

Doxorubicin and its effect on CVDs. Doxorubicin (DOX) was discovered in 1969 as a homolog of daunorubicin and was isolated from a soil bacterium, *Streptomyces peucetius*. DOX is an anthracycline antibiotic, and its toxic effect on cardiomyocytes is an important research area. DOX can cause cardiotoxicity in a dose-dependent manner. A meta-analysis of 22,815 DOX-treated patients revealed that 17.9% of them developed subclinical cardiac dysfunction, and 6.3% experienced clinical heart failure. Among the identified risk factors, cumulative dosage remains the most critical predictor of doxorubicin-induced cardiotoxicity (DIC) (Linders et al., 2024).

Despite extensive research, the mechanisms underlying DIC remain controversial due to discrepancies in experimental conditions. In human patients, blood concentrations of DOX after administration typically range from 0.025 to 0.250 μmol/L. However, *in vitro* studies often employ doses exceeding 1 μmol/L. Furthermore, animal models such as mice and rats can tolerate significantly higher concentrations, with tolerable blood levels reaching 0.7—2.1 μmol/L (10—30 mg/kg) (Rawat et al., 2021). This species-specific tolerance suggests that different mechanisms may drive DIC in rodents versus humans.

DOX exerts its cardiotoxic effects through multiple pathways:

- *DNA damage and epigenetic modifications*. In the nucleus, DOX induces DNA damage, disrupts epigenetic regulation, and shortens telomeres. These alterations compromise cellular repair mechanisms and contribute to myocardial dysfunction.
- *calcium dysregulation*. In the cytoplasm, DOX inhibits calcium reuptake, leading to elevated intracellular calcium levels. This dysregulation impairs cardiomyocyte contractility and promotes cell stress.
- *mitochondrial dysfunction*. DOX directly increases mitochondrial reactive oxygen species (ROS) production and inhibits the electron transport chain, amplifying oxidative stress (Linders et al., 2024).

The combined effects of these cellular disturbances manifest themselves through hypertrophy, diastolic dysfunction, atrial fibrillation, prolonged QT intervals, and myocardial fibrosis.

Rodents display greater resilience to DOX compared to humans, necessitating higher dosages in preclinical studies. Importantly, the concentration-dependent activation of distinct molecular pathways implies that the mechanisms of DIC in animal models may not fully replicate those in human physiology. This divergence underscores the need for careful interpretation of preclinical data and its translation to clinical settings.

In vivo small animal (rodent) models of doxorubicin-induced CVDs. In our previous study, we have discussed various small animal models of CVDs for evaluating the cholesterol-lowering activity of probiotic strains. It was shown that the DOX-induced CVD model is one of the best perspective *in vivo* models for evaluating the cholesterol-lowering activity of probiotic strains in human CVDs caused by high cholesterol levels (Starovoitova et al., 2025). Therefore, this section of the article focuses on utilizing this model to evaluate the prophylactic and therapeutic potential of probiotic microorganisms in mitigating human cardiovascular diseases associated with elevated cholesterol levels in the host.

Emerging evidence suggests that alterations in the composition and function of intestinal microbiota, known as dysbiosis, are intricately linked to the progression of DIC via the regulation of the gut-microbiota-heart axis. Despite these associations, the precise role of gut microbiota and its metabolites in the pathogenesis of DIC remains largely unexplored, warranting further investigation (Huang et al., 2024).

In experimental work (Spivak et al., 2013a), it was shown that the optimal cumulative

DOX dose for inducing congestive heart failure (CHF) was 12.45 mg/kg. At higher doses, more than 40% of the animals died, while lower doses did not induce significant clinical or general ultrasound (US) criteria for CHF. Congestion, accompanied by weight gain, led to reduced animal mortality. The suggested model, involving an optimal DOX dose of 2.5 mg per animal and a cumulative dose of 12.45 mg/kg administered in four intraperitoneal (IP) injections every three days, can be used for research purposes. Moreover, 30 nm gold nanoparticles (AuNPs) and their AuNPs-Simdax conjugate have demonstrated promising biosafety and biocompatibility profiles in both *in vitro* and *in vivo* studies. AuNPs-Simdax and AuNPs exhibit comparable cardioprotective effects in rat models of DOX-induced CVD, with both surpassing the efficacy of Simdax alone (Spivak et al., 2013b).

Another study (Abu-Elsaad et al, 2015) has demonstrated that probiotics and antioxidants significantly mitigate DIC through functional food. Sprague-Dawley rats were divided into five groups: an enriched diet group (yogurt, green tea extract, carrots), a carvedilol group, a combined treatment group, and control groups. Cardiomyopathy was induced by intraperitoneal injection of DOX (2.5 mg/kg) every 48 hours for two weeks. The enriched diet normalized the QT interval, reduced heart-to-body weight ratios, and lowered the serum angiotensin-II (Ang-II) and atrial natriuretic peptide (ANP) levels. Histopathological analysis revealed reduced vacuolization and fibrosis, while biochemical assays showed decreased creatine kinase-membrane bound (CK-MB), lactate dehydrogenase (LDH), triglycerides, cholesterol, LDL-C, and tissue malondialdehyde (MDA) levels. Additionally, increased Na+K+ ATPase and cardiac reduced glutathione (GSH) levels were observed, along with reductions in TNF-α and IL-6. The findings suggest that functional food containing *Lactobacillus acidophilus*, green tea, and carrots improves cardiac integrity and contractility in DIC by modulating oxidative stress and inflammatory mediators.

The next investigation (Afonso et al., 2023) focused on evaluating the effects of different doxorubicin (DOX) dosages on the cardiovascular dysfunction in Wistar rats. Rats were divided into groups receiving DOX at 2, 4, or 5 mg/kg/week (cumulative doses: 8, 16, and 20 mg/kg, respectively) for four weeks, with a saline-treated

Table 2. **Data on the modeling of doxorubicin-induced CVD in small-animal models (rodents)**

Sex, age	Dose of DOX	Administration frequency
		Rat
Wistar (weighing 180—200 g)	Cumulative dose 2.49 mg/animal or 12.45 mg/kg	4 times a week
Wistar (180—200 g)	Cumulative dose 3.03 mg/animal or 15.15 mg/kg	5 times a week
Wistar (180—200 g)	Cumulative dose 12.0 mg/kg	—
Adult male Sprague-Dawley (300—350 g)	2.5 mg/kg → 15 mg/kg	every 48 hours for two weeks
Male Sprague—Dawley (300—400 g)	25 mg/kg	For 3 days; on 12th, 13th, and 14th days
Male Wistar (225—280 g)	18 mg/kg	For three days in the study
Male Sprague-Dawley (220—250 g)	4 mg/kg → 12 mg/kg	3 times: 1, 6, 11 days

control group. Physiological parameters such as blood pressure, heart rate, and LF/HF ratio (autonomic activity marker) were measured, along with cardiac collagen content. Key findings included dose-dependent cardiovascular changes: hypotension, bradycardia, increased fibrosis, and impaired autonomic control at cumulative doses ≥16 mg/kg. These results highlight the importance of DOX dose in inducing cardiovascular dysfunction.

The study (Pan et al., 2022) utilized a rat model to investigate biomarkers of acute and chronic myocardial injury induced by DOX. Acute injury was modeled with a single intraperitoneal dose of DOX (40 mg/kg), showing elevated creatine kinase (CK), fatty acid-binding protein 3 (FABP3), and cardiac troponin I (cTnI) levels, with cTnI peaking at 8 hours. Chronic injury was induced via weekly caudal vein injections of DOX (1—3 mg/kg) for up to 8 weeks, revealing significant increases in cTnI, FABP3, and miR-146b, with cTnI and miR-146b demonstrating high predictive value for chronic damage.

High-intensity interval training (HIIT) has the potential to exacerbate cardiotoxicity, particularly when performed shortly after DOX administration. This is due to the acute increase in reactive oxygen species (ROS) production during the exercise, with the extent of ROS generation being influenced by the exercise duration and intensity. Therefore, in another pilot study (Legault et al., 2024) of female C57BL/6 mice, aged 70 days, a single bolus of DOX was administered via intravenous tail vein injection at a dose of 20 mg/kg. Three exercise groups underwent a single high-intensity interval exercise (HIIE) session, consisting of 16 sets of 1-minute intervals at 85—90% of peak running speed, at 1 day, 2 days, and 3 days post-DOX injection. Echocardiographic assessments were conducted under light anesthesia (isoflurane 0.5—1%) before and 7 days after DOX injection. On day 9, the animals were sacrificed, and their hearts were collected for morphometric and histological analyses. This study demonstrated that a single session of HIIE did not exacerbate acute DOX-induced cardiotoxicity. However, the timing of the exercise session relative to DOX administration and compliance with the exercise regimen may influence the extent of DOX-induced cardiac dysfunction.

Information about features of doxorubicin-induced CVD small-animal models is summarized in Table 2.

	Route of administration	Toxicity assessment	Reference
models			
	IP	General ultrasound	Spivak et al., 2013a
	IP	General ultrasound	Spivak et al., 2013a
	Intrapleurally, intravenously	Ultrasonography	Spivak et al., 2013b
	IP	Histopathological analysis	Abu-Elsaad et al, 2015
	IP	Echocardiography (ECHO), histology	Barıs¸ et al. 2019
	IP	Electrocardiogram (ECG)	Aygun & Gul 2019
	IP	ECHO	Wang et al. 2019

Sex, age	Dose of DOX	Administration frequency
Male Sprague-Dawley 12 weeks	1 mg/kg →10 mg/kg	10 times every day
Male Wistar 4 weeks	Three cumulative doses: 7.5, 10 or 12.5 mg/kg	Once a week for 6 weeks
Male, Wistar (200—300 g)	1.25 mg/kg → 20 mg/kg	4 days a week during for 4 weeks
Male (220—250 g)	2.5 mg/kg → 15 mg/kg	Six equal injections over a period of two weeks
Male Sprague-Dawley 7 weeks (174—213 g)	40 mg/kg (10 ml/kg)	Once
Wistar 12 weeks	2 mg/kg/week, DOX8, n = 8 4 mg/kg/week, DOX16, n = 8 5 mg/kg/week, DOX20, n = 8	4 weeks
		Mouse
Male 12—14 weeks	5 mg/kg	—
Female 10 weeks	4 mg/kg → 24 mg/kg	3 times a week
Female 10—12 weeks	8 mg/kg → 24 mg/kg	Weekly
Male 8 weeks	Cumulative 15 mg/kg	—
Male 8 weeks	Cumulative 25 mg/kg	—
— 15—16 weeks	Cumulative 25 mg/kg	—
Male 9—10 weeks	20 mg/kg	Once
Male 10 weeks	15 mg/kg	Once
Male 8 weeks	4 mg/kg → 20 mg/kg	Weekly
Male 8 weeks	10 mg/kg	Once
Male 6 weeks	15 mg/kg	Once
Female C57bl/6 mice	20 mg/kg	Once
Male C57BL/6j mice 8 weeks (20—25 g)	2.5 mg/kg →15 mg/kg	3 weeks (six injections)
—	8 mg/kg → 24 mg/kg	Weekly

Continuation of Table 2

	Route of administration	Toxicity assessment	Reference
	IP	ECHO, histology, troponin	Medeiros-Lima et al. 2019
	Intravenous injection (tailvein)	ECHO, histology	Chakouri et al. 2020
	IP	ECHO, histology	Aykan et al. 2020
	IP	ECG, histology	Elhadidy et al. 2020
	intraperitoneal	histopathological	Pan et al., 2022
	IP	ECG	Afonso et al., 2023
models			
	IP	Troponin	Bai & Wang, 2019
	IP	ECHO, troponin	Gioffré et al., 2019
	IP	MRI	Allen et al., 2019
	Subcutaneous pellets	Histology	Allen et al., 2019
	Subcutaneous pellets	Histology	Allen et al., 2019
	Subcutaneous pellets	MRI, histology	Naresh et al., 2020
	IP	ECHO, CK-MB, LDH, histology	Mizuta et al., 2020
	IP	ECHO, troponin, CK	Hu et al., 2020
	IP	ECHO, troponin, NT-proBNP, histology	Sabatino et al., 2020
	IP	Histology	Peres Diaz et al. 2020
	IP	ECHO, LDH, CK-MB, histology	Ye et al. 2020
	intravenous tail vein intraperitoneal	histology ECHO, biochemical detection	Legault et al. 2024 Wang et al., 2024a
	IP	ECHO, histology	Hu et al., 2024

Ultrasound-guided evaluation of probiotic efficacy in CVD models. Traditionally, research on small laboratory animals (e.g., mice, rats) has relied on euthanasia and dissection to obtain anatomical and physiological data. Non-invasive imaging methods, such as magnetic resonance imaging (MRI), have been employed; however, these typically require high-cost, specialized equipment with powerful magnetic fields to achieve sufficient resolution for small anatomical structures. Ultrasound biomicroscopy (UBM) has also been utilized but remains accessible only in a limited number of specialized centers (Spivak et al., 2013b; Spivak et al., 2013c; Bubnov et al., 2019).

In contrast, Spivak, Bubnov, and colleagues have developed a model based on the application of conventional ultrasound (US) diagnostics using widely available equipment as a core tool for dynamic *in vivo* monitoring in experimental studies (Spivak et al, 2013a; Spivak et al, 2013b; Spivak et al, 2013c; Bubnov et al, 2019; Bubnov et al, 2017a; Bubnov et al, 2017b). This approach enables real-time assessment of structural and functional parameters without the need for euthanasia, thereby significantly reducing the number of animals required for longitudinal studies.

US has been demonstrated to provide several key advantages in small animal models: 1) real-time imaging; 2) high-quality and high-resolution images that outperform some other imaging techniques when studying small structures using widely available equipment; 3) dynamic assessment of structural and functional changes in organs and tissues throughout the entire experiment; 4) non-invasive evaluation of the vascular system using Doppler imaging; 5) non-invasive assessment of tissue density using sonoelastography; 6) effective guidance for interventional procedures (e.g., injections or biopsies); 7) screening studies involving a large number of animals.

In the context of probiotic research related to metabolic and liver disorders, US has proven particularly useful. In models of diet-induced obesity, it enabled accurate measurement of liver dimensions and visceral (mesenteric) fat thickness in mice. Administration of probiotic strains (e.g., *Lactobacillus, Bifidobacterium*) resulted in observable reductions in liver size and mesenteric fat, as quantified by US. These changes correlated with decreases in body weight and serum cholesterol levels. Importantly, US-derived parameters of liver condition and fat distribution were found to be more sensitive indicators of the metabolic status than body weight alone. Moreover, US allowed estimation of the visceral fat-to-muscle ratio, a recognized marker of metabolic health, and was effectively used for screening large experimental groups (Spivak et al, 2013a; Spivak et al, 2013b; Spivak et al, 2013c; Bubnov et al, 2019; Bubnov et al, 2017a; Bubnov et al, 2017b).

US has also been employed for cardiovascular assessment, including measurements of ejection fraction, chamber dimensions, and identification of pleural effusion. Given the well-established links between the gut microbiota, metabolic syndrome, obesity, and cardiovascular diseases such as atherosclerosis, the US methodology proposed by Spivak and Bubnov holds significant promise for evaluating the cardiometabolic impact of probiotic interventions in experimental settings.

In summary, integration of US diagnostics into experimental models represents a valuable, non-invasive, and quantitative approach for the longitudinal assessment of structural and functional changes *in vivo*. This method has been successfully applied to evaluate the effects of probiotics and nanomaterials in models of obesity and liver fibrosis, providing important insights into their potential role in improving metabolic and cardiovascular health.

Conclusions. CVDs, particularly acute myocardial infarction, remain a foremost global health challenge, driven by risk factors such as hypercholesterolemia and compounded by the

limitations and side effects of existing treatments. While conventional lipid-lowering medications are effective, their constraints have underscored the need for alternative approaches. Probiotics, postbiotics, and functional foods have emerged as promising candidates for addressing the multifaceted pathology of CVDs by modulating the gut microbiota, enhancing lipid metabolism, and mitigating oxidative stress and inflammation.

The utilization of doxorubicin-induced CVD models has been instrumental in elucidating the mechanisms underlying cardiotoxicity and evaluating therapeutic interventions. These models, when combined with advanced insights into the gut-microbiota-heart axis, provide a robust platform for assessing the prophylactic and therapeutic potential of probiotics and functional foods in managing hypercholesterolemia-induced CVDs.

Future research should prioritize optimizing experimental models to better replicate human physiology, exploring the molecular interactions within the gut-microbiota-heart axis, and conducting clinical trials to translate these findings into effective, patient-centered therapies. Notably, cholesterol-lowering probiotic strains and functional food products have demonstrated significant promise in experimental and clinical settings, offering a safer complementary strategy to conventional therapies. By integrating these advancements into holistic treatment regimens, the multifaceted pathophysiology of cardiovascular diseases can be more effectively targeted, ultimately improving patient outcomes and reducing the global burden of such conditions.

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РОЛЬ ПРОБІОТИКІВ У ПРОФІЛАКТИЦІ ТА ЛІКУВАННІ СЕРЦЕВО-СУДИННИХ ЗАХВОРЮВАНЬ: ДОСВІД, ОТРИМАНИЙ НА ДОКСОРУБІЦИНОВІЙ МОДЕЛІ

Серцево-судинні захворювання (ССЗ), зокрема гострий інфаркт міокарда, є критичною глобальною проблемою охорони здоров'я, обумовленою багатофакторними ризиками, включаючи гіперхолестеринемію. Хоча традиційні методи зниження рівня ліпідів залишаються ефективними, їх побічні ефекти та обмеження стимулювали пошук альтернативних підходів. Пробіотики, постбіотики та функціональні продукти харчування стали інноваційними стратегіями, які здатні модулювати мікробіоту кишечника, покращувати ліпідний обмін та зменшувати оксидативний стрес і запалення, відкриваючи нові можливості для управління ССЗ. У цьому огляді підкреслюється значущість моделей, індукованих доксорубіцином, для вивчення механізмів ССЗ та оцінки терапевтичного потенціалу. Завдяки використанню знань про вісь кишечник-мікробіота-серце, ці моделі сприяють розробці нових інтервенцій, спрямованих на ССЗ, викликані гіперхолестеринемією. Пробіотичні штами, що знижують рівень холестерину, та функціональні харчові продукти вирізняються своєю здатністю забезпечувати більш безпечні та доповнюючі варіанти до традиційних терапій. Подальший розвиток досліджень у цій галузі вимагає оптимізації експериментальних моделей, вивчення молекулярних шляхів та переведення отриманих результатів у клінічну практику через ретельні випробування. Інтеграція цих інноваційних рішень має потенціал для покращення серцево-судинного здоров'я, задоволення невирішених клінічних потреб та зниження глобального тягаря ССЗ.

Ключові слова: *серцево-судинні захворювання, пробіотики, постбіотики, функціональні продукти харчування, мікробіота кишечника, метаболізм холестерину, доксорубіцин-індуковані моделі, терапевтичні втручання*